

The Influence of Nitrous Oxide on Hearing.

by
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This is dedicated to

Dr. Tania Gerzina for inspiring me to do research,

Dr. Richard Morris for giving help in research,

Dr. Greg Murray for keeping me going

and to

Jelle Lahnstein.

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1.1 Literature Review

An examination of some of the effects of nitrous oxide (N₂O) on hearing is the subject of this work. Over the years, research has been done on the effect of N₂O on neural pathways in the human (Corssen *et al* 1966) and some work has reported subjective hearing changes (Westerlund *et al* 1961).

The most notable effect of nitrous oxide on hearing has traditionally been considered to be an increase in auditory acuity (Langa 1976). Sir Humphrey Davy was the first to report on the effects of N₂O and finding that he had developed "more acute hearing" whilst breathing N₂O (Kaufman *et al* 1990). Fenwick and co-workers (1979) reported from their experiment of ten subjects inhaling up to 40% N₂O that a "common subjective experience was the increase in auditory acuity during the experimental situation. One subject reported that he could not hear the expiratory valve on the mouthpiece until he was inspiring 20% nitrous oxide." McMenemin and co-workers (1988) reported that some of their subjects noticed that the "background noise appeared magnified". Langa (1976) stated that during N₂O sedation, "the patient's sense of hearing becomes more acute". Absolute belief in this concept of increased auditory acuity has therefore been firmly entrenched in dental anaesthesiology. Studies, such as Kaufman and co-workers (1990), however asked basic qualitative questions of the subjects such as: "Did you experience diminished sound intensity of voices or ambient noises? Did you experience accentuated acuity in hearing?" but without defining any quantitative threshold changes. Westerlund and co-workers (1961), stated that their subjects had a decrease in acuity, thus raising the question "what does happen to hearing under the influence of N₂O?" The aim of this work is to define if any effects occur on a subject's hearing performance and if so - in which manner, for example increased acuity or not. The definition of an increase in acuity, whilst breathing N₂O, could be considered as the ability to hear quieter sounds better (or louder) than during the controls.

Hearing acuity can be defined as the quietest intensity level (threshold) that can be perceived for a particular frequency and in the average adult human individual the threshold for 500 Hz to 8 kHz is around 0 (and can be under 0 dB) to 20 dB (Davis *et al* 1963, Zwicker *et al* 1990). Davis and co-workers (1963) stated that "the term 'acuity' is slightly ambiguous and is sometimes misunderstood as referring instead to the ability to discriminate between two tones that are nearly the same."

There have been some studies on hearing thresholds with subjects breathing N₂O. Delisle Burns and co-workers (1960) measured various sensory thresholds and noted that there were "a significant and sometimes dramatic increase in the thresholds for touch, skin pain, warmth, vision and hearing" during 25% N₂O inhalation. This states that there are increases in threshold levels for hearing as well as other senses, which implies that hearing does not become more acute. Thus, studying the threshold levels of various frequencies, within the human hearing range, could indicate acuity changes. Westerlund and co-workers (1961) employed a hearing test using a range of frequencies: 250 Hz, 1 kHz, 2 kHz and 4 kHz, on 17 subjects inhaling between 15% to 40% N₂O and reported that "a gradual increase in the intensity of the sound was necessary to provoke a response" thus suggesting a decrease in acuity. Tomlin and co-workers (1973) reported a study whereby subjects were tested "objectively" at two frequencies, 1 and 4 kHz, under oxygen (O₂) and then between a range of 40% to 80% N₂O (also a third test with methoxyflurane), and found that: "Despite all the subjects' claims that hearing improved during the inhalation of the anaesthetic agent the results of objective testing did not confirm that this was so but indicated that hearing remained unchanged almost to the point of unresponsiveness when in all except one subject there was a small loss in auditory acuity." Tomlin *et al* (1973) used such high dosages of N₂O that the subjects' ability to accurately respond would be affected (see 2.1.2 Sequence of Testing), in addition, only two frequencies

were tested although the human ear can distinguish frequencies outside the two that were utilised.

The methods that are used in this work (see 2. Methods) aims to clearly define from the subject's perspective (and as objectively as possible) what influence N₂O has on hearing by any changes in auditory acuity (see 2.2.4 Auditory Threshold). This can define the effects of N₂O and so supplement findings in current neurological studies. Any sensory perception is important in appreciating one's place in the world but the subjective interpretation is just as important. Thus this work also examined how a sound is interpreted (see 2.2.6 Subjective Intensity) and remembered (see 2.2.5 Intensity Matching).

Berry (1965) stated that memory of auditory cues (by finding the missing alphabet letter(s) of 7 presented) is affected by the rapidity of that information being given to the 16 subjects "(aged 18-33)" and N₂O inhibits retention of auditory cues by delaying transfer of information from the "first to the second" memory storage areas (assuming that there are two such areas). Berry employed 15%, 25% and 35% N₂O levels. This work did not use words nor letters since association can be formulated with another sense that can help to retain the memory of that word or letter, e.g. the letter "b" can be remembered as a "bee" by the sound or in a visual context. Thus in this work (see 2.2.5 Intensity Matching), only a pure tone is employed, so that there is no association with another sense to help the subject retain memory of that tone, thus any alteration in auditory perception, memory and judgement was determined.

Langa (1976) suggests that the dental operatory has a "psychologically disturbing effect upon the dental patient" and when with an "almost medieval perception" of dentistry, any unfamiliar or ambient noise can be translated into a fear-inducing situation, which can influence the treatment and outcome. This may be more serious under sedation or general anaesthesia, as the patient may only believe what he has interpreted not what was actually heard of the events

and sounds occurring in the nearby vicinity for the deep subconsciousness is absolutely "devoid of humor" (Cheek 1959).

Studies such as that of Houston and co-workers (1988) state that "there was no change in subjective pure tone threshold" and that the changes in the cortical auditory evoked potential (AEP) "is not linked uniquely to subjective hearing levels", by employing ten subjects (18 to 32 years old, 5 male), and 10%, 20% and 40% N₂O levels and measured cortical AEP with the threshold level for the 2 kHz pure tone frequency. There is ongoing research into AEPs (Jessop *et al* 1991). The AEPs are responses that can be recorded from the central cortex (recorded by an EEG) to sound clicks (Corssen *et al* 1966). Corssen and co-workers (1966) derived an experimental model for research into this area and found that there is some depression of the AEP while using N₂O. This kind of research may help to identify if patients can hear during a general anaesthesia (Jones *et al* 1986) but will not identify if they can appreciably understand such communications. Jessop and co-workers (1991) stated that there was some sound recognition by the change in the P300 component of the AEP while the 6 subjects were under 20% to 65% N₂O but the work did not try to identify if this was a clinically significant effect from the subject's point of view. Fenwick and co-workers (1979) stated that it "is interesting that the subjective acuity of hearing and the amplitude of the cortical evoked response are not related when the subject is given nitrous oxide. Several subjects reported an increase in the subjective sensitivity of their hearing at the higher concentrations of the gas when the evoked cortical response was almost absent."

Fenwick and co-workers (1979) presents the view that the "auditory system is especially sensitive to low concentrations of nitrous oxide and is therefore easily affected". They used low concentrations, such as 10% and 20% N₂O, as at higher concentrations subjects found responding difficult (see 2.1.2 Sequence of Testing), to discover the influences on hearing and may give indication as to how N₂O affects the auditory system.

How does N₂O affect hearing? Whilst studies into neurophysiology and research into AEPs continue, N₂O does seem to increase middle ear pressure (MEP), as with any enclosed gaseous space, e.g. intestine, maxillary sinus (Patterson *et al* 1976, Ramírez-Camacho *et al* 1984). Thomsen and co-workers (1965) noted that during myringoplastic surgery, "a bulging of the skin or vein graft" occurred and attributed this to MEP increase due to N₂O usage. They also found that the eustachian tube does have an influence by passive venting or yawning. Waun and co-workers (1967) studied patients undergoing various levels of N₂O and non-N₂O anaesthesia and found that N₂O does increase MEP with a combined decrease in compliance (Comp) of the ear drum and hearing acuity. Positive airway pressure (PAP) could also possibly influence hearing by producing changes in the middle ear (Ramírez-Camacho *et al* 1984) however Waun and co-workers (1967) state that they had no effect from PAP. This has been considered in the current work where MEP with Comp were measured (see 2.2.3 Acoustic Impedance).

Patients undergoing anaesthesia with N₂O and narcotic agents have demonstrated a greater chance of recall of the operative events compared with patients undergoing anaesthesia with other anaesthetic gases (Jelcic *et al* 1993). Negative experiences and recalling of events can have possible ramifications (Saucier *et al* 1983, Troyer 1983, Jones *et al* 1986) especially in view of reports by the mass media where experiences are embellished for example, patients being awake whilst under a general anaesthesia (Fynes-Clinton 1993). Browne and co-workers (1973) have stated, in regard to general anaesthesia, that hearing "appears to be the last sensation retained before loss of consciousness and is probably the first to return when consciousness is regained". Thus there is interest in the study of hearing acuity in relation to whether a patient can hear under the influence of N₂O. In addition to possible medico-legal complications (Troyer 1983), a patient's personal well being could be at risk, as patients could misinterpret information given to them or hear statements that weren't 'meant for their ears'.

An understanding of the method employed in this work, e.g. a ten minute lag time between stages, requires an understanding of the gas, N₂O, itself. The next section of the Introduction will describe N₂O by explaining its physical and chemical properties, its manufacture, and the physiological and pharmacological actions which relate to this work. Knowledge of its properties allows us to understand the physiological actions of N₂O. The manufacturing process will determine if the likelihood of hazardous side reactions and possible by-products could be produced. The physiological actions of N₂O need to be understood in order to determine if the subjects did inhale N₂O and an analysis was done on their experience to prove that N₂O was used.

This work studied the subjective and objective effects on hearing of N₂O inhalation. The null hypothesis will be that N₂O does not affect hearing in any objective or subjective manner.

1.2 Physical and Chemical Properties

Many synonyms have been created to identify nitrous oxide (N₂O) by its actions or molecular structure: dinitrogen monoxide, "laughing gas", factitious air, nitrogenii oxidium and hyponitrous acid anhydride (Pharmaceutical Codex 1979, Merck Index 1983).

N₂O is a simple inorganic molecule and is a gas at room temperature. Its physical properties are "similar to those of the non-polar carbon dioxide" (Bailenson 1972, Mahan 1975, Eger 1985, Henry *et al* 1989). The physical and chemical properties of N₂O are;

Molecular Weight; 44.01 (63.65% is nitrogen, 36.35% is oxygen)

Boiling Point; -88.5 °C (vaporisation energy (bp): 3.956 kcal/mole)

Melting Point; -90.81 °C

Critical Temperature; 36.4 - 36.5 °C

Density/Gravity; 1.53 kg/m³ at 21 °C, 101.33 kPa

Solubility Coefficients; In water (i.e. water/gas); 0.41 ml (at 38 °C and 1 atm)

Blood/gas; 0.47 (N₂; 0.013)

Blood/tissue; 1.13 (heart), 1.06 (brain) and 1.0 (lung)

Oil/blood; 3.0

Oil/water; 3.2

Oil/gas; 1.4

Reaction with; Metal parts of anaesthetic equipment; no reaction
Rubber parts of anaesthetic equipment; does react
Soda Lime; no reaction
Other anaesthetic drugs; no reaction

Inhaled Concentration for; Analgesia; 35 - 40%
Anaesthesia; >85% (see 1.2.1)
MAC; 110% (see 1.2.1)
Respiratory Arrest; unobtainable
Asphyxiation; when less than 21% O₂ is employed with N₂O

Cell/Plasma Ratio; 1:1

Oil/Water Distribution Ratio; 3.2 (37 °C)

Colourless, slight 'sweetish' odour/taste

Non-flammable, supports combustion, low temperature hazard

Constituent of the Earth's Atmosphere; 0.00005% by volume (0.5 ppm)

(Severinghaus 1954, Bailenson 1972, Mahan 1975, Shane 1975, Collins 1976, Carrie *et al* 1982, Weast *et al* 1982, Hill *et al* 1983, Merck Index 1983, Eger 1985, CIG 1991)

1.2.1 Physiological Considerations

An appreciation of the physical properties of N₂O enhances the knowledge of its handling capabilities and the effect of the gas on living organisms. Nitrous oxide, for example, does not react with the metal parts of anaesthetic machines, nor does it react with soda lime nor other anaesthetic agents, however, it does impregnate and can diffuse through the rubber mask or tubing (Collins 1976, Bailenson 1972). In the current work, plastic tubing was used with the anaesthetic machine, but the full face mask was rubber.

In its gaseous state, at 21°C and 101.3 kPa, the density of N₂O is 1.53 kg/m³. This means little on its own, however when compared to some relatively common substances it identifies a specific quality;

Air: 1.0 (Bailenson 1972, Collins, 1976)

Helium: 0.138 (CIG 1991, Collins, 1976)

Oxygen: 1.1, Carbon dioxide: 0.96, Nitrogen: 0.96 (Collins, 1976).

Nitrous oxide has a specific gravity of 1.53 which is heavier than air (air is 1) and thus will gravitate to sea level rather than rise (Hill *et al* 1991). In this study, subjects sat in a chair (see 2.3 Armamentarium) which prevented possible contamination of their breathing medium by waste N₂O during the control stages of the experiment. There was normal building air conditioning to help remove the waste gases. The experimental room's door was constantly open to a large office environment throughout the entire experiment which aided in the removal of the gas. A 5 metre long expiratory tube opened into the next area.

The solubility of any substance is defined as the volume of gas (cm³ or ml) that will dissolve in 100 ml of water or blood; this also identifies its polar or non-polar status. The coefficient of solubility for N₂O (in water or blood and at human body temperature) is 0.47 ml.

It is relatively insoluble in water and "does not change the pH of the water" (Collins 1976, Hill *et al* 1983). Collins (1976) qualifies that the N₂O solubility is "relatively low....compared to other anaesthetic agents". Nitrous oxide has a non-polar nature and so is non-reactive with the water content of the body (i.e. does not chemically alter plasma or water). Norris *et al* (1971) qualifies this by stating; "Anaesthetic agents must be soluble in water if they are to be dissolved in the plasma and carried to the brain. They must also be soluble in oil if they are to pass readily to the lipid tissue of the brain. Most anaesthetics therefore have a high oil/water solubility ratio." Nitrous oxide, being non-polar, will easily dissolve in similar non-polar semi-solid or liquid environments e.g. fatty tissue.

The ability of N₂O to dissolve into, and out of, gas spaces in the body is more rapid than nitrogen (N₂ blood-gas solubility is 0.013). Hill *et al* (1991) applies the idea of solubility into practical application; "Nitrous oxide has a low blood gas partition coefficient of 0.47, i.e. it is relatively insoluble and thus its partial pressure in the blood and tissues rises rapidly and its onset of action is rapid. At saturation, 45 ml gas will dissolve in 100 ml blood. A further consequence of the insolubility of this agent is that when inhalation is discontinued the nitrous oxide dissolved in the blood is rapidly eliminated via the lungs."

Thus N₂O can increase the pressure of an air space in the body by rapidly dissolving out of the blood into an air space while N₂ is unable to move out of the same space as rapidly, e.g. increases of middle ear pressures (see 2.2.3.1 Middle Ear Pressure (MEP)). Severinghaus (1954) quantifies the difference between N₂O and N₂ (Bailie *et al* 1988, Patterson *et al* 1976, Casey *et al* 1982, Munson 1974, Saidman *et al* 1965): "N₂O is 32 times more soluble than N₂ in blood; it is 20 times more soluble than N₂ in fat. With 20 per cent of the body being fat, the average solubility of N₂O will be 30 times that of N₂."

At the end of N₂O inhalation, N₂O is more rapidly dissolved from the blood into the alveoli, while N₂ cannot move as rapidly back into

the blood from the alveoli. The result is an increase in total gas pressure within the alveoli with a drop of the partial pressure of oxygen within the alveoli which produces a hypoxic state and this phenomena is called "diffusion anoxia" (Fink 1955). Frumin and co-worker (1969) state that diffusion anoxia is not clinically significant, unless there is respiratory depression/obstruction. In this experiment, no subject had respiratory problems and no clinically significant effects were noticed at the end of stage 3 (see 2.1.2 Sequence of Testing).

Different dosages of N₂O produce different effects, for example, analgesia requires 35 - 40% administered N₂O and anaesthesia requires greater than 85% (Collins 1976). Surgical anaesthesia is unattainable unless hypoxic mixtures are utilised as N₂O alone is an asphyxiant and survival requires 21% oxygen (Carrie *et al* 1982, Merck Index 1983, Hill *et al* 1983). Minimum alveolar concentration (MAC) is the percentage of anaesthetic gas (value is only given, as the units are assumed to be in percentages) in the alveolus which causes 50% of people to not respond "to a painful stimulus" and refers to "alveolar, not administered, concentration" (Komesaroff 1986, Eger 1985, Tolmie *et al* 1986). It is useful data in comparing strengths of varying anaesthetic gaseous agents; N₂O this has been equated to 110 (some state 104 or 101 but all agree that it is 'over 100'), compared to halothane: 0.75, enflurane: 1.68 and isoflurane: 1.15 (Komesaroff 1986, Tolmie *et al* 1986). To maintain a general anaesthetic state, Lunn (1979) states that during maintenance of anaesthesia, the inspired concentration of any anaesthetic gas would be "about 50% greater than MAC during spontaneous ventilation and about half MAC during controlled ventilation with muscle relaxants." To achieve and maintain a general anaesthetic state is not possible with N₂O and oxygen alone, thus additional anaesthetic agents are usually administered. In the current work, low percentages of N₂O were employed as the subjects maintained consciousness; the safety of the individual was thus guaranteed and conscious cooperation was consistent.

The physical qualities of N₂O are colourless (Pharmaceutical Codex 1979, CIG 1991), odourless and tasteless (Pharmaceutical Codex 1979), however N₂O is also described as possessing a "slight sweetish taste" (CIG 1991) and "a characteristic, faintly sweet odor; but the patient will, most likely, be more aware of the rubbery odor of the anesthetic mask than that of the gas" (Bailenson 1972). This information was used to determine if the subjects could identify the smell and taste of N₂O during inhalation in this thesis thus proving that it was used (see 2.2.2.5 Subjective Perceptions).

N₂O is non-flammable and non-explosive (Carrie *et al* 1982) however it can support combustion "even in the absence of oxygen" (Bailenson 1972), only when environmental temperatures exceed 450°C;



This produces a "33% oxygen-rich mixture" (Hill *et al* 1983) thus "Vigorously accelerates combustion" (CIG 1991) (Eger 1985, Merck Index 1983). Thus it is a 'relatively' stable molecule as environmental temperatures rarely exceeded these levels. Nitrous oxide is non-explosive but all "inhalation anaesthetics are more flammable in nitrous oxide than in oxygen" (Bailenson 1972). The experimental room, in this current work, was in an office environment where air conditioning maintained even temperatures and no hazardous substances or materials were in close proximity to the working area (see 2.3 Armamentarium).

N₂O is a "low temperature hazard and should not be allowed to contact skin or clothing" (CIG, 1991) as it requires heat to convert from liquid to gaseous phase. Energy or heat is taken from the environment and the immediate vicinity, thus air or equipment in contact with the released gas should have a lowered temperature (Vaporisation heat (bp): 3.956 kcal/mole, Merck Index 1983). This also indicates that if a cylinder of N₂O has been recently utilised, the reducing valves are cool. This knowledge assists in detection of drug

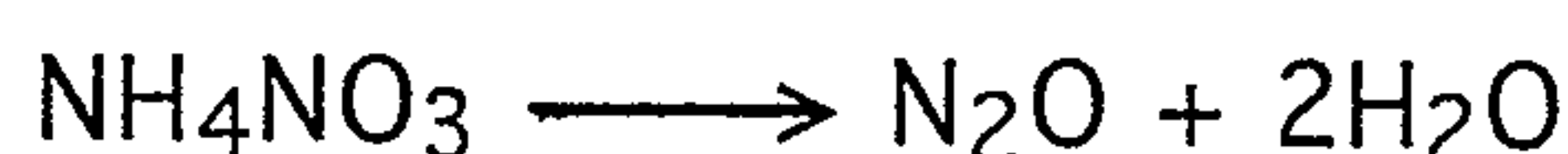
abuse by staff. In this experiment, the cylinders were securely attached to the portable anaesthetic machine.

1.3 Manufacture of Nitrous Oxide

Besides its physical qualities being regarded as safe for this experiment, the manufacture of the agent in sufficient quantities and purification standards needs to be addressed, in order to appreciate the method by which the experiment was conducted.

Nitrous oxide can be produced from automobile exhaust, the biological decomposition of fertilisers, and 'bacterial denitrification' of the soil and ocean (Eger 1985). Even though N₂O is naturally occurring in the atmosphere, it is unable to be extracted for commercial use as (i) retrieval is expensive, (ii) insignificant quantities would be extracted (Private communication with CIG engineers).

Nitrous Oxide is synthetically produced from "the thermal decomposition of ammonium nitrate", NH₄NO₃ (Mahan 1975). NH₄NO₃ is a colourless crystal, molecular weight; 80.04, melting point; 169.6°C, boiling point; 210°C and density; 1.725 (Weast *et al* 1982) which indicate that it is easily handled at room temperatures. The temperature required to decompose ammonium nitrate is 240-270°C (Carrie *et al* 1982, Hill *et al* 1983). The reaction is (The British Oxygen Co. Ltd. 1967, Mahan 1975, Hill *et al* 1983);



This is an exothermic reaction and produces 10.6 kcal of energy (The British Oxygen Co. Ltd. 1967), which is slowed by the addition of water (Private communication with CIG Engineers, Sydney). At temperatures above 290°C "decomposition becomes explosive....and higher percentages of nitric oxide, nitrogen dioxide, and nitrogen are formed" (Eger 1985).

Since N_2O is synthetically produced there are by-products and impurities. "Oxygen is produced physically and any impurities present were presumably in the air from which it was produced" (Burns 1980). Heated ammonium nitrate can form other compounds, as this reaction does occur over several steps: ammonia, nitric acid and the higher oxides of nitrogen, nitric oxide (NO), nitrogen dioxide (NO_2), oxygen and carbon dioxide may be present (Hill *et al* 1983, Merck Index 1983). The chief impurity is nitrogen (N_2) (Merck Index 1983). The actual amount of impurities produced is only 1% compared to "99 per cent yielding the desired nitrous oxide" if the operating temperatures are maintained (The British Oxygen Co. Ltd., 1967). If the operating temperature increases so does the percentage of yielded impurities. The sequence for the manufacture of the resultant gas is basically as follows:

- (1) Purification
- (2) Compression
- (3) Drying
- (4) Testing
- (5) Liquefaction
- (6) Storage

The stage of liquefaction is most important to this study. Liquefaction involves the freon cooling of the gas to 40°F (4.4°C) which "condenses all the water that remains except 60 ppm. Absorption by activated alumina removes the remainder of the water and any trace of lubricating oil as well" (Latimer 1967). Water content is less than 25 ppm for medical liquid supply, and less than 100 ppm for medical cylinder supply (CIG 1991). These levels of water content indicate that the gas is extremely dry. Humidification at the time of using N_2O on the patient may be necessary for prolonged procedures, e.g. as in general anaesthesia. In dentistry, N_2O is used in an unclosed system and normal air can be breathed via the oral cavity around the loose fitting nasal mask (Sher *et al* 1984). In this experiment, a full face mask was employed to prevent air

dilution and at the end of stage 3 (20% N₂O, see 2.1.2 Sequence of Testing), the subjects had moisture from their breath condensing within the mask.

An understanding of the manufacture, purification, percentages available and storage methods available can lead one to decide the best facilities and location in which to conduct this research. Due to its easy transportability, the anaesthetic machine and accompanying cylinders were taken into a quiet office environment.

1.4 Pharmacology of Nitrous Oxide

The pharmacokinetics of N₂O helps define why certain procedures were used in this work. In addition the pharmacodynamics are briefly discussed here but in relation to this work it shall be further discussed in Methods (see 2.1 Questionnaire).

1.4.1 Pharmacokinetics

Pharmacokinetics is the "action of drugs in the body over a period of time" (Dorland's Illustrated Medical Dictionary, 1985), i.e. the pathway of drugs in and through the body. It includes basically four processes; absorption, distribution, metabolism and elimination and these will be discussed in relation to nitrous oxide.

1.4.1.1 Absorption

Absorption is the process whereby a substance can cross from the environment or tissue plane into another tissue plane or cell. There are many possible routes of absorption into the body, e.g. parenteral injection, but being a gas, N₂O is rapidly absorbed into the blood vessels through the alveolus via the inhalation route. The introduction of an anaesthetic agent into the alveolus depends upon a number of factors; (i) Introduction factors; physical factors of the anaesthetic agent, amount/percentage of the anaesthetic agent, flow

rates, rebreathing/non-rebreathing anaesthetic circuit, (ii) Recipient factors; physical/medical status of the patient i.e. clear airway through to the alveolus and no alveolar abnormalities (Norris *et al* 1971), depressant drugs, ventilation rate, blood perfusion through the alveolus, and the conscious state of the recipient. Conscious individuals can maintain an airway and respond to commands (Berne *et al* 1988). This study used healthy subjects, only utilised N₂O and oxygen, and maintained subject consciousness throughout the experiment. Inhalation has "two distinct processes.... (1) establishment of an alveolar concentration of an anesthetic and (2) uptake by the blood and tissues of the agent" (Collins 1976).

The first stage, to establish an alveolar concentration, requires a simultaneous action of denitrogenation and introduction of the anaesthetic into the alveolus. Any nitrogen (N₂) in the alveoli decreases the partial pressure of the anaesthetic agent, thus decreasing the agent absorption into the blood. During denitrogenation, in a normal individual, the amount of "gaseous N₂ remaining in the lungs after the 10 minute washout....should be less than 2 per cent of lung gas, or 60 ml" (Severinghaus 1954). However, there is 700 to 1,200 mls of nitrogen dissolved in the tissues which "continues to be picked up by the blood and delivered to the alveoli over a 5- to 18-hour period" (Collins, 1976). "The rate and degree of denitrogenation is determined by two factors: (1) the degree of ventilation of the alveoli, and (2) the tension of nitrogen present in the inhaled atmosphere" (Hamilton *et al* 1955). The typical rates at which nitrous oxide can be introduced and denitrogenation occur, was described by Eger (1964) who interpreted the work and data of W.K. Hamilton and D.W. Eastwood (1955), by stating that the "rate at which normal ventilation introduces agent into the lung is extremely rapid. If this effect of ventilation were unopposed, the concentration of anaesthetic in the alveoli would rise from zero to 95 per cent of the inspired concentration within 2 minutes."

The second stage is the uptake of nitrous oxide. When a foreign substance is absorbed by blood, it is either bound by protein (usually

haemoglobin or serum albumin) or dissolved into the plasma. Nitrous oxide dissolves into the plasma. The rate that the gas is absorbed at is determined by its presence in the plasma and there are two limiting factors; diffusion and perfusion. When none or little gas is dissolved in the plasma this leads to a high rate of diffusion across the thin alveolar membrane thus it is "diffusion limited". Berne and co-workers (1988) succinctly describes the "perfusion-limited" rate of nitrous oxide uptake across the alveolar membrane and into the blood;

"When nitrous oxide moves across the alveolar wall, it dissolves in the blood, but it does not combine with any substance in the blood. As a result, the partial pressure of nitrous oxide in the blood increases rapidly. Hence, by the time the red cell is only one tenth of the way along the capillary, the partial pressure of nitrous oxide on both sides of the membrane are the same, preventing further gas transfer. Continued transfer of nitrous oxide can occur only if new blood is supplied. Thus the amount of nitrous oxide taken up by the blood depends almost entirely on the rate of perfusion."

Severinghaus (1954) predicts: "by volume, 30 times more N₂O than N₂ will dissolve in the body at the same concentration", when inspiring 80% N₂O to produce equivalent gas tensions as N₂ (Saidman *et al* 1965, Casey *et al* 1982, Patterson *et al* 1976). This implies that N₂O can transfer across cell membranes or tissues more rapidly than N₂, e.g. the brain (a highly vascular organ) reaches arterial levels of concentration at the same times as the arterial levels (Parbrook 1967). He calculated from his work that the "average rate of uptake of N₂O. was described approximately by the equation: Rate = 1,000 t^{-0.5} ml. per min.". Collins (1976) states from Severinghaus' work and others (Onchi 1958) that the rate decreases with time, and arterial saturation occurs in 3 stages; firstly the time to reach 50% saturation is 5 minutes, the time to reach 90% saturation is 30 to 90 minutes, and lastly the time to reach full saturation including tissue saturation is 5 hours. Parbrook 1967 states that 90% arterial saturation by nitrous oxide only takes 10 minutes, then a second slow uptake occurs to reach inspired levels. Bailenson (1972) states that

saturation in the vessel rich groups "is nearly complete before 15 minutes have elapsed." This is significant as the method by which this research was undertaken involves the employment of 10 minutes (minimum) of nitrous oxide administration before experimentation at each stage commenced.

1.4.1.2 Distribution

The distribution of N₂O involves the movement of N₂O with the plasma throughout the body. Therefore, the influence of N₂O on the tissues is dependent on three factors and these factors do have interplay;

- (1) Peripheral factors; the blood perfusion pathways through the tissues.
- (2) Cardiovascular factors.
- (3) Tissue factors; the response of the tissues to nitrous oxide (i.e. N₂O affecting the cell)

Peripheral factors involves the perfusion by blood into the various tissues. "Tissue perfusion depends on arterial pressure and local vascular resistance, and arterial pressure in turn depends on cardiac output and total peripheral resistance" (Berne *et al* 1988). Firstly, tissues have individual anatomical perfusion qualities (Collins 1976, Eger 1964), e.g. there is a low blood flow to bone, tendons etc. (vessel poor group, VPG) compared to the next group which is fat (fat group, FG), then muscle (muscle group, MG) and the highest anatomically perfused group is the vessel rich group (VRG), e.g. brain, heart, kidney, liver. The second factor influencing distribution, cardiovascular factors, can alter the pressure and amount of the blood flowing through the tissues, e.g. exercise decreases blood flow to the stomach but increases it to the muscles. The subjects were physiologically assessed as to their blood pressures, heart rates, oxygen saturations and consciousness to determine safety for the individual. In the individual undergoing N₂O sedation or general anaesthesia, the recipient is in a quiet state, i.e.

not actively moving, either supine or upright in a chair. In this study, subjects were in the same 'quiet' state.

In summary, N₂O distributes throughout the whole body, wherever the circulatory system infiltrates and can disperse into various tissues. "Saturation of the blood and brain occurs within 3 to 5 minutes" (Pallasch 1980). "The 'depth' of anaesthesia depends on the degree of saturation of the brain. Using nitrous oxide with oxygen as the sole agent, complete saturation takes about 15 minutes in an adult" (Vaughan 1969). Once the VRG of tissues are fully saturated, then the other groups become saturated in order; MG, FG, lastly VPG. Thus the method that was used in this study was to wait at least ten minutes, after the desired expired concentrations of N₂O were achieved, to start testing. The first tests were always physiological, e.g. blood pressure, etc. This gave time for the full 15 minutes to lapse for brain saturation.

The "factors which control the diffusion of the drug into the cells themselves are not well understood" (Norris *et al* 1971). This statement was made in relation to anaesthetic gases in general, but it can be stated as true for nitrous oxide.

1.4.1.3 Metabolism

A long held belief is that N₂O "appears" not to be metabolised in the body as it is excreted unchanged. Collins (1976) states that; "No chemical reactions are known to occur in the body." Hong and co-workers (1980) cited a reference "that nitrous oxide was not metabolised by the liver" (Sawyer *et al* 1977). However, research seems to indicate that there is some metabolic effect on the N₂O in the body. Hong and co-workers (1980) cited in its introductory paragraph, that N₂O can be reduced by bacteria which reside in the gut lumen, producing nitrogen and free radicals via the reduction pathway (Hong *et al* 1980).

N₂O may also be an intermediary agent itself, in the metabolism of nitrites and nitric oxide to N₂ (Eger 1985). Another metabolic site is the liver. Cytochrome P450 may metabolise N₂O, yet only 0.03

(± 0.05)% is removed from the liver's blood flow (Eger 1985). It is conclusive that N_2O is metabolised, even though a great percentage is expired unchanged.

Thus metabolism of N_2O was not of concern to this study other than it can be seen that N_2O does diffuse into gaseous spaces.

1.4.1.4 Elimination

Most of the N_2O appears to be expired unchanged via the lungs with minute amounts diffusing through the skin (unless it is metabolised) (Eger 1985). Since the uptake of N_2O during administration is perfusion-limited, then its perfusion into the blood is determined by its concentration in the alveolus and in the blood. The same occurs in elimination. If one side of the alveolar/cell membrane or interstitial fluid has high levels of N_2O , these molecules will move and equilibrate across that barrier, moving from high to low concentrated areas. Since blood is constantly moving, new segments of passing blood will have differing concentrations of N_2O thus molecular movement occurs till equilibration. In the elimination of N_2O , once the administration of N_2O has ceased, the direction of flow of the N_2O occurs from high to low concentration areas, from the cells, to the blood, to alveolus and to the environment. The rate of elimination is different to absorption by time length of administration of the gas.

Recovery from N_2O inhalation is rapid when compared to other inhalation and intravenous anaesthetic agents (Eger 1985). The low blood solubility of N_2O assists in its quick movement from one compartment to another, whether it is absorption or elimination (Eger 1985).

Diffusion hypoxia is a phenomenon occurring when N_2O is eliminated from the body without supplementation of oxygen, resulting in a low haemoglobin oxygen saturation level (SaO_2) (Fink 1955, Frumin *et al* 1969). This occurs due to the difference of solubility of N_2O and other gases. The solubility of N_2O is greater than that of N_2 , thus N_2O leaves the blood and enters the alveolus in

greater quantities than N₂ can enter the blood stream. Thus there is a dilution of present alveolar gases. The partial pressures of N₂, oxygen and carbon dioxide decrease in the alveolus and less exchange of these gases occurs with the blood, thus (Young *et al* 1988);

- (1) Hypoxia (a reduction in the oxygen saturation of haemoglobin (fall in SaO₂)) occurs resulting in "headaches, vomiting". [Note that anoxia (no oxygen) does not occur.]
- (2) Dilution of carbon dioxide decreases the respiratory drive.
- (3) N₂ insolubility and increase in alveolar nitrous oxide result in increase in alveolar size, thus "expansion of the lung."

This phenomenon does not occur to any significant adverse degree. Milles *et al* (1991) studied supplementation with oxygen/air after N₂O administration and discovered that (1) with 100% oxygen, the average SaO₂ had risen by 1.9% (2) with air SaO₂ had decreased by 1.2%. Milles *et al* (1991) concluded; "Although a significant decrease in SaO₂ occurred in subjects who received room air only during the recovery period, this decrease did not cause a significant change in vital signs or increase the incidence of unpleasant experiences in the post administration period." Hill *et al* (1983) states that after N₂O administration, the gas is cleared from the lung in "5 minutes of breathing normal air" and no clinically significant effect of hypoxia was mentioned by the researchers. Spiro (1972) states that a long N₂O administration period may influence the extent of diffusion hypoxia period. In this experiment, the administration of N₂O was continuous over 1-2 hours and the results show negligible ill effects on this group of healthy individuals.

In conclusion, the pharmacokinetics of N₂O have been discussed which has a significant bearing on this research and determines varying aspects of the method that was chosen.

1.4.2 Pharmacodynamics

Pharmacodynamics can be defined as "the study of the biochemical and physiological effects of drugs and the mechanisms of

their actions, including the correlation of actions and effects of drugs with their particular chemical structure; also, such effects on the actions of a particular drug or drugs" (Morland's Illustrated Dictionary, 1985). The 'simple' definition of pharmacodynamics is the effect a drug has on the body. Only the factors pertinent to this study will be discussed, such as the psychological and more noticeable effects detected by the conscious individual.

Any drug has many effects on the body, however each is to a differing extent and the major influence on the body defines the role/employment for that agent. Kaufman *et al* (1990) states that "the inhalation of the N₂O-containing mixture produced specific and well defined sensations or certain changes in sensations".

In relation to the dental/medical area, its major role is to influence the psychological aspect of the individual, however it does have influence in other areas. The two aspects to be discerned is the (a) psychological aspect and the (b) physical aspect of nitrous oxide's impact.

1.4.2.1 Psychological Impact

From a dental viewpoint, the main reason for the use of nitrous oxide is its psychological impact. Nitrous oxide has the ability to sedate the patient which is one adjunct to pain control, thus helping in the overall treatment of the patient. Bennett (1984) states that the five pathways to pain control are;

- (1) removed the noxious agent e.g. retract the hand from the flame
- (2) block the pain pathway e.g. local anaesthesia
- (3) increase the pain threshold e.g. nitrous oxide, narcotics, analgesics
- (4) cortical depression e.g. general anaesthesia
- (5) psychosomatic methods e.g. hypnosis, or simply gain patient's confidence.

Hill *et al* (1983) stated the effect that nitrous oxide has on the patient is threefold; (a) sedative (b) analgesic (c) "a degree of anterograde amnesia." The possibility of 'amnesia' in relation to hearing is one aspect that is examined in this study.

But what does the individual perceive under nitrous oxide sedation? Patients define their experiences as a wave of relaxation, dulled perceptions, "butterflies" in their stomach disappear, heavy limbs and tingling sensations in their limbs, like the effect of drinking a 'can of beer'. Not all experience these sensations all the time and in such definite amounts. The other sensations are a lack of control and suffocation. The result is to use the noun "euphoria" to describe the individual's experience of nitrous oxide (Hill *et al* 1983, Meyers *et al* 1976).

The response to nitrous oxide is many and varied. Children seem to respond well to the effects of nitrous oxide. They require smaller amounts to produce an effect as their respiration and heart rates are high with a relatively small blood volume which aids in a quicker introduction, absorption and rapid distribution (Drake-Lee *et al* 1983). There is a wide range of experiences which are not all experienced by each individual, also the effects are not generally perceived to be as strong as in the child, and each time that nitrous oxide is administered is different to the previous one due to their current psychological attitude and pre-conceived ideas. Thus the psychological effect can be broadly defined as euphoria, however each patient is different and each patient's experience will be different to the previous ones (Hill *et al* 1983).

This study asked the volunteers questions on various aspects of their body sensations to identify if any had changed during N₂O inhalation. This was used to confirm that N₂O was being supplied to the subject and that they were breathing it (see 2.2 Assessments).

1.4.2.2 Physical Impact

Most studies into nitrous oxide's physiological effects are discovered during surgical anaesthetic procedure or animal studies. This study was designed to use healthy volunteers and only N₂O and oxygen with no extra influencing drugs nor agents.

N₂O does have varied influences on human physiology and the specific impact will be discussed in Methods, as discussion can be related to the specific questions asked of the subjects.

A generalised view of nitrous oxide's impact has been described by various authors, Parbrook 1967 and Langa 1976. Hunter and co-workers (1983), describes some psychological and physiological alterations experienced by the subject/patient while under various levels of N₂O:O₂ sedation and Plane 1 (5 - 25% N₂O) and 2 (20 - 55% N₂O) are most significant to this research (Plane 3 is a deep sedative level, with higher N₂O concentration and need not be discussed as N₂O study did not utilise those concentrations). Hunter and co-workers (1983) stated that not all the following sensations will be experienced by the subject/patient in Plane 1:

"The patient may feel tingling in the fingers, toes, cheeks, tongue, back, head or chest. There is usually a marked sense of relaxation, and an elevation of the pain threshold and a diminution of fear and/or anxiety. The patient is obviously relaxed and responds clearly and sensibly to questions or commands.

"Other senses such as touch, hearing, vision, and proprioception are impaired in addition to pain sensation."

The more significant features of Plane 2 N₂O sedation, in relation to this thesis, are:

"As the patient enters this plane psychological symptoms described as dissociation or detachment from the environment may be experienced. Sometimes this dissociation is minimal, at other times it is profound. The dissociation may also take the form of euphoria similar to alcoholic intoxication. The patient may feel suffused by a warm wave, slight humming or buzzing in the ears, or a drowsiness or light headedness sometimes described by the patients as a 'floaty' or 'woosy' feeling."

Other signs or symptoms that can be found in the subject whilst under N₂O:O₂ inhalation are "paraesthesia or tingling sensation Indifference to surroundings or passage of time Pulse rate, blood pressure, respiration, skin colour, pupils are all normal verbal

contact is maintained but the reply may be sluggish" (Hunter *et al* 1983).

As stated in the Psychological Impact section above, the effect of N₂O is slightly unpredictable in humans. Generalisations can be made such as the reaction times increase significantly, short-term memory performance decreases, tinnitus, nausea, paraesthesia, and disorientation also occur at various N₂O levels (Eger 1985).

In cerebral tissues, N₂O does have an influence on the physical parameters, by increasing metabolism and blood flow, resulting in increases in intracranial pressures and oxygen consumption (Eger 1985). The EEG have changes in voltages and frequencies resulting in (Eger 1985):

- (i) subanaesthetic levels (e.g. 30%) produce increases in frequency (activity) and decreases in voltage
- (ii) higher concentrations (50-70%) produced higher voltages
- (iii) and at higher pressures (1.0-1.7 atm) frequency decreases and voltage increases.

The changes in frequency and voltage indicates that N₂O does produce a more 'aroused' state in (i) and a 'sleep' like influence in (iii) (Berne *et al* 1988). There is some evidence that N₂O does produce or affect convulsions shortly after N₂O administration has ceased (Langa 1976, Eger 1985). There were no such occurrences in this study.

What is important to note is that consciousness (thus judgement) is affected even at 30% N₂O, thus this study maintained levels below 30% to obtain optimal subject cooperation and judgement to determine any N₂O influences on hearing.

1.5 Physiological Qualities of Nitrous Oxide

The physiological qualities of nitrous oxide are:

- (a) Non allergenic (Bailenson 1972).
- (b) Non irritating to respiratory mucosa (Bailenson 1972).

(c) Anti-gagging. With "light levels of nitrous oxide analgesia virtually eliminate gagging on intraoral x-ray films in all cases and in all areas of the mouth." (Bailenson 1972).

(d) Euphoric (Hill *et al* 1983, Meyers *et al* 1976). Thus nitrous oxide is coined 'laughing gas'. Merck Index (1983) states that it is a "Narcotic in high concns" (concentrations).

(f) Analgesic (Langa 1976, Carrie *et al* 1982)

(g) Non toxic (Bailenson 1972). "Nitrous Oxide is generally regarded as non-toxic, but there have been occasional reports of reversible agranulocytosis after prolonged administration of the gas in intensive care."

(h) Asphyxiant (Bailenson 1972).

(i) Increases in air spaces in volume or pressure.

(j) Weak but a "true" anaesthetic and excellent carrier vehicle (Hill *et al* 1983, Carrie *et al* 1982, Bailenson 1972).

(k) Stable, relatively inert and doesn't react with other drugs (Bailenson 1972).

(l) Rapid effect and elimination (Bailenson 1972).

(m) Not biotransformed and does not combine with haemoglobin (Bailenson 1972).

(n) Not a totally predictable effect on the psyche of the patient (Hill *et al* 1983).

(o) Mild central nervous system depression (Bailenson 1972).

(p) Popular, convenient and portable (Carrie *et al* 1982).

1.6 Medical Utilisation of Nitrous Oxide

A chemical such as N_2O has many favourable physical and physiological features that are compatible with life. Its potential and current use make it a profitable venture for the manufacturer. The areas where nitrous oxide is employed are simply divided into industrial and medical areas. This research applies mainly to its application in the medical areas thus identifying its industrial use is not necessary in this thesis other than shows the diversity of N_2O usage:

(a) Chemical reactions. Merck (1983) states that nitrous oxide is employed to "oxidize organic compds" (compounds) "at temps" (temperatures) "above 300o" and used "to make nitrites from alkali metals at their boiling points".

(b) Combustion qualities. At high temperatures N_2O can support combustion, thus can be an engine fuel "for automotive purposes" (CIG 1991), and "in rocket fuel formulations (with carbon disulfide)" (Merck 1983). N_2O is also used in atomic absorption spectrophotometers (CIG 1991).

(c) Food additive. Merck (1983) states that it is employed in the manufacture of "whipped cream" as "under pressure it dissolves in the cream, and when the pressure is released it fills the cream with many small bubbles, simulating ordinary whipped cream" (Pauling 1959).

The general public are highly aware of the existence of 'laughing gas'. The expectations of its effect on the individual are many and varied. In "the earliest days the amnesic and analgesic properties of the gas have been well known, but little was done to exploit these properties. The earliest use of nitrous oxide invariably relied upon a degree of anoxia to achieve anaesthesia" (Hill *et al* 1983) but time and experience has redefined its subtle qualities thus influencing its use in the medical realm. There are two main areas in which nitrous oxide is employed;

1.6.1 Individual pharmacological impact

Nitrous oxide is employed as a sedative (Hill *et al* 1983, Bell 1975, Spiro 1981), an anxiolytic agent (Henry *et al* 1989), an analgesic (Heft *et al* 1984, Hill *et al* 1983, Bailenson 1972, Bell 1975, Henry *et al* 1989, Carrie *et al* 1982), and to induce amnesia and hypnosis (Hill *et al* 1983).

1.6.2 Specific areas

(i) The use of nitrous in dentistry has long been recognised (CIG 1991, Hill *et al* 1983; Bell 1975, Spiro 1981, Heft *et al* 1984, Henry *et al* 1989) The term employed by the dental profession when nitrous oxide is given to a patient is relative analgesia or RA. Relative analgesia is not an accurate term to describe its function in dentistry. Council on Dental Therapeutics (1972) states that the analgesic component of nitrous oxide is not totally effective in abating pain, as local anaesthesia is also employed and Council on Dental Therapeutics (1972) continues stating the "term sedation or

psychosedation is a far more accurate description than the term analgesia". However this point of view will not alter what has been accepted and entrenched in the dental vocabulary.

(ii) The areas in medicine where nitrous oxide is employed:

(ii-i) Anaesthesia as a base anaesthetic (CIG 1991, Heft *et al* 1984, Hill *et al* 1983, Spiro (ed) 1981, Bailenson 1972) also to assist in venipuncture (Langa 1976).

(ii-ii) Encephalography uses nitrous oxide rather than air in "contrast gas" studies of the cranial ventricles as it disperses rapidly and post-examination headaches are less compared to air. (Sonnenschein *et al* 1948, Stark 1980)

(ii-iii) Cardiology employs nitrous oxide sedation as an analgesic while oxygen is supplied to decrease the stress on the heart during a myocardial infarct/angina attack. (Heft *et al* 1984)

(ii-iv) Obstetric use has been well recognised by the general population and its popularity in this area is superseded by dentistry.

(ii-v) Cryosurgery employs nitrous oxide as a freezing agent (CIG 1991).

Thus implications for testing the effect of N₂O on hearing can affect the any of these areas of medicine and dentistry.

The physical and chemical aspects of N₂O have been discussed to enhance understanding of the pharmacological aspects of N₂O which helps explain the methods that were chosen in this thesis.

1.7 Summary of Work

This work looked at the effects of nitrous oxide (N₂O) on hearing as there is a belief that N₂O increases hearing acuity. Increased hearing acuity could be defined as improved ability to hear lower intensity sounds (quieter sounds) better (louder).

Some studies have noted hearing changes whilst under the influence of various levels of N₂O and have tried to define them, with conclusions stating that hearing becomes more acute (Langa 1976), acuity decreases (Westerlund *et al* 1961) or no hearing changes can be detected (Tomlin *et al* 1973).

Given that there are inconsistencies in the literature, this work aimed to determine if hearing was altered by 10% and 20% N₂O in a quantitative and qualitative manner. This can be considered of

scientific interest and have implications for care of the patient with possible medico-legal implications.

2. Methods

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2.1 Subjects and Sequence of Testing

2.1.1 Subjects

Seventeen subjects volunteered of which one did not complete the experiment. The 16 subjects who completed the whole experiment were volunteers from the University of Sydney Dentistry course (n=10) or were postgraduate science personnel working in the private sector (n=6). Volunteers were not asked about their ethnicity but principally came from various Asian and European races, typical of the Australian community. Subjects were healthy, had no previous nitrous oxide experience, no known current nor long-term hearing, ear, respiratory, neurological problems, and were able to answer questions intelligently and decisively. The subjects had no physiological or physical contraindications to the use of N₂O (e.g blocked oro-nasal passages, psychological problems).

Subjects did not receive any instructions prior to the experiment, e.g. fasting.. Subjects were given a brief outline of the procedure just prior to the experiment. There was no discussion about the possible effects of N₂O which could influence the results. Subjects could halt the procedure at any time which had occurred in other experiments; Fenwick and co-workers (1979) experiment where a female became frightened at the initial high N₂O concentration, and McMenemin and co-workers (1988) had one person "experienced slight nausea". Subjects were given opportunity to ask questions at the start of the experiment and written informed consent was obtained.

Nitrous oxide was administered through a full face mask which was firmly held against the face by the subject, thus allowing easy removal of the mask should any volunteer want to discontinue the experimental procedure.

All subjects gave written informed consent and all experimental procedures were approved by the Ethics Committee at St. George Hospital, Kogarah, N.S.W., Australia.

2.1.2 Sequence of Testing

Assessments of hearing sensation and physiology were conducted under each of four breathing gas conditions (see: Methods 2.2 Assessments):

- (1) Air (a)
- (2) 10% N₂O : 90% O₂
- (3) 20% N₂O : 80% O₂
- (4) Air (b)

These N₂O levels were chosen so that subjects would be fully aware of instructions and able to respond effectively and also minimal side effects should occur: that is in Plane 1 of N₂O:O₂ sedation (Bell 1975, Barber *et al* 1972, Fenwick *et al* 1979, Haughton 1980, Parbrook 1967, Sonnenschein *et al* 1948). In the dental surgery patients may breathe these levels of 10% and 20% N₂O as leaking nosepieces or mouth breathing can lower the inspired concentrations that the dentist has set, and even without direct administration of N₂O there may be waste gases in the operatory (Badger *et al* 1982).

Nitrous oxide is a mild central nervous system (CNS) depressant (Bailenson 1972) and some studies have shown that there was no loss of consciousness during administration of 25%-50% N₂O (Treiger *et al* 1971; Chapman *et al* 1943), yet others have shown that 30% N₂O can possibly result in loss of consciousness in some people (Bell 1975). Therefore, a maximum of 20% N₂O was employed in this study and this also ensured adequate oxygenation. Further evidence that this level is an appropriate maximum comes from Eger (1985) who states that "Reaction times on a choice-decision test do not increase significantly until 10 to 20% nitrous oxide is breathed. Short-term memory performance decreases with 30% nitrous oxide. Tinnitus, nausea, paresthesias, and disorientation also occur at 20 and 30% nitrous oxide." As with general anaesthesia, there are "planes" of N₂O:O₂ sedation (Hill *et al* 1983), and questions were asked to determine if the subjects were in Plane 1 which is considered to occur at levels of 5% to 25% N₂O (95% to 75% O₂) (Hunter *et al* 1983;

Parbrook 1967) (see Methods 2.1.2 Questionnaire 2, and 2.2.5 Subjective Perceptions).

Subjects ventilated spontaneously and there was no intermittent positive pressure ventilation, which ensured that there was no artificial forcing of the breathing medium through the eustachian tube into the middle acoustic meatus (Casey *et al* 1982; Drake-Lee *et al* 1983). The forcing or dissipating of gases through the eustachian tube can artificially influence the effect of N₂O's physiological diffusion into the middle ear, thus altering middle ear pressure (MEP), which in turn create bigger changes in MEP and could influence hearing.

Baillie and co-workers (1988) writes in a letter to the editor, that increased middle ear pressure could persist post-operatively. In this thesis, time was given to allow the N₂O to dissipate from the middle ear.

Recovery occurs quickly after cessation of N₂O administration. Hunter and co-workers (1983) reported that following continuous administration of N₂O for over 2 hours 90% of the N₂O is eliminated within 15 minutes, and this is consistent with the quick recovery of the subjects. Milles and co-workers (1991) stated that, after healthy subjects breathed 40% N₂O for 15 minutes and then room air in the recovery phase, diffusion hypoxia did occur during the recovery phase, however the resulting reduced oxygen saturation "did not cause a significant change in vital signs or increase the incidence of unpleasant experiences".

For convenience, room air was employed instead of 100% oxygen (O₂) in the control stages (Air (a) and Air (b)) (Dripps *et al* 1982, Herwig *et al* 1984, Hill *et al* 1991). Westerlund and co-workers (1961) demonstrated that there was no difference in auditory threshold responses between breathing room air or 100% O₂ thus this gives an assurance that the room air can be adequately utilised instead of O₂. Bruce and co-workers (1974) do not report the use of O₂ after N₂O administration in the experimental sequence and failed to state if complications had occurred, thus indicating that the use of

room air instead of O₂ can be considered safe for experimental procedures. Hempenstall and co-workers (1990) recommends routine use of O₂ after general anaesthesia and for oral surgical procedures to prevent diffusion hypoxia by noticing significant differences in the blood oxygen saturation between pre- to post-operative levels, but failed to report on any clinical significance. Milles and co-workers (1991) report that even though there is a statistically significant decrease in saturation levels when room air is used instead of O₂ during recovery phase, there are no clinically significant effects in healthy young patients. Thus the data obtained during both control stages allowed an assessment of any time-dependent effects such as changes in volunteer reporting, or effects of delayed recovery from MEP changes intra-N₂O inhalation.

When the breathing medium was altered between the stages, assessments of physiology and hearing status did not commence until a period of at least ten minutes lapsed after end-tidal concentrations of 10% or 20% N₂O were achieved (see 2.2.4 End-tidal N₂O Concentration) to allow for "gas equilibration at each concentration" (Houston *et al* 1988) and for maximum effect of N₂O. Treiger and co-workers (1971) states that the influence of N₂O on coordination and psychomotor function changes are "time and dose related, appearing within the first minute and reaching a peak within five minutes. Complete recovery occurs within three to five minutes after cessation of N₂O." Bourne (1960) quotes from other studies that the time needed for N₂O to produce its "maximum effect" is in the range of seven to fifteen minutes and continues to state that in his study ten minutes minimum was sufficient. Thus this ten minute pause gives sufficient time for N₂O to be 50-90% arterially saturated which is sufficient time for any N₂O effect to be noticed (Parbrook 1967; Collins 1976; Bailenson 1972).

All testing was done in one session in the late afternoon. If more than one session had been needed to collect data, then this could create many influences on the volunteer, which could alter the results:

- (1) The time in the day the test was done (emotional or physical status could change during the day and between the days, should testing be done on different days or times).
- (2) The length of the hair which might influence earphone placement if testing was done on different days (Glorig 1965).
- (3) It is unknown if possible tolerance to N₂O could develop between different testing times or days. Avramov and co-workers (1990) reports on acute short term tolerance by comparing EEG readings on patients undergoing abdominal surgery with 65% N₂O (plus other anaesthetic agents were involved). This present thesis utilises 10% and 20% N₂O and it is unknown whether these levels create acute tolerance.
- (4) Not to give opportunity for discussion to occur between the subjects, which may influence the results.
- (5) Subjects found it more convenient to do all testing in one session.

2.2 Assessments

In total, 25 assessments of hearing sensation and physiological status, and 2 questionnaires were given to each subject. All tests were designed for convenience in application, and ease in recording and volunteer answering. Each will be discussed.

2.2.1 Questionnaires

Questionnaire 1 was completed in Air (a) prior to all other assessments, while Questionnaire 2 was completed in Air (b) after all other assessments were completed.

2.2.1.1 Questionnaire 1 (see Appendix 6.1)

The questionnaire defined past and current medical status (including any ear or respiratory disturbances). A recent history of food and drink consumption could result in nausea during N₂O

inhalation and thus influence the results. Kaufman and co-workers (1990) asked subjects "to refrain from eating about 5 hours prior to their experiment" as air may be incorporated into the food and descend to the stomach which acts as an air pocket and as N₂O diffuses into air cavities in the body (Munson 1974) this could influence the subject's status. Alternatively, fasting could influence body sensations and possibly eliminate any diabetic from the experiment, thus in this experiment no food or drink demands were made on the subjects. It was found that there were no cases of nausea thus no need to comment on this further.

2.2.1.2 Questionnaire 2 (see Appendix 6.2)

This questionnaire was designed to determine whether N₂O had other effects not tested by the assessments of hearing sensations, e.g. influences on the subjective perception of time, hearing extraneous noises, concentration ability etc.. Kaufman and co-workers (1990) states that in their pilot study, there are "taste, smell and thermal" sensory changes while under 35% N₂O. They also reported "changes in auditory and visual acuity".

This questionnaire was asked at the completion of all other assessments so that the statements would not influence any of the prior assessments, e.g. should a subject have prior knowledge that time could be affected, or extraneous noises heard, then the subject would pay special attention to time passing or extraneous noises and not on the task at hand.

By simply asking these questions to the subject, draws the subject's attention to the fact of that medium, which is being questioned, has altered in some way e.g. Block and co-workers (1990) questioned subject's perception of time and this causes the volunteer to suspect that time had been altered. Also Block and co-workers used the term "faster" and did not give the volunteer the term "slower" thus indicating to the volunteer the direction in which time is meant to have changed. Thus all questions in this present thesis were designed open ended or had a choice of 'opposites' to allow the

subject more latitude in answering and to express any new sensations that have not been asked. Each will be discussed. Questions are presented are in italics.

Did you find concentration on the task easy/difficult?

This question was asked to determine if any assessments were too easy or difficult, and if N₂O affects the subject's concentration. It was open-ended to allow any comments about any aspect of the experiment.

Did you hear any extraneous noises? Y/N What where they?

Westerlund *et al* (1961) reported on the possibility of auditory "hallucinations". Subjects may possibly hear room/background noises being "distinct but distant" (Bennett 1984). If any aberrant noises were heard it could interfere with the hearing assessments and possibly disturb the subject's concentration, thus influence the accuracy of the assessments.

Do you remember any commands/statements given to you during the procedure? Y/N What was it?

Many statements were presented during the experiment and it is not expected that they would all be accurately recalled. An answer to this question determines two factors:

(i) If a particular statement(s) was more readily remembered and why was this so, i.e. was it a repetitive or inconsistent statement. A repetitive statement could mean that the subject was possibly annoyed at the repetition and indicated that they were conscious throughout the experiment. An inconsistent statement that was not part of the procedure could indicate that the subject was hallucinating.

(ii) This question forces the subject to quickly scan his memory of the previous couple of hours during the experiment, to confirm that the subject was not unconscious during the experiment.

Did the passage of time seem as quick/slow as you expected it to be?
Block and co-workers (1990) asked a similar time experience question, as mentioned earlier, but did not state whether their subjects felt that time was perceived as moving faster/slower while under N₂O. Robson and co-workers (1960) used 30-40% N₂O on humans, where human subjects tapped an electrical key pad every 15 seconds, and found that length of time estimations increased (even up to 40 seconds) under N₂O inhalation even though subjects subjectively thought that time had passed rapidly. This present thesis asks the subject for an analysis of time passage to confirm Robson and co-workers (1960) objective analysis, even though the N₂O levels are lighter than Robson and co-workers levels.

Did you feel like yawning/coughing during the procedure? Y/N When?
Did you feel as though you needed to "pop" your ears at any time? Y/N When?

During N₂O inhalation, N₂O diffuses into the middle ear and causes the middle ear pressure (MEP) to rise (Davis *et al* 1979, Matz *et al* 1967, Thomsen *et al* 1965). Yawning or coughing is an active venting process that causes the Eustachian tube to open and thus allow middle ear pressure to equilibrate with that in the oropharynx. If the venting process does not occur, then hearing may alter due to increases in MEP or "spontaneous rupture of the tympanic membrane" may occur (Waun *et al* 1967). Davis and co-workers (1979) state that passive venting occurred at 150-300 mm H₂O with their subjects breathing 67% N₂O. Eardrum rupture would not occur in this present work, as pressures would not reach this level and subjects are conscious and would automatically swallow with high pressures. This question determines if the subject is conscious of swallowing or yawning often, which may give indication to the fact that the MEP changes are noticeable to the subject. It was difficult to monitor such actions, as a black full face mask was employed.

Did you experience any thermal changes in parts of your body and head? Y/N If yes, was it; cold/heat sensations, and where? Could it have been the room?

Bennett (1984) states that at 35-40% N₂O, warmth is perceived, others state that lower levels can produce thermal changes. Discovering whether the subject can feel a "warm wave" is one sensation that indicates that the subject is in "plane 1" of N₂O sedation (Hunter et al 1983). Noting if the room was warm or not, rules out the possibility of influential environmental factors and confirms that the subject does feel thermal changes due to the inhalation of N₂O.

How you feel during the experiment?

This allowed opportunity for any further comments.

Would you do it again? Y/N

This question "sums up" the subject's whole experience of the procedure, and determines their desire to undergo N₂O:O₂ sedation again. (NB: Subjects were not financially reimbursed.)

Any further comments about your sensations under N₂O or the procedure would be appreciated;

This question gave opportunity for additional sensations or thoughts or views to be stated.

2.2.2 Physiological Functions

Physiological monitoring is essential for ethical considerations and to determine any possible physiological changes due to N₂O and which could possibly influence hearing sensation. There was continuous physiological monitoring however only one recording was taken in each stage, which was representative of the physiological status during that stage.

Physiological alterations under N₂O are reported to be either none or negligible or minor (Bailenson 1972; Fenwick *et al* 1979; Henry *et al* 1989; Hill *et al* 1983; Spiro 1981; Treiger *et al* 1971).

2.2.2.1 Blood Pressure (BP)

A sphygmomanometer was placed on the upper arm to record BP. The results from previous studies are conflicting as to whether N₂O has an effect on BP. For example, Collins (1976) wrote in his book that there were no changes in BP nor in heart "rate, rhythm or output", while Treiger and co-workers (1971) employed 25-70% N₂O and demonstrated that there were "small but significant changes in blood pressure" which were dose and time related (initial increases in BP, possibly due to "influence of the experimental setting" and "novelty of breathing through a nasal mask", followed by the BP returning to baseline possibly due to drug effects). Bailenson (1972) reports that BP is stable, but may decrease as the sedation progresses. Jatsak and co-workers (1991) summarised the current literature and concluded that there appears to be minimal effects from N₂O on the cardiovascular system yet the evidence was still conflicting. A more recent study (Craft *et al*, 1992) concluded that N₂O has systemic vascular "sympathomimetic" actions and is a "myocardial depressant".

In conclusion, whatever the effects of N₂O, it appears that the effects are observed at higher concentrations, which is above those employed in this study. Therefore, it is unlikely that any effects would be clinically detectable. Nonetheless, BP was monitored.

Recording of the physiological data of BP, heart rate, oxygen saturation and end-tidal N₂O concentration, was done on all subjects at various times, i.e. not all subjects had their physiological parameters written down for every stage even though the examiner continually monitored physiological status and recorded any changes from control levels in all subjects. Statistical analysis of these physiological data involved determining means and standard deviations for all data recorded (n=10 to 16, see Table 2.1 in Results).

Data was divided into age and gender groups (see Table 2.2 - 2.5 in Results). An ANOVA with repeated measures was also done on data from those subjects in which recordings were taken throughout all stages (n=9). Subjects who had no recordings for some stages were excluded from this analysis.

2.2.2.2 Heart Rate (HR)

Measurements were made by the pulse oximeter attached to the Datex monitor. Statistical analysis was the same as for 2.2.1 Blood Pressure. Treiger and co-workers (1971) states that there is a small decrease in HR while breathing 25-70% N₂O. Bailenson (1972) states there are "no changes in heart rate and cardiac output directly attributable to nitrous oxide."

2.2.2.3 Oxygen Saturation (SaO₂)

In Methods 1.2 Sequence of Testing is an explanation of using room air relative to using O₂ in the two control stages, Air (a and b). From this there may be some statistical significance.

Measurements were made by the pulse oximeter attached to the Datex monitor. The statistical analysis was for 2.2.1. N₂O inhalation does not affect end tidal carbon dioxide concentrations thus this was not measured (Fenwick *et al* 1979).

2.2.2.4 End-tidal N₂O Concentration

This was not recorded but the Datex machine monitored the end-tidal gaseous concentrations and adjustments could be made, when necessary by the examiner, to keep the concentrations of N₂O stable. The end-tidal N₂O level was never below 10% and 20% N₂O, in their respective stages, and maintained between 0.1% to 3% above those levels. An analysing gas line was connected between the anaesthetic tubing and the face mask, and was connected to the Datex monitor

(see 3.3 Gas levels and application). This data did not require any statistical analysis, but constant maintenance of levels.

2.2.2.5 Subjective Perceptions (see Appendix 6.3.1 and 6.3.2)

Collins (1976) and Parbrook (1967) state that the senses are depressed by N₂O as the concentration increases. The questions below were designed to provoke the subject into determining if any familiar smells, tastes, etc. were recognised. Eger (1985) reports that tinnitus, nausea, paraesthesia, and disorientation occur at 20% and 30% N₂O. The levels used in this work were at 10% and 20% N₂O which were used to prevent nausea and disorientation occurring, which could have impaired the subjects' judgements during testing.

In this present work, an assessment of subjective perceptions provided information on: (1) the subject's level of consciousness in their ability to answer the questions, (2) whether subjects could distinguish changes in the examiner's voice and (3) that N₂O was appropriately utilised, i.e. rather than another anaesthetic agent and that the concentration levels were correct. The latter assessments (Threshold Intensity, Intensity Matching and Subjective Intensity), were designed to determine whether N₂O had any effect on the hearing of pure tones, with using different frequency and loudness levels, as in the course of normal human conversation.

Subjects were given one sheet of paper (Appendix 6.3.1) with questions and no space for answers. The examiner wrote the answers on a separate sheet shielded from the subject's field of vision (Appendix 6.3.2).

The questions below (in italics) were given towards the end of each stage. A final retrospective question was included to allow for a non-pharmacological assessment of the subject's own view of their status during the influence of N₂O (Block *et al* 1990). Each question will be discussed.

Hearing; Did the examiner's voice seem.....?

The female, human voice was used as the "examiner's voice" for it is in the middle of the human speaking frequency range, that is between that of the male and a child (Malmberg 1968). The examiner was the same throughout the experiment. Subjects were asked their viewpoint of the examiner's voice as this experiment aims at determining possible hearing changes from a number of different aspects. Answers were purely subjective.

Hearing, under N₂O, apparently becomes "acute" (Langa 1976) however it is not known at what concentration this occurs nor is it more discriminating of different frequencies or intensities? To define "acute" by analytical methods is difficult, as "acuity" seems to have a subjective rather than an objective quality. This is the basic question of this thesis: to determine the nature of the influence of 10% and 20% N₂O on hearing, if any, and to discover how hearing is altered. The questions below were used to determine any subjective changes in hearing that the volunteers noticed.

distant / normal / closer

Bailenson (1972) state that sounds appear to alter during N₂O inhalation, to become distinct and distant, yet have an echoing quality, but does not state at which N₂O concentration for this alteration of hearing. Spiro (1972) reports that at 15% N₂O, and "for almost 30 to 45 seconds", sounds appear distant and distinct. Bennett (1984) reports that these alterations occur at higher N₂O levels: 35% to 40%. None of the authors describe what kind of sounds that these relate to, e.g. human voice or machinery.

distinct / normal / muffled

Writers described the hearing changes as becoming more "distinct". (Spiro 1972, Bailenson 1972, Bennett 1984)

echoing / normal / clear

As stated above, Bailenson (1972) describes sounds appearing as having a "certain echoing quality" whilst breathing an unknown concentration of N₂O.

high pitched / normal / low pitched

This question was used to describe any possible pitch or frequency changes detected by the subject.

humming / normal / ringing

There have been descriptions of a buzz, hum, ring detected while under N₂O inhalation (Bailenson 1972), and these extraneous sounds could occur at 15% N₂O (Spiro 1972) or at higher concentrations, 35-40% (Bennett 1984).

Thermal; cold / fine / hot / other

There have been reports of thermal changes with concentrations of 15% N₂O and more, which consist of an increase in "warmth" in parts of or the whole body (Bell 1975, Bennett 1984, Hoshiya 1989, Kaufman *et al* 1990, Spiro 1972). Collins (1976) states that capillary and venous dilation occurs and this may result in skin warming. Bailenson (1972) agrees that cutaneous venodilatation occurs under N₂O inhalation and this may effect temperature regulation, "but the total effect is not clinically significant because the central temperature-regulating centers are not affected."

Visual; blurred / normal / clear / colour changes

Vision is one of the five senses and may be affected by N₂O. Westerlund and co-workers (1961) states that some of their subjects, whilst under 15% to 60% N₂O inhalation, claimed "shrinking fields of vision and diminishing light perception". Bailenson (1972) agrees that whilst under N₂O inhalation (concentration is unknown), an effect of "lessened visual acuity" where bright lights appear very far away. Kaufman and co-workers (1990) reported that whilst his subjects were under 35% N₂O, no colour perception changes occurred yet blurred vision was statistically significant ($P < 0.001$). This question was also asked to discover if the subjects could see any visual changes. It also affirms that the various answer sheets could be read, and understood, by the subjects.

Smell; perfume / pungent / dusty / rubbery / none / other

Bailenson (1972) states that N₂O "possesses a characteristic, faintly sweet odor; but the patient will, most likely, be more aware of the rubbery odor of the anesthetic mask than that of the gas". Not all smell labels were used, but options were given, i.e. "other", if another smell could be sensed by the subjects, e.g. sweet, nutty.

Taste; sweet / salty / sour / bitter / other / none

Nitrous oxide is reported to have a sweet, even nutty, taste and odour (Collins 1976). Kaufman and co-workers (1990) states that the results of the 44 volunteers inhaling 35% N₂O, "sweet" was the commonest answer (58%), while "sour" (21%) and "salty" (10%) were next. With the low levels of N₂O in this study, it is unlikely that taste sensations would be reported.

Concentration; easy / normal / difficult

As with any anaesthetic agent, there are various CNS depressive effects. However, one would not expect concentration to be difficult under the relatively light levels of N₂O inhalation used in this study. Nonetheless, an attempt was made to ascertain whether mental concentration was effected (see 2.1.2 Sequence of Testing).

Body Sensations; How do you feel....?

In the study by Block *et al* (1990) a question similar to this was asked, however, they only used "euphoric" synonyms, e.g. happy/excited, and excluded any antonyms, e.g. sad/relaxed. As previously mentioned, this can lead to biased answering, where the subject is required to answer in a particular way, rather than having the option to answer the opposite. In this experiment, the following options were given:

excited / normal / relaxed

Anaesthetic agents tend to produce relaxation/sleep, and this is to be expected of N₂O. Parbrook (1967) quotes from various authors that relaxation and sedation begins in Zone 1 ("zone" should not be confused with Guedel's anaesthetic classification system of "planes"), which is between 6-25% N₂O. In this study, some of the subjects may feel "excited" due to the novelty of the event, but it is expected that most will be "normal" or "relaxed".

happy / normal / sad

Nitrous oxide has been described as "laughing gas" (The Pharmaceutical Codex 1979, Merck Index 1983) and Parbrook (1967) reports that laughing only occurs at "higher concentrations, e.g. 40 per cent". With the low levels used in this study, the "happy" adjective is unlikely to be chosen.

lightness / normal / heaviness

Bennett (1984) described that at 35-40% N₂O a subject has a "sensation of heaviness or feels as if he is floating" and Kaufman and co-workers (1990) reports similar findings with 35% N₂O. With the suspected "relaxation" that subjects could experience (from a previous question), one would expect that the body perception may be altered.

tremors / normal / stillness

Subjects were told that this related to any intrinsic movement of the limbs. Kaufman *et al* (1990) states that their subjects experienced some "tremor" in the muscles at 35% N₂O. Bailenson (1972) states that "skeletal muscle relaxation is poor" with N₂O. Thus with the levels used in this study, one could assume the subjects to answer: "normal". While "relaxation" could be a sense that subjects experience, whilst under N₂O inhalation, "stillness" could be a more common answer than "normal".

tingling / normal / paraesthesia

Bennett (1984) states that with 10-15% N₂O there is some numbness and tingling of extremities and with 35-40% N₂O numbness occurs in "hands, feet, thighs and the circumoral area". Spiro (1972) includes tingling sensations around the lips and the tip of the tongue. Barber

and co-workers (1979) states that paraesthesia can occur. Parbrook (1967) states that paraesthesia is a common side effect in Zone 2 (about 26% to 45% N₂O). Thus in this study, this could not be experienced by the subjects as N₂O concentration is low. However, due to the length of time that the experiment took place, and that subjects stayed in one position of the room, paraesthesia may be experienced in certain body parts, e.g. derriere.

Any comments? Yawning, coughing, burping?

This question was placed in this section to remind the examiner to watch for active venting of the middle ear cavity in the subject (see Methods 2.2.3.1 Middle Ear Pressure).

The answers given not only provide an additional assessment of the effects, if any, of N₂O, but also indicate that no toxicity nor deleterious effects occurred in the subjects during this study.

Analysis involved assessment of the proportion of subjects giving particular responses.

The whole thesis is aimed at determining any N₂O influences on hearing via, as much as possible, a consistent objective path, and any subjective analysis on human voices are recorded and briefly discussed, as this questionnaire has done. Any changes in the perception of the human voice, by the subject, under these levels of N₂O, could give indication as to the perception of patients undergoing light N₂O inhalation and the patient's ability to hear, understand and respond to commands.

2.2.3 Acoustic Impedance

Acoustic impedance measurements gives an indication of the physical status of the middle ear by using an audiometer to measure pressure changes in the external auditory canal and presenting a tone to the tympanic membrane (Yost *et al* 1977). Attached to the

audiometer is an ear cuff which is placed in the ear. This cuff needs a unbroken seal around it to create pressure fluctuations between -312 to 200 decaPascals (daPa) and presenting a tone of 226 Hertz (Hz) to the tympanic membrane. Pressure changes in the external auditory canal influence the stiffness of the eardrum, thus altering the tympanic membrane's response to the tone by the reflection of the tone (Micro Audiometrics Corp. booklet 1984-1990). Three assessments can be determined in this single step performance which can be used in this study: middle ear pressure, physical volume and compliance. An ANOVA (with repeated measures) was used on each of the three assessments, using Microsoft Excel 4.0 (1992), to determine any significance between the stages.

2.2.3.1 Middle Ear Pressure (MEP)

The MEP is the air or gas pressure in the middle ear cavity and is expressed in decaPascals (daPa). Davis and co-workers (1979) state that if there is a change in MEP relative to external pressures, this creates varying degrees of inflexibility in the tympanic membrane and alter the ability of the drum to perceive sound pressure. The MEP measurement is aimed to determine any significant pressure changes that occur during N₂O inhalation (Coe 1987, Davis *et al* 1979). Rasmussen (1967) used 50% N₂O and found that N₂O is present in the middle ear and maxillary sinus, which leads one to consider that N₂O does physically enter air cavities in the body (Aust. Dent. Assoc. Newsletter 1991). This alteration in the MEP could interfere with hearing. The application of positive airway pressures (PAP) can increase MEP by direct pressure through the Eustachian tube, yet tracheal intubation can also cause MEP to rise by the diffusion of N₂O into the middle ear (Patterson *et al* 1976, Ramírez-Camacho *et al* 1984, Thomsen *et al* 1965). This study does not use the PAP technique, but lets the subject breathe spontaneously. These changes in MEP can persist from intra- to post-operative stages (Bailie *et al* 1988).

Normally with any human individual, the MEP is the same as the atmospheric pressure, as the eustachian tube equilibrates the pressure between the middle ear and external areas (Denes *et al* 1973). The eustachian tube opens during yawning, swallowing, sneezing, coughing and nose blowing (Davis *et al* 1963). Davis and co-workers (1963) states that the eustachian tube also needs to work to change the air in the middle ear, as when there is an air bubble in the body, that bubble is dissolved by a gradual absorption of oxygen first then nitrogen, thus the same changes in the pressures in the middle ear can occur.

2.2.3.2 Physical Volume (PV)

Physical volume is the air or gas volume in the ear canal from the measuring cuff to the eardrum and is measured at 200 daPa (the tympanic membrane becomes stiff and rigid thus reflecting sound). This measurement, in millilitres (ml) cannot occur unless the cuff has sealed the canal. Normal adult values are up to 2.5 ml (young children are 0.4-0.8 ml). Perforated eardrums, even microscopic perforations, produce values over 3 mls in adults (Micro Audiometrics Corp. 1984-1990). This measurement was taken to determine if there were any damaged eardrums, or patent eustachian tubes, that could influence the results.

2.2.3.3 Compliance (Comp)

Compliance is the flexibility or mobility of the tympanic membrane to reflect to sound waves and is also measured in millilitres (ml). Compliance is associated with the elastic features of the tympanic membrane, oval and round windows (Waun *et al* 1967). Normal values are about 1.5 ml as compared with 3 ml for flaccid eardrums and conduction problems in the middle ear. Values greater than 3 ml are associated with a 50 dB hearing loss (Micro Audiometrics Corp. 1984-1990).

Ramírez-Camacho and co-workers (1984) state that with 60% N₂O, there is an increase in MEP associated with a decrease in Comp and increased resistance (resistance is associated with the "frictional resistance in the ossicular chain" (Waun *et al* 1967)). These changes, along with positive airway pressure (PAP), can produce a "conductive-type hearing loss of short duration" (Ramírez-Camacho *et al* 1984). Waun and co-workers (1967) compared patients undergoing anaesthesia with various levels of N₂O to those who did not receive N₂O, and found in patients undergoing N₂O inhalation that there was a decrease in Comp and an increase in resistance, while PAP didn't "alter resistance or compliance measurements". Only Comp needs to be measured, as resistance and Comp are closely associated. This study did not use PAP, as the subjects were conscious and spontaneously breathing. If any hearing changes do occur, whilst subjects are under N₂O, then the changes in hearing can also be associated with decreases in Comp due to the effects of N₂O in the middle ear.

2.2.4 Auditory Threshold

Auditory threshold is a test to assess the minimum threshold decibel (dB) level (i.e. "just audible" (Zwicker *et al* 1990)) of a particular or many frequencies, that can be perceived by the human ear. It is also the most objective test given, as subjects must state whether they can or can't hear a particular loudness level, not to subjectively interpret how loud a sound is, as in the Subjective Intensity test.

A standard audiometric assessment was made in each volunteer, and in each stage of the experiment. The assessment involved presenting each of the frequencies, 500 Hz, 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz and 8 kHz, and which were presented to each subject in descending order of loudness intensity, to determine as precisely as possible the auditory threshold (Malmberg 1968). Sounds were presented as 3 short bursts of tone over 1-2 seconds (to prevent

"fatiguing" with loud intensities (Beatty 1932)). Subjects indicated that they heard a sound by pushing a hand held button control connected to the audiometer. The device recorded the lowest loudness (dB) intensity for each frequency that the subject could detect. The audiometer tested around the threshold level in every frequency to determine that the level was reproducible. The audiometer did this by decreasing the loudness levels until the subject no longer responded to a particular level, then it would retest to the last two levels for accuracy in the subject's responding or do further tests. An example of this is the subject responding to 25 dB, 20 dB, 15 dB but not 10 dB, thus the audiometer retested 15 dB and 10 dB to determine that 15 dB was the threshold level of that frequency.

The term auditory threshold defines the quietest intensity level that the subject can hear, just before that sound is considered inaudible or the subject can define it from silence. Zwicker and co-workers (1990) states that for a single individual, the minimum threshold is highly reproducible at around ± 3 dB. Subjects were given instructions to be decisive and consistent in reporting a doubtful tone (Glorig 1965).

The human ear can perceive frequencies from about 20 Hz to 15 kHz (children can hear up to 20 kHz; Lieberman *et al* 1988, Malmberg 1968). "Sounds of frequencies below 500 Hz and above 8 kHz must be made more intense in order to be perceived" (Newby 1979). The human auditory system is most sensitive to 1 to 4 kHz (Malmberg 1968). Normal human speech is between 100 Hz to 7 kHz (Zwicker *et al* 1990), with Davis and co-workers (1963) stating that: "A particularly important part of the auditory area is the range of frequencies most important for the understanding of speech. This range extends from roughly 400 to 3000 cps. Speech contains frequencies both above 3000 cps and below 400 cps but they are not necessary for almost perfect intelligibility of everyday conversational speech." Thus the frequencies chosen are around the sensitive range and that used for conversational speech. To study if these frequencies are affected,

whilst a subject is breathing N₂O, gives insight into that which the patient can hear for treatment or medico-legal reasons.

The null hypothesis (H_0) is that N₂O has no effect on the human auditory threshold for each individual frequency. In this thesis, terminology of the form "4 kHz (10%)" refers to the mean minimal intensity level, in this case, 4 kHz, while the subject was inhaling 10% N₂O. Statistical analysis utilised two methods (see 4.0 Data Analysis):

(1) Statistical analysis was done on all data simultaneously, with repeated measures ANOVA (Program 5V) to determine if any relationship exists between the various factors, that were over 25 vs under 25 years age groups, left vs right ear sides, female vs male gender groups, and treatment changes (Air (a) vs 10% N₂O vs 20% N₂O vs Air (b)).

(2) Statview 512+ (1986) and Excel 4.0 (1992) was used for presenting tables of mean and standard deviations of the minimum threshold levels. This analysis also produced the comparison table, whereby an individual frequency's minimum threshold levels were compared between the stages and the resultant table is in the format of Appendix 6.4 which shows the results if H_0 is true (see 2.4 Data Analysis for explanation of symbols used). Further analysis was done to compare between the frequencies and between the stages.

2.2.5 Intensity Matching

Intensity matching determines the ability of the subject's auditory sense to remember the intensity of an initial reference sound, and the ability of that subject to detect, interpret and judge comparison sounds (Glorig 1965). This test chiefly looks at the memory and discriminating (judgement) capacity of the subject's auditory system and the null hypothesis (H_0) is that N₂O affects the auditory memory. This test was conducted because the senses are depressed by nitrous oxide inhalation, a stimulus needs to be more intense for that sense to be registered, by the subject, and memory

can also be affected, the ability to perform intellectual tasks and concentrate is altered (Bailenson 1972). Eger (1985) states that short-term memory performance is decreased during inhalation of 30% N₂O and in this thesis 20% N₂O was used as a maximum, so as not to have any adverse hearing effects due to lack of memory performance.

This experiment used a maximum level of 20% N₂O and an assessment was made as to whether auditory memory loss also occurs at these levels. The data should give some indication about a situation where, if instructions were given to a patient during a procedure involving N₂O inhalation, would they recognise and remember that statements were said to them, but this information will not necessarily give indication that those statements were comprehended. The null hypothesis (H₀) is that N₂O, at these levels, does not influence hearing memory.

To determine the ability of a subject to remember the intensity of a sound at a defined frequency, the same frequency of sound was presented to each subject, at a number of different intensities. Continuous sounds with varying intensities appears to be an easier way to perceive intensity changes, however the method of discrete sounds is the most objective method to determine hearing memory and acuity (Glorig 1965). Spoken human language is presented in discrete bursts of words, thus testing was done using discrete sounds and allowing time for judgement.

Volunteers had to compare the 6 sound intensities to an initial reference sound of 4 kHz frequency. The reference sound was set at 20 dB higher than the hearing threshold level for 4 kHz, during the control air stage, for a particular ear in that subject, for example, hearing threshold level of 15 dB for the left ear assessed at 4 kHz in Air (a), intensity matching experiment's reference sound would be set at 35 dB (i.e. 15 dB + 20 dB) and this reference level would be used throughout the entire 4 stages for the left ear; the same procedure was used for the right ear. In each stage, the reference sound was initially given to the volunteer for as long as requested but not

repeated during that stage, i.e. they had to remember that intensity level. Each ear was separately tested to prevent memory confusion of different intensity levels for the different ears. Appendix 6.5 is the answer sheet used by the examiner.

The 6 comparison sound intensities differed from the reference sound by a factor of 5 dB, for example, for using left ear, as above, the 6 comparison sounds would be: 30 dB, 30 dB, 35 dB, 35 dB, 40 dB and 40 dB. The order of presentation of each comparison sound was random and the subjects did not know at what intensity, nor frequency, that they were being tested at. Subjects indicated with their finger on an answer sheet if the sound was the same, louder or softer than the initial reference sound. The examiner recorded their answers on another answer sheet and used "N" for same, "L" for louder and "S" for softer. The answer sheet was hidden from the subject's view. Below is a typical examiner's answer sheet with the intensity levels that are from the above example, and corresponding answers. This is shown to help explain the procedure for analysing the data.

Intensity Matching

(1) Initial reference at 4 kHz (Threshold level)	Right Ear		Left Ear	
	10.....dB		0....dB	
(2) Threshold level (4 kHz) plus 20 dB	30.....dB	L/N/S	20...dB	L/N/S
- 5 dB	25.....dB	S	15...dB	S
- 5 dB	25.....dB	N	15...dB	L
0 dB	30.....dB	N	20...dB	N
0 dB	30.....dB	N	20...dB	L
+ 5 dB	35.....dB	L	25...dB	L
+ 5 dB	35.....dB	S	25...dB	N

For a particular sound to be perceived as being approximately twice as loud as another, that sound's intensity is usually about 6 dB greater (Liebermann *et al* 1988). The difference of 5 dB in comparison intensities was chosen for convenience as the machine manufactured sounds in 5 dB increments. This assessment of intensity matching

provides details as to whether subjects can (a) determine 5 dB differences and (b) remember the initial reference sound. This leads to an understanding if spoken statements, to the patient, can be recalled by a patient whilst the patient was under 10% or 20% N₂O inhalation, as in the dental or surgical operatory, but not give indication as to whether the patient appreciably understood those statements.

Answers were collated after the experiment and issued a number: +1, 0, -1. The method for determining which number to assign an answer involved comparing that answer to the level of intensity presented relative to the reference level. If the subject thought that the comparison sound was softer, the same or louder than the reference sound and that answer was correct, then "0" was scored by the examiner, and if the answer was incorrect, then a score of "-1" or "+1" was given. The score of "-1" indicates that the subject thought the comparison sound was softer than, or the same as, the reference sound when in fact it was louder. The score of "+1" denotes that the subject thought the comparison sound was louder than, or the same as, the reference sound when in fact it was softer. An example is given below of this with the scoring in italics:

Intensity Matching

(1) Initial reference at 4 kHz (Threshold level)	Right Ear 10.....dB			Left Ear 0.....dB	
(2) Threshold level (4 kHz) plus 20 dB	30.....dB	L/N/S		20...dB	L/N/S
- 5 dB	25.....dB	S	0	15...dB	L +1
- 5 dB	25.....dB	N	+1	15...dB	S 0
0 dB	30.....dB	N	0	20...dB	N 0
0 dB	30.....dB	S	-1	20...dB	L +1
+ 5 dB	35.....dB	L	0	25...dB	N -1
+ 5 dB	35.....dB	S	-1	25...dB	N -1

The number of correct (0) or incorrect (+1, -1) answers were added up, then two types of analysis were performed and are reported

in the Results 5. Intensity Matching. The two analyses are (see 4.0 Data Analysis):

(1) Statistical analysis was on the number of correct answers between the four stages. (A comparison of the incorrect (+1,-1) answers would not yield any additional information.) Statistical analysis was done on all data simultaneously (Program 5V, see 4.0 Data Analysis), to determine if any relationship exists between the various factors, that were over 25 vs under 25 years age groups, left vs right ear sides, female vs male gender groups, and treatment changes (Air (a) vs 10% N₂O vs 20% N₂O vs Air (b)).

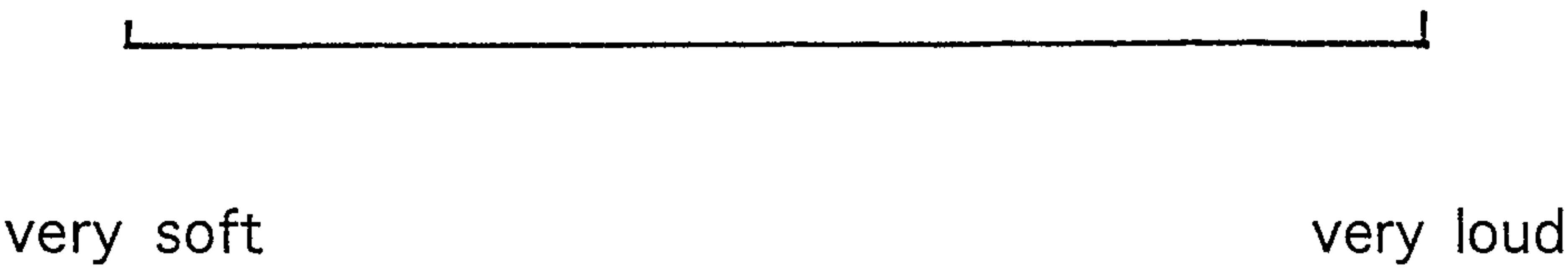
(2) Individual tables were prepared for each group, e.g. female group data only, then male group data, etc. The number of 0, -1 and +1 responses throughout the experiment are reported in the Results (see Results, 5. Intensity Matching). This table provides an indication as to whether sounds were more likely to be recorded as being softer or louder than they actually were. If the subject's judgement of a particular intensity level during the N₂O inhalation stage is different to the control stages, this could have influence on how particular intensity levels are perceived and could have direct bearing on the results from the Subjective Intensity test. Statview 512+ (1986) and Excel 4.0 (1992) was used for analysis.

2.2.6 Subjective Intensity

Subjects were given a frequency of 4 kHz and loudness levels of 40, 60 and 80 dB, and recorded their interpretation of the loudness of the tones. The volunteer did not know the loudness level (i.e. intensity) nor in which sequence it was presented. Both left and right ears were randomly and alternatively tested for example, left ear 40 dB, then right ear 80 dB, right ear 40 dB, left ear 60 dB, etc.. A total of six measurements were taken for each subject in each stage.

Subjects recorded their interpretations of loudness intensities on a recording line by placing a mark (line) across the recording line. The subjects' record sheet consisted of six 10 cm recording lines,

each line was labelled A, B, C, D, E, or F (in that order down the page and the subject recorded down the page, one for each of the six measurements). The only indicators were; "very soft" and "very loud" at either end of the scale:



Measurements (mms) were conducted using the left end of the line as the zero point to the spot where the subject's mark intercepted the recording line. One page was given to each subject in each stage and after that stage was completed, it was removed from the subject's view to prevent comparisons made by the subject to previous recordings. No notations of the length or centimetre markings were on this line. This was to prevent influencing how they interpreted the intensity, and also markings may influence their later recordings, e.g. they may remember that a particular intensity in one ear was recorded at a particular "notch" or marking from the end of the line.

Due to the random selection of levels and ear tested within each stage, the sequence was recorded by the examiner on the examiner's sheet (see Appendix 6.5) using the letters: A, B, C, D, E, and F, which corresponded to the subjects' record sheet. One example of the examiner's record sheet may thus have looked like:

	Right Ear	Left Ear
40 dB	A	F
60 dB	D	B
80 dB	C	E

Sound intensities of 40, 60 and 80 dB were chosen as they are representative of sound intensities typically encountered in everyday life. Davis and co-workers (1963) states that "Conversational speech at 1 yard is about 65 dB". The 80 dB intensity has been described as a "few inches in front of someone shouting", while 40 dB is slightly louder than the noise levels of a " 'quiet' average room - 30 dB" (Lieberman *et al* 1988), or "a home living room" or "normal office environment" (Davies *et al* 1988). "Faint but intelligible speech in a quiet room is about 40 to 45 dB" (Davis *et al* 1963). The loudness levels of 40 and 80 dB are the borders of the intensity "range" that was given to the subject, while 60 dB is between the two intensities, thus looking at 60 dB and its relationship to the two "borders" gives an indication of how the subject can interpret such levels whilst under N₂O, and one could relate that to the patient - dentist relationship with treatment or medico-legal implications that can be drawn from it. Using a defined hearing intensity range, the relationship of the scoring of the three loudness levels to each other can be analysed, especially any changes that occur in their relationship during N₂O inhalation.

The frequency of 4 kHz was chosen as it is within the range that the human ear is most sensitive (see Methods, 2.4 Auditory Threshold).

The null hypothesis (H_0) for this analysis states that N₂O has no effect on subjective hearing perception of a 4 kHz frequency at 40 dB, 60 dB or 80 dB compared to the controls. Two analyses were done on the data (see 4.0 Data Analysis):

(1) Statistical analysis was done on all data simultaneously, with repeated measures ANOVA (Program 5V) to determine if any relationship exists between the various factors, that were over 25 vs under 25 years age groups, left vs right ear sides, female vs male gender groups, and treatment changes (Air (a) vs 10% N₂O vs 20% N₂O vs Air (b)).

(2) Further statistical analysis used Statview 512+ (1986) and Excel 4.0 (1992) for determining means and standard deviations also

comparing mean values with ANOVA (repeated measures) within specific groups, e.g. female group data only, then male group data, etc.. Appendix 6.6 shows how a comparison table is presented if the null hypothesis is true (see 2.4 Data Analysis, for explanation of symbols used). A short hand method will be utilised to describe the loudness intensity at a particular stage, e.g. 40 dB (10%) indicates a mean loudness intensity of 40 dB at the 10% N₂O stage.

2.3 Armamentarium

2.3.1 Location

A quiet, windowless office room, air-conditioned and isolated from theatres, at the St. George Hospital Anaesthetic Department (Kogarah, N.S.W., Australia) was employed. The room was bare (see Methods 3.4 Positions for the floor plan) to prevent volunteer distraction. These features provide optimum conditions to conduct the experiment (Malmberg 1968). Experimentation was performed after 6 pm.

2.3.2 Equipment

Nitrous oxide gas was obtained in cylinders and directly attached to the anaesthetic machine. Gas was obtained from CIG (Australia) and was medical grade purity. Normal office furniture was employed.

The audiometer was Earscan (Micro Audiometrics Corp., Florida, U.S.A.) with acoustic impedance facilities and was used throughout the experiment. The manufacturer gave written permission to use their name. The system uses headphones to diminish outside/background noise and deliver sounds directly to the external auditory meatus. This system allows sound to be heard directly by the subject without travelling from a loudspeaker placed in the room,

which is more likely to allow extraneous noises to be picked up by the subject (Haughton 1980).

The portable anaesthetic machine had independent N₂O and O₂ gas cylinders attached. Anaesthetic tubing was routinely replaced before the experiment.

A Datex physiological monitor with an inbuilt gas analyser was attached to the anaesthetic machine. Heart rates, oxygen saturation and blood pressure were displayed on the machine and recorded.

2.3.3 Gas levels and application

The control stages Air (a) and (b) utilised room air. Post-N₂O administration of oxygen was not given as these subjects were young, did not hyper- nor hypoventilate, had not undergone a recent operation, nor did they have any respiratory pathologies (see 1.2 Sequence of Testing).

Nitrous oxide was administered via the anaesthetic machine. A full face mask was employed to prevent dilution of the breathing mixture with room air. A gas analyser was attached to the anaesthetic tubing near the face mask. This allowed the N₂O and oxygen levels to be calculated within the breathing circuit. The Datex physiological monitor analysed the gases to achieve 10% and 20% N₂O administration.

2.3.4 Positions

Subjects sat beside the desk, facing away from the anaesthetic machine to prevent them noticing the N₂O and O₂ levels, and facing away from the silent clock on the wall. The audiometer, Earscan, was placed on the desk with the control panel shielded from the view of the subject. Volunteers held a full face mask during the N₂O application. During the experiment, they could sit in any position they desired (one subject sat on the floor), providing there was direct

access to the anaesthetic machine and the audiometer (see Appendix 6.7).

2.4 Data Analysis

Statistical analyses have already been partially described within each methodological section (above). For Auditory Threshold, Intensity Matching and Subjective Intensity, two types of analyses were done:

(1) Program 5V from the BMDP Statistical Software Package, ULCA, 1990, was used for simultaneous ANOVA analysis of all data and factors and identifying any significance between the various factors. Comparing between the treatment stages the data from the two Air stages ((a) and (b)) were combined and also the data from the two N₂O stages (10% and 20%).

(2) Microsoft Excel 4.0, 1992, Microsoft, USA, and Statview 512+, 1986, Abacus Concepts Inc., Brainpower Inc., Calabas, USA, was used to produce tables. Specific analysis was done on some factors in some of the tests.

The outcome of these analyses will be presented in a format corresponding to the above numbers (e.g. in Results, the "(1)" will indicate the results of analysis done using method (1), and "(2)" indicates results using method (2))

There were four factors chosen for analysis. The first factor is the influence of breathing air or N₂O on the subjects. Bourne (1960) described that volunteer responses to N₂O inhalation were dependent upon physique, age, gender and metabolic rate and that these factors should be considered in an analysis. Gender and age influences the physique and metabolic rate of the volunteer, so gender and age were chosen as the next two influencing factors. Lastly, the left ear was positioned closer to the anaesthetic machine, which had inherent noises emanating from it, thus ear side was considered a fourth factor. Each of these factors is divided into two or four groups.

Comparison tables between various groups, in the different tests, were used and the symbols are universal for all the tests: "*" indicates that the significance level ($P < 0.05$), while "NS" indicates non-significant differences ($P > 0.05$).

2.4.1 Treatment Influences

Analysis was used to determine if there was any influence of N_2O on hearing and there were four groups as directed by the stages: Air (a), 10% N_2O , 20% N_2O and Air (b).

2.4.2 Age

Physiological variations occur with age, and thus data was divided into those over and under 25 years of age (Glorig 1965). The age of 25 years was decided as the body has completed its development and "stabilized into the adult condition" (Timiras 1972). As humans age, there is a decreased hearing sensitivity, notably in the higher frequencies (Zwicker and co-worker 1990). The division resulted in two groups of approximately equal size.

2.4.3 Ear

Data was collected in left and right ear groups, thus the data can easily be divided for analysis. The position of the left ear next to the anaesthetic machine (which has its own inherent noises) may influence the results. Denes and co-workers (1973) describes that masking can occur and does occur in two areas (1) the masking tone masks those tones that are neighbouring in frequency (of same intensity) and (2) lower frequencies effectively mask higher frequencies, but not as well vice versa.

Davis and co-workers (1963) states that hearing with one ear is not as effective as hearing a sound with two ears. There is a gain in sensitivity of about 3 dB using both ears. This experiment uses single

ear testing because (1) the audiometer was designed for single ear testing, and (2) the ears can be tested for their least possible hearing interference from the other ear, and (3) minimise masking effects as much as possible.

2.4.4 Gender

Physiological variations exist between the sexes, thus data was divided into male and female, to determine if gender had an influence in these experiments (Glorig 1965). Subjects were not asked if they were taking sex steroids or hormones.

3. Results

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3.1 Questionnaires

3.1.1 Questionnaire 1 (see Appendix 6.1)

3.1.1.1 Personal Data (see Table 1.1)

The mean values of physical data of subjects' weights and heights are within acceptable normal values (MIMS Annual, 1989).

3.1.1.2 Past and Current Medical History

No volunteers had current acute or chronic hearing problems, nor ear infections, nor neurological problems. On the experimental day, one had a slight cough, no other respiratory impairment and this did not interfere with the experiment.

3.1.1.3 Present Physical Status

No alcohol was consumed in the past 24 hours and only one subject smoked cigarettes. Although the experiments were performed in the evening all, except one, slept well the previous night and there were no changes to their daily routines. Only two ate within 2 hours of the experiment. Thirteen drank caffeine drinks (tea, coffee) within the past 24 hours. Food intake may influence the subject's comfort as air pockets in the stomach can distend during N₂O inhalation (Munson, 1974), and possibly cause some interference, e.g. pain, but no subject reported abdominal discomfort.

3.1.1.4 Physical Assessment

All subjects had no known current pathologies with their tympanic membrane. The oropharynx region was healthy in all, except one, mentioned above. All could manage the audiometer's hand held device. Blood pressure, heart rate and haemoglobin oxygen saturations were recorded (see 2. Physiological Functions).

3.1.2 Questionnaire 2

The results are given below for each of the italicised questions asked.

Did you find concentration on the task easy/difficult?

Nine subjects answered that it was easy, seven replied difficult, one did not answer this question.

Did you hear any extraneous noises? Y/N What where they?

Ten answered yes, however the noises were of either from the air conditioner, the hum of the fluorescent lights, people walking past the corridor. Six answered that no extraneous noises were heard.

Do you remember any commands/statements given to you during the procedure? Y/N What was it?

Four did not provide an answer, nine answered "yes" and three answered "no". No reasons were given as to why they answered as they had.

Did the passage of time seem as quick/slow as you expected it to be?

Two stated that time seemed to pass normally, four replied that it went slower, and ten replied that it was faster.

Did you feel like yawning/coughing during the procedure? Y/N When?

Did you feel as though you needed to "pop" your ears at any time? Y/N When?

Most subjects verbally told the examiner that they hadn't "paid attention" to this action. It was difficult for the examiner to notice this as a full face mask was used. Answers for both were identical: twelve replied "no" and four replied "yes" that they yawned/coughed/popped their ears.

Did you experience any thermal changes in parts of your body and head? Y/N If yes, was it; cold/heat sensations, and where? Could it have been the room?

Eight answered that there was a thermal change, and eight said that there wasn't. Thermal changes experienced were usually warm/hot. Changes occurred in various parts, ranging from over the whole body or specifically in the hands, feet. One indicated the face, and this can be related to the humidity during mask breathing.

How you feel during the experiment?

Every subject answered this question. The answers to this question related to their experience during the N₂O inhalation stages as answers ranged from being lightheaded/relaxed/happy, to being in an inebriated/dizzy state.

Would you do it again? Y/N

Fifteen replied "yes" and most verbally commented that it was enjoyable. One replied "no" and no reason was given.

Any further comments about your sensations under N₂O or the procedure would be appreciated;

No other comments were made, except retelling or elaborating on their answers in a verbal manner, e.g. that they would like to experience N₂O again.

3.2 Physiological Functions

3.2.1 Blood Pressure (BP)

Recordings were in the traditional measurements of mmHg and the average of systolic and diastolic pressures are given in Table 2.1 for all data presented. Tables 2.2 to 2.5 show age and gender group measurements. Statistical analysis (ANOVA) showed no influence of age or sex on blood pressure throughout the experiment ($p > 0.05$).

3.2.2 Heart Rate (HR)

Overall HR recordings are recorded on Table 2.6. Tables 2.7 to 2.10 are recordings for age and gender groups. ANOVA (with repeated measures) showed no influence of these groups on HR throughout the experiment ($p>0.05$).

3.2.3 Oxygen Saturation (SaO₂)

Overall haemoglobin SaO₂ recordings are on Table 2.11. Tables 2.12 to 2.15 are means and standard deviations for SaO₂ in age and gender groups. ANOVA (with repeated measures) showed no influence of age or gender on the SaO₂ ($p>0.05$).

3.2.4 Subjective Perceptions

The questions (in italics) were given during each stage, with a final retrospective answer. This retrospective question was given in the last control stage (Air (b)) and subjects were asked to retrospectively review their experiences whilst under the influence of N₂O. Totals are included on the table, but percentages are presented here. The maximum number of responses to any question was 16 in each stage and grand total of 80 (including the retrospective question). Most questions had between 72-79 responses. Subjects were not asked why they did not respond to a question.

Analysis involved assessment of the proportion of subjects giving particular responses. This work is aimed at determining any N₂O influences on hearing of known frequencies and intensities of sounds. A subjective analysis on human voices are recorded and briefly discussed in this section. However, the human voice is inconsistent in its frequency and intensity and thus it is difficult to analyse any data obtained on judgement of the human voice other than looking at the number of responses, as in this case. Any changes in the perception of the human voice, by the subject, under these levels of N₂O, could give an indication as to the perception of patients

undergoing light N₂O inhalation and the patient's ability to hear, understand and respond to commands.

Hearing; Did the examiner's voice seem.....?

distant / normal / closer (Table 2.16)

From the totals, 57 of 77 (74%) of replies were "normal". It is interesting to note that in the 20% N₂O stage, 5 of 16 (31%) responses were "distant".

distinct / normal / muffled (Table 2.17)

Most of the responses were "normal" 41 of 74 (55%), with 28 (38%) being "distinct". Only 5 of 74 (7%) responded "muffled" and of those, 3 of 5 were from a retrospective view.

echoing / normal / clear (Table 2.18)

The most frequent response was "normal" (43 of 77, 56%), while 34 of 77 (44%) responses were either echoing/clear.

high pitched / normal / low pitched (Table 2.19)

Of the 78 responses, 58 (74%) replied "normal". The responses for "high pitched" are to be expected as the examiner was a female. It is interesting to note that the number of "high pitched" responses, whilst the subject was under 20% N₂O, has increased relative to the other three stages.

humming / nothing/ ringing (Table 2.20)

"Nothing" was the most frequent response, with 61 of 74 answers (82%). In the retrospective view (while being under N₂O influences), 4 of 16 (25%) of the responses were either humming/ringing.

Thermal; cold / fine / hot / other (Table 2.21)

The two most frequent answers were "fine" (55 of 78, 71%) and "hot" (17 of 78, 22%). "Fine" could be interpreted as "normal". There was no subject that answered "cold". During the procedure, 6 responses were "other" (e.g. head was warm but fine elsewhere, or joints, feet and hands were warm).

Visual; blurred / normal / clear / colour changes (Table 2.22)

There were 72 responses out of a possible 80 (90%) and is one of the two lowest responding questions. There were 59 of 72 (82%) "normal" responses, with 10 of 72 (14%) for "blurred" vision. Some of the verbal responses were not included in the table as classification was difficult, thus there were only 72 of 80 responses. Some verbal responses were: images seemed distant, hard to focus, everything seemed bright.

Smell; perfume / pungent / dusty / rubbery / none / other (Table 2.23)

There were 76 of 80 responses, and 43 of 76 (57%) responded that there was "no smell". The next most frequent response was "rubbery" (17 of 76, 22%), then "other smells" (9 of 76, 12%), i.e. a sweet and rubbery smell, hospital odours. The "perfume" smell (3 of 76, 4%) could possibly be interpreted as "sweet".

Taste; sweet / salty / sour / bitter / other / none (Table 2.24)

There were 79 of 80 possible responses which is the most number of responses for any question in this assessment. The most frequent answer was 'no' taste (69 of 79, 87%), the next being "salty" (4 of 79, 5%) which was in the 20% N₂O stage and a retrospective view. "Bitter" was another response during N₂O inhalation.

Concentration; easy / normal / difficult (Table 2.25)

Of the 77 responses, 42 (55%) were normal, and 25 (32%) had difficulty in concentration. During N₂O inhalation, the responses for "difficult" had increased, while "normal" decreased. The retrospective view during N₂O inhalation shows that 9 of the 13 responses (69%), were "difficult".

Body Sensations; How do you feel?.....

excited / normal / relaxed (Table 2.26)

"Relaxed" was the most frequent answer (39 of 77, 51%), and of that 11 (11 of 39, 28%) responses were from a retrospective view of sensations felt during the N₂O inhalation stages. The next most frequent response was "normal" with 32 of 77 (42%). Excitement was only reported in the first two stages and may have to do with the unique experiences encountered by the subject.

happy / normal / sad (Table 2.27)

Even though N₂O has been described as the "laughing gas" (Merck Index 1983, Pharmaceutical Index 1979), there was a total of 15 responses to "happy" (19%) while "normal" had 63 responses out of 78 (81%). Under N₂O inhalation, there was a shift of responses from "normal" to "happy" and this was not tested for significance. There were no responses to "sad". Retrospective view had 6 of 14 (43%) responses for "happy", while 8 of 14 (57%) responded to "normal".

body: lightness / normal / heaviness (Table 62.28)

Overall there were 44 (57%) responses for "normal" and 22 (29%) for "lightness". Under 10% N₂O inhalation, 9 of 15 (60%) subjects felt "normal", but 6 (40%) felt either "heavy" or "light", while with 20% N₂O, 5 (30%) subjects responded "normal".

muscle: tremors / normal / stillness (Table 2.29)

Most responses (93%) were "normal" with 5 non-"normal" responses. There was some difficulty for some subjects to identify the difference between some of the choices.

tingling / no sensations / paraesthesia (Table 2.30)

There were 72 responses out of a possible 80 (90%). This is one of the two lowest responding questions. The majority of responses were "no sensations" (49 of 72, 68%). The 16 that respond to "tingling", were in the N₂O stage and with a retrospective view. Paraesthesia also had a total of 7 (10%) responses over all stages except Air (a).

3.3 Acoustic Impedance

Measurements of ear impedance were made and recorded below.

3.3.1 Middle Ear Pressure (MEP) (See Table 3.1)

Recordings indicate that MEP does increase under N₂O inhalation and return to normal values after cessation of N₂O inhalation. Tables 3.2 to 3.7 show means and standard deviations for age, ear and gender groups.

Statistical comparisons are presented in Tables 3.8 to 3.14. There were various significant differences between the stages ($p < 0.05$). By dividing the data into age, ear and gender groupings, there was no significant difference between 10% N₂O and Air (b) (see 4.3.1 Middle Ear Pressure) which occurred in all groups except for females. The significant difference in the female group could be due to either differences between the genders or the low number of subjects in that group.

3.3.2 Physical Volume (PV) (See Table 3.15)

The PV mean and standard deviation for all data, in all stages, falls within normal limits. Tables 3.16 to 3.21 show means and standard deviations for age, ear and gender groups.

Statistical comparisons (see Table 3.22) indicate that there were no significant differences between the stages for all data presented and for age, ear and gender groups ($p > 0.05$). This is to be expected as it is a physical measurement of a bony structure.

3.3.3 Compliance (Comp) (See Table 3.23)

The mean and standard deviations for all data are within normal limits. Tables 3.24 to 3.29 show means and standard deviations for age, ear and gender groups.

Statistical comparisons (see Table 3.30) indicate that there were no significant differences between the stages for all data presented and for age, ear and gender groups ($p > 0.05$).