The Effect of Caffeine on Tinnitus: Friend or Foe?

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For God and my Mother, Judith

who share this thesis

who joined me in its living and telling

who made it whole.

My appreciation also goes to Dr Simon Kemp, for his guidance in helping me to complete this manuscript. Thank you to all the subjects who participated in this study - without your time this research would not have been possible.
There is no previous scientific evidence to support the anecdotal and self-report literature proclaiming the adverse affect of caffeine on the auditory disorder tinnitus. The present study investigated the relation between these two factors. Three models of caffeine action were postulated, implicating cyclic 3'5'-AMP, adenosine, glucose, adenine and hypoxia. It was predicted that the stimulatory action of caffeine would increase or vary the sensation of tinnitus resulting from excitation anywhere within the auditory system. Sixteen subjects with unilateral versus bilateral or head tinnitus were randomly administered a placebo, 100mg or 300mg of caffeine using a double-blind procedure. Pitch matches to a tone, thresholds of sensitivity, loudness matches to a tone at the matched tinnitus frequency and to broadband noise, and the subjective ratings of tinnitus frequency and loudness were recorded prior to, and 30 or 60 minutes after oral ingestion of caffeine. Caffeine did not affect the pitch of tinnitus or tone threshold but noise thresholds were elevated after 100mg but not 300mg of caffeine and loudness matches to noise increased after both 100mg and 300mg of caffeine. Changes in loudness matches to a tone and subjective ratings of loudness were dose- and time-dependent. The results were discussed in relation to the proposed models and mechanisms of action. Results suggest that for certain tinnitus sufferers caffeine has a stimulatory effect and that the cessation of caffeine-containing beverages would eliminate gross increases or variations in tinnitus. For others, however, the results suggest a depressant action, raising the possibility of using caffeine as a therapeutic, management technique.
INTRODUCTION

I. Tinnitus

Phantom perception within the auditory modality of humans has been described in the literature as the pathological condition of tinnitus. Subjective tinnitus, a disorder defined as sound perceived solely by the individual, has been the focus of increasing attention during recent years (McFadden, 1982; Donaldson, 1978). The origin of tinnitus is not known, yet as many as 35% of the American and British population (Coles, 1984; Coles, Davies and Haggard, 1987; Vernon, 1987) report episodes of some form of tinnitus. The widespread occurrence of this auditory dysfunction and the lack of effective therapeutic methods have stimulated attempts to determine its cause.

Tinnitus may be peripheral or central in origin. In the first case it could be due to a loose coupling between stereocilia and the tectorial membrane (Tonndorf, 1976, 1980; Jastreboff, Brennan and Sasaki, 1988), to a disruption of the multiple interconnections between the nerve fibres and the sensory cells (Aran, 1981; Bredberg, 1977; Engstrom, 1970), or to a vascular injury (Pulec, 1974; Pulec, Hodell and Anthony, 1978). On the other hand, several authors have described a central tinnitus following surgical procedures (Pulec et al., 1978) or viral infections and vascular lesions of the auditory cortex (Ross, Jossman, Sabin and Geschwind, 1975). It is not unusual in the few patients in whom the cochlea nerve and the cochlea are left intact following middle fossa vestibular section or middle fossa removal of an acoustic neuroma where vascular supply to the inner ear is injured, to develop tinnitus (Pulec, 1974; Sasaki, Kauer and Babitz, 1981).

In addition, it is possible that the site of origin of this sensation could involve neuromechanisms along the entire auditory pathway from the inner ear to higher cortical centres (Israel, Connelly, McTigue, Brummett and Brown, 1982). These include hypoxia from vascular involvement, biochemical changes and the effects of certain drugs (Pulec, 1974; Pulec, Hodell and Anthony, 1978). A number of disorders have been associated with subjective tinnitus, however, understanding tinnitus - its causes and symptoms - is far from complete. The lack of understanding of tinnitus is
evidenced by its multiple and varied explanations. A summary of the known and associated causes of tinnitus have been compiled and are presented in Table I.

**Cochlea Origin of Tinnitus.** The fact that tinnitus can arise from any part of the auditory pathway means that each site will have a somewhat different pathogenesis. It is possible that several different mechanisms could occur within the cochlea. Although some controversy exists regarding the coupling between the stereocilium and the overlying tectorial membrane, it seems likely that each stereocilium has a reasonably rigid connection to the tectorial membrane (Dallos, 1973; Gelfand, 1981; Pickles, 1982; Whitfield, 1967).

One class of hypothesis considers that increased spontaneous activity of auditory neurons results from hyperactivity of cochlea hair cells. Such hyperactivity could, for example, result from the pathological changes in mechanical properties of stereociliary attachment of hair cells to the tectorial membrane (Tonndorf, 1976, 1980; Jastreboff et al., 1988). Tonndorf suggested that the loss of stereociliary stiffness could result in partial decoupling of hair cells from the tectorial membrane and thereby cause an increase in their inherent thermal noise level (Harris, 1968). Recent findings concerning the active mechanical role that outer hair cells may play in tuning of cochlea micromechanics (Kim, 1984; Brownell, Bader and Bertrand, 1985; Flock and Orman, 1983; Tilney and Saunders, 1983) and changes observed in the stereocilia after noise exposure (Slepecky, Hamernik and Henderson, 1981) further support the importance of proper mechanical stereociliary coupling with the tectorial membrane for normal functioning of the cochlea.

Bredberg, Ades and Engstrom (1972), with the aid of scanning electron microscopy, observed lesions that formed on the apical ends of the cochlea stereocilia in cats after exposure to intense sound. Behavioural audiograms revealed a more profound hearing loss than seemed to be warranted by the sensory loss, demonstrated by light microscopy. Bredberg et al. (1972) also found other changes of the stereocilia of the hair cells which consisted of reduction of size or a complete disappearance of hairs. The growth of stereocilia to "giant" hair cells was also observed. It is possible that lesions, when present on the stereocilia, partially decouple the
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<td><strong>Source:</strong> The Ear</td>
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<tr>
<td>Presbyacusis</td>
</tr>
<tr>
<td>Hearing Loss</td>
</tr>
<tr>
<td>- Conductive</td>
</tr>
<tr>
<td>- Sensorineural</td>
</tr>
<tr>
<td>Labyrinthitis</td>
</tr>
<tr>
<td>- Allergic</td>
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<tr>
<td>- Viral</td>
</tr>
<tr>
<td>- Bacterial</td>
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<tr>
<td>- Spirochetal</td>
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<tr>
<td>Acoustic Trauma</td>
</tr>
<tr>
<td>Vestibulary Disorders</td>
</tr>
<tr>
<td>Giant stereocilia</td>
</tr>
<tr>
<td><strong>Source:</strong> Metabolic Disorders</td>
</tr>
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<td>Diabetes Mellitus</td>
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<td><strong>Source:</strong> Circulatory Disorders</td>
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<td>Hypertension</td>
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<tr>
<td>Decrease in blood flow to the ear</td>
</tr>
<tr>
<td><strong>Source:</strong> Tissue Inflammation</td>
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<tr>
<td>Tumor on the Eighth Facial Nerve</td>
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<tr>
<td><strong>Source:</strong> Central Nervous System (CNS)</td>
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<td>Lesions on the Auditory Cortex</td>
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<td>Alterations in the rhythmic activity of the reflex arc</td>
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<tr>
<td><strong>Source:</strong> Other</td>
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<tr>
<td>Aging</td>
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<td>Bell's Palsy</td>
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<td>Noise Exposure</td>
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connection between the tectorial membrane and the hair cells, and cause a tinnitus of mechanical, cochlea origin.

A second mechanism which could produce tinnitus within the cochlea involves the injury or loss of the afferent and efferent nerve endings to the cochlea hair cells (Bredberg, 1977; Engstrom, 1970). Disruption of the complicated and multiple interconnections between the nerve and the sensory cells could be expected to produce an abnormal response to any sound. In addition, the reinnervation of nerve fibres as a function of CNS behavioural plasticity, may result in aberrant growth connections resulting in some hair cells having no nerve connection or an inappropriate interconnection (Aran, 1981; Bredberg, 1977; Engstrom, 1970).

Damage to the nerves of the inner ear (which is one of the most common causes of hearing loss; Goodey, 1986) results in fewer messages being passed up the hearing nerve to the brain cells. Changes in transmission output alter the reflex arc (composed of afferent and efferent fibres conducting a steady discharge from hair cells through the thalamus to the cortex and back) in such a way that the perception of sound is increased for those frequencies which the damaged hair cells or neural pathways normally receive or transmit. The rhythmic hyperactivity of the disturbed auditory pathway could result in a tinnitus analogous to an epileptic state (Crue, 1970).

Melding, Goodey and Thorne (1978), Shea (1983), Shea and Emmet (1983) and Shea and Harrell (1978) concurred with Crue's (1970) analogy by classifying tinnitus as a form of sensory epilepsy within the auditory pathway that is caused, at least in part, by alteration in cochlea function. The suppressive effect of lignocaine fits well with the concept of sensory epilepsy, as lignocaine is a potent, short-term anti-convulsant (Engelsson, Larson and Lindquist, 1976; Fowler, 1953; Gejrot, 1963 and 1976; Lewy, 1973; Melding et al., 1978; Sakarta and Umeda, 1976; Shea and Harrell, 1978). Hence, drugs which exacerbate the rhythmic hyperactivity of the reflex arc may compound tinnitus. Drugs which are vasoconstrictors probably produce or potentiate tinnitus through pre-existing cochlea damage or compromised CNS circulation (Brown, Penny, Henley, Hodges, Kupetz, Glenn and Jobe, 1981).

Theories of tinnitus of cochlea origin, generally assume, explicitly or
implicitly, that it is associated with spontaneous overactivity of the cochlea nerve fibres. However, investigations of cochlea nerve activity in experimentally induced chronic cochlea pathologic function in cats (Kiang, Liberman and Levine, 1976) generally revealed depression of spontaneous neural activity. Because tinnitus is predominantly associated with pathological conditions of the cochlea, Kiang et al. (1976) proposed that tinnitus might result from reduced activity in the cochlea nerve.

Research by Mongan, Kelly, Nies, Porter and Paulus (1973) demonstrated, however, an increase in all threshold fibres of 20 dB to 60 dB above normal within minutes of acutely administered sodium salicylate (400mg/kg given intravenously; such blood concentrations are associated with tinnitus in humans). Under these conditions of salicylate administration, an increase in spontaneous discharge rate was found. Jastreboff et al. (1988) found that after salicylate injections the mean rate of the cell population increased from 29 Hz to 83 Hz and the median from 26 Hz to 74 Hz. Evans and Borerwe (1982) found an increase in spontaneous activity of units of the auditory nerve resulting from intravenous injections of salicylate. It has been suggested, therefore, that the occurrence of tinnitus is related to a change in the temporal pattern of the spontaneous activity and to a change in the firing rate (Evans and Borerwe, 1982).

These findings represent an important exception to the hypothesis of depression of cochlea fibre spontaneous activity in the pathological conditions of the cochlea studied to date. Another potentially important finding is the report of a similar increase in spontaneous discharge rate in a minority of cats examined about one month after noise overstimulation (Liberman and Kiang, 1978). Permanent tinnitus often follows noise overstimulation in humans.

While it is still possible that tinnitus caused by cochlea pathology could arise (on account of contrast enhancement mechanisms in higher neural centres) in association with depressed spontaneous activity of cochlea fibres, it appears likely, from these animal model results, to be associated with increased activity in the cochlea itself. Electrical stimulation of the cochlea or the round window have resulted in suppression of tinnitus (Aran and Cazals, 1981; Brackmann, 1981; Graham and
Hazell, 1977; Hazell, Graham and Rothera, 1985; House and Brackmann, 1981; Iurato and Zito, 1984; Lyttkens, Lindberg, Scott and Melin, 1986) and it has been shown that during electrical stimulation of the cochlea, direct current decreases the spontaneous activity in single fibres of the auditory nerve (Teas, Konishi and Wernick, 1970).

**Central Origin of Tinnitus.** Tinnitus may also originate in higher centres. It is likely that lesions involving the auditory cortex may produce tinnitus (Pulec, 1974). Myers (1975) has suggested that tinnitus may become fixed centrally after it has persisted for a period of time. Brown et al. (1981), Donaldson (1977) and Melding et al. (1978) have suggested that central tinnitus corresponds to the "gate theory" of pain proposed by Melzack and Wall (1965). This theory suggests that the efferent pathways control the pre-synaptic mechanisms, so that the ease with which cochlea information penetrates the brain stem is determined by efferent cochlea activity and by central cortical processing through a feed-back system. A change in the feedback system at the central level, that is, a central input which was out of proportion to the peripheral input, might result in neuronal hyperactivity and may be a cause of tinnitus.

Symptoms of tinnitus exhibit similarities to other disorders of sensory perception, for example, the pain of trigeminal neuralgia. The pain in this syndrome and other pain states of central origin are thought to be related to a central pool of neuronal hyperactivity (Anderson, Black, Abraham and Ward, 1971).

Gates and Chen (1975) illustrated the hyperactive nature of central tinnitus through the induction of audiogenic seizures in Balb C mice (a strain not normally susceptible to audiogenic seizures) following priming by noise exposure. These authors suggested that cochlea damage caused by such noise exposure produced a state of hyperexcitability within the auditory pathway. They did not speculate as to where in the auditory pathway this phenomenon occurred. Observations such as these have led to the speculation that tinnitus is also a manifestation of spontaneous hyperactivity and that it is probably generated within central pathways rather than peripherally.

If the phenomenology of tinnitus is an accurate reflection of its origin, then
some of those people with narrowband tonal tinnitus may have highly localised lesions, while some of those with broadband and complex tinnitus may have numerous or widespread sites of origin. Central tinnitus is usually described by the patient as being general in location, whereas peripheral tinnitus can frequently be localised to one ear (Meyerhoff and Cooper, 1980).

Measurement of Tinnitus. In the majority of the research specification of tinnitus has involved adjusting an external tone to match the pitch and then the loudness of tinnitus. A survey of literature prior to 1981 suggests that subjects with tinnitus are able to make consistent matches of the external stimuli to the pitch and loudness of their tinnitus (Bailey, 1979; Graham and Newby, 1962; Reed, 1960; Vernon, 1976). The determination of pitch and loudness of the patient's tinnitus is an important part of the procedure for fitting tinnitus maskers (Vernon, Johnson, Schleuning and Mitchell, 1980). A closer examination of these studies reveals, however, that either variability is not addressed or a bracketing/averaging technique (that is, matches were continued until the patient chose approximately the same frequency several times) was used. Utilisation of this technique renders consistent matches which essentially give no information on variability (Goodwin and Johnson, 1980; Graham and Newby, 1962). Penner (1983) provides a critique of the bracketing technique.

Despite claims of "inordinately reliable" matches (Goodwin and Johnson, 1980; Graham and Newby, 1962; Vernon et al., 1980) more recent research has demonstrated that there is large variability in matches made to the tinnitus (Burns, 1984; Man and Naggin, 1981; Penner, 1983, 1986, 1988; Tyler and Conrad-Armes, 1983). Some explanations of the large variability in matches to tinnitus include: a) the decision criteria utilised in the matches (Burns, 1984; Penner, 1983); b) the variability of tinnitus (Burns, 1984; Penner, 1983; Tyler and Conrad-Armes, 1983); and c) the possible interaction of the external tone with the tinnitus (Levi and Chisin, 1987; Penner, 1983, 1984, 1986; Vernon et al., 1980). The work of Sachs and Kiang (1968) suggests the possibility of tinnitus suppression by an external tone.

Tyler and Conrad-Armes (1983), Vernon and Meikle (1981) and Vernon and
Fenwick (1983) argued that consistent pitch matches to the tinnitus might be obtained if matches were made to only one sound, that is, to the loudest component. Hence, research of late has adopted the technique of ipsilaterally matching tinnitus to the prominent pitch (Burns, 1984; Penner, 1983, 1986, 1988; Tyler and Conrad-Armes, 1983). The adoption of this technique has not, however, diminished the reports of variability. Thus far, to the author's knowledge, no research has addressed limiting the variability associated with matching techniques by assessing all the pitches of tinnitus reported by a subject population.

Clear association between the degree of hearing loss and tinnitus intensity has been reported (Man and Naggin, 1981). Associations between frequency of severest hearing loss and the frequency of the measured tinnitus have also been found (Hazell, Wood and Cooper, 1985; Jakes et al., 1986; Man and Naggin, 1981; Nodor and Graham, 1965; Risey, Briner, Guth and Norris, 1989). In addition, significant relationships have been found between the subjective description of the tinnitus and its matched pitch on the one hand, but not the intensity of tinnitus on the other (Hazell, 1979; Jakes et al., 1986; Man and Naggin, 1981). Based on information obtained from 1800 tinnitus patients, Meikle and Tyler-Walsh (1984) found that self-reported severity was not related to the type, quality or pitch of the tinnitus sound heard. For some subjects there was significant day-to-day variability in subjective level which was greater than the variability incurred within a single day (Burns, 1984).

Although patients complain bitterly about tinnitus, over 80% of the cases experience tinnitus with sensation levels less than 20 dB, and less than 5% of sufferers have a tinnitus of 40 dB SL or greater (Donaldson, 1978; Graham and Newby, 1962; Man and Naggin, 1981; Meyerhoff and Cooper, 1980; Penner, 1983, 1986; Reed, 1960; Tyler and Conrad-Armes, 1983; Vernon, 1976). In many patients, it is believed that the level of disability is more closely related to the apparent level of anxiety and fatigue rather than to the tinnitus magnitude itself (Hazell, 1979). Risey et al. (1989) suggested that the discrepancy between objective and subjective loudness measures was a consequence of employing traditional procedures which underestimated the loudness of tinnitus expressed in decibel
sensation level. In a factor analytical study of both loudness self-report and audiometric measures, the results of Jakes et al.'s (1986) investigation concur with the low association between subjective complaints and objective measures which has been widely reported in this field. Jakes et al. (1986) suggested that loudness judgements were variable because they were influenced by emotional factors.

To an unknown degree, however, this lack of relationship may simply be indicative of the unreliability of the measures employed. At present there exist numerous procedures for measuring tinnitus and unfortunately, they do not always produce the same outcome. It may be that some particular methods will eventually prove more reliable and valid than others for particular forms of tinnitus, but at the moment it is premature to specify particular psychophysical procedures for different forms of tinnitus.

In addition, it should be noted that estimates of tinnitus loudness are usually based on sensation levels. Recalling the principle of recruitment, where the dynamic range is reduced, sounds that ordinarily should be comfortable may be perceived as unpleasant (Goodwin and Johnson, 1980; Hallam, Jakes, Chambers, Hinchcliffe, 1985; Jakes et al., 1986; McFadden, 1982; Penner, 1986).

Treatment of Tinnitus. The psychological study of the nature and the treatment of tinnitus is a relatively new area of behavioural medicine. The range of problems associated with tinnitus have been described in general terms (Hallam, Rachman and Hinchcliffe, 1984; Tyler and Baker, 1983) but there have been few systematic attempts to develop assessment devices with known psychometric properties. At present there is little understanding of the role environmental and psychological factors play in tinnitus. However, it is clear that a significant proportion of tinnitus sufferers report distress as a consequence of their tinnitus (Coles, 1984; Duckro, Pollard and Scheiter, 1984; Hallam et al., 1985; Reich and Johnson, 1984; Stephens and Hallam, 1985; Tyler and Baker, 1983). A treatment for tinnitus that is widely used is EMG biofeedback relaxation training (Haralambous, Wilson, Platt-Hepworth, Tonkin, Hensley and Kavanagh, 1987; House, Miller and House, 1977; Malatesta, Sutker and Adams, 1980).
An almost infinite variety of medications have been advocated by various authors for the treatment of tinnitus (Donaldson, 1978; Melding and Goodey, 1979; Shea and Harrell, 1978). Several drugs (anti-convulsants) are directed toward interrupting proposed pathophysiologic mechanisms for the production of tinnitus; while others are produced to help the patient tolerate his or her condition. Agents aimed at increasing blood flow have been advocated on the theory that ischemia (that is, inadequate blood flow) to the end organ or even, perhaps, the central auditory system is a plausible etiology for tinnitus (Snow and Suga, 1975). These medications include adrenergics, cholinominetics, anticholinesterase agents, cholinolytics, smooth muscle relaxants, plasma polypeptides and vitamins. In a review of the relative efficacy of these drugs, Snow and Suga (1975) concluded that papaverine, a smooth muscle relaxant, was the drug of choice for increasing cochlea blood flow. Vitamins, primarily A, vitamin C, nicotinic acid and Vitamin B₁₂ have been utilised for their beneficial effects on the vascular system as well as on the individual as a whole. Examining the action of anti-convulsant drugs in the treatment of tinnitus may enhance understanding of the mechanism(s) by which caffeine alleviates or potentiates tinnitus.

Partly because pharmacological treatment and technical aids have had only moderate success, but mainly on account of the progress of non-physiological therapies, increased interest has been paid to mechanisms related to psychological adaptation to tinnitus. This has also set the focus on alternative treatment strategies based on learning principles which are the basis of the clinical advance in the field of behavioural medicine (Gentry, 1984). The treatment may aim at either reducing distress due to the tinnitus sound itself, or at problems caused by or associated with tinnitus. However, most specific treatments have been primarily developed to handle the tinnitus itself and the annoyance it causes.

Subjective tinnitus is undoubtedly a symptom of a wide variety of different and microscopic abnormalities in the hearing mechanism. For the purposes of treatment, most of these must be thought of as amounting to a neurological condition. In the CNS generally, nerve tissue does not regenerate once it has been damaged, and tinnitus is very largely a symptom of this kind of damage in the auditory system. It is, therefore,
rather naive to expect any simple chemical compound, or drug, or surgical intervention, to result in a reversal of misfortune. But it is reasonable to expect that alterations in the CNS or sensory modalities of the body as a result of chemical and drug ingestion namely, caffeine, could potentiate or alleviate tinnitus.

II. Caffeine

Theobromine, theophylline and caffeine are three closely related alkaloids. Alkaloids are a diverse group of nitrogen-containing substances that are produced by plants and have potent effects on body function. Examples of alkaloid drugs are morphine, quinine, atropine and codeine. At least half the population of the world consumes tea (containing caffeine and small amounts of theophylline and theobromine), cocoa and chocolate (containing theobromine and some caffeine), coffee (the greatest source of caffeine) and cola-beverages (containing considerable amounts of caffeine). The caffeine content of a cup of coffee is (on average) 80mg, with an extreme range from about one half to twice that amount (Bunker and McWilliams, 1979; Burg, 1975; Dews, 1982; Gilbert, Marshman, Schweider and Berg, 1976; Ritchie, 1975). Naturally, the daily ingestion of even this amount of a potent alkaloid is bound to exert some pharmacological action.

Table II presents an overview of caffeine-containing beverages, medication products and their associated caffeine content. As indicated by Table II, caffeine is widely available in both beverages and medications. Individuals in everyday life can unknowingly ingest 250mg, an amount considered to be a large dose (Ritchie, 1975; Truitt, 1971).

In a series of experiments, Blount and Cox (1983) demonstrated that people were able to judge the dosage of caffeine they had consumed with some accuracy. In Experiment I, 40 subjects ingested capsules containing 0, 200, 400, or 600mg of caffeine. After a 90 minute delay, subjects made magnitude estimates of the caffeine ingested. Results showed linear trends between actual and judged caffeine levels. In a second experiment, 89 subjects tasted samples of coffee with concentrations corresponding to the actual levels. Blount and Cox (1983) concluded that subjects
Table II. A list of caffeine-containing beverages and medications which are regularly consumed. The corresponding milligrams (mg) of caffeine contained in each item is also reported\textsuperscript{1}.

<table>
<thead>
<tr>
<th>Source:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beverages:</td>
</tr>
<tr>
<td>Percolated coffee</td>
</tr>
<tr>
<td>Dripilated coffee</td>
</tr>
<tr>
<td>Brewed coffee</td>
</tr>
<tr>
<td>Instant coffee</td>
</tr>
<tr>
<td>Brewed black tea</td>
</tr>
<tr>
<td>Brewed green tea</td>
</tr>
<tr>
<td>Instant tea</td>
</tr>
<tr>
<td>Decaffeinated coffee</td>
</tr>
<tr>
<td>Cocoa</td>
</tr>
<tr>
<td>Cola Drinks</td>
</tr>
<tr>
<td>-Coca-cola</td>
</tr>
<tr>
<td>-Mellow Yellow</td>
</tr>
<tr>
<td>-TAB</td>
</tr>
<tr>
<td>-Pepsi-cola</td>
</tr>
<tr>
<td>Prescription Medications:</td>
</tr>
<tr>
<td>APCs (aspirin, phenacetin and caffeine)</td>
</tr>
<tr>
<td>Phenacetin</td>
</tr>
<tr>
<td>Migral</td>
</tr>
<tr>
<td>Over-the-Counter Medications:</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Anacin</td>
</tr>
<tr>
<td>Cope, Easy Menstruation</td>
</tr>
<tr>
<td>Pre-Mens</td>
</tr>
<tr>
<td>Excedrin</td>
</tr>
<tr>
<td>Nodoz</td>
</tr>
<tr>
<td>Alert</td>
</tr>
<tr>
<td>Many cold preparations</td>
</tr>
<tr>
<td>Many stimulants</td>
</tr>
</tbody>
</table>

1. The list of caffeine-containing products and the corresponding mgs. have been derived from the following references: Axelrod and Reichenthal, 1953; Bunker and McWilliams, 1979; Burg, 1975; Dimaio and Garriott, 1974; Gilbert, Marshman, Schweider and Berg, 1976; Truitt, 1971.

were able to scale caffeine concentrations accurately on the basis of gustatory and olfactory cues alone or on the basis of physiologic effects alone.

Coffee appears to be consumed for the bodily effects it provides and for its taste.

The major caffeine-related reasons people list for drinking coffee are "the lift of
energy it provides", "to stay awake", "to get started in the morning", and "its taste" (Blount and Cox, 1983). These subjective reports imply underlying perceptual abilities based upon flavour and bodily arousal.

Pharmacology. Caffeine, theophylline and theobromine are methylated xanthines. They are often spoken of as xanthine derivatives, methylxanthines, or merely xanthines. Their structural similarity to purine acid is believed to facilitate their use within the body (Carlson, 1986; Rall, 1980; Ritchie, 1975). The xanthines differ markedly in the intensity of their actions on various structures (Ritchie, 1975; Truitt, 1971). A large body of experimental data corroborates common experience and demonstrates that caffeine is a central nervous system (CNS) stimulant. Caffeine diffuses readily into the CNS (Axelrod and Riechenthal, 1953; Carlson, 1986; Rall, 1980; Ritchie, 1975) and cerebrospinal fluid levels reach half plasma levels within 4-8 minutes (Teschemacher, Herz, Hess and Noroczek, 1968). The cerebral cortex, medulla and spinal cord are reportedly affected sequentially in a dose-dependent manner (Ritchie, 1975). Cortical effects appear to be correlated with changes in alertness and enhanced performance on a number of psychomotor measures (Alhoun, 1971). These effects occur despite the vasoconstrictive action of caffeine on cerebral vessels.

In its cranial vasoconstrictive capacity (Truitt, 1971), caffeine has been shown to cause tachycardia (an increase in heart rate above normal; Bunker and McWillaims, 1979), extra systole (premature heart beat) and decreased ventricular fibrillation thresholds (Josephson and Stine, 1976). Caffeine affects a variety of systems within the body, serving as: a diuretic; a cardiac muscle stimulant; a CNS stimulant; and a smooth muscle relaxant (Carlson, 1986; Dews, 1982; Foote, Holmes, Pritchard, Hatcher and Mordes, 1978; Moyer, Tashnek, Miller, Snyder and Bowman, 1952; Rall, 1980; Ritchie, 1975; Shorofsky and Lamm, 1977). It has also been reported to: elevate blood glucose (Cheraskin and Ringsdorf, 1968) reduce the competence of the esophageal sphincter, resulting in reflux and symptoms of heartburn (Cohen and Booth, 1975); increase gastric acid secretion; and in large amounts, to be erosive to the gastric mucous membrane (Cohen and Booth, 1975). A positive
correlation has been shown between coffee-drinking and serum-lipid and lipidprotein levels (Bellet, Kerschbaum and Finke, 1973; Ferrent and Shane, 1968).

**Metabolism.** Caffeine is rapidly and essentially completely absorbed from the gastrointestinal tract within one hour (Rall, 1980). After oral ingestion, caffeine doses of 0.22mg/kg to 5.0mg/kg have been reported to reach their plasma peak by 30 minutes (Axelrod and Riechenthal, 1953), 45 minutes (Bonati, Latini, Galletti, Young, Tognoni and Garattini, 1982), 60 minutes (Robertson, Frolich, Carr, Watson, Hollifield, Shand and Oates, 1978; Robertson, Wade, Workman, Woosley and Oates, 1981), between 30 and 60 minutes (Karacon, Thornby, Anch, Booth, Williams and Salis, 1976; Sved, Hossie and McGilveray, 1976), and after 90 minutes (Blount and Cox, 1985; Patwardhan, Desmond, Johnson and Schenker, 1980). Substantial levels of caffeine have been reported as present in the blood by 15 minutes (Robertson et al., 1981; Robertson et al., 1978) and after 120 minutes (Bonati et al., 1981; Robertson et al., 1981; Robertson et al., 1978). There is evidence to suggest that caffeine does elicit a rise in glucose concentration (Bellet, Feinberg, Sandberg and Hrabayashi, 1968; Bellet, Kerschbaum and Aspe, 1965; Butcher and Sutherland, 1962; Naismith, Akinyanju, Szanto and Yudkin, 1970; Sasaki, Babitz and Kauer, 1981). Caffeine passes quickly into the CNS and into various tissues in approximate proportion to their water content; tissue response is proportional to caffeine content (Axelrod and Riechenthal, 1953).

Cellular metabolic effects of methylxanthines include increase of muscle lactic acid (a simple sugar that forms in the cells as the end-product of glucose metabolism in the absence of oxygen) stimulation of oxygen consumption peripherally, deprivation of oxygen tension, centrally, and muscle twitches and contractures in high concentrations (Bellet, Roman, DeCastro, Kim and Kerschbaum, 1967; Burg, 1975; Levi, 1967; Truitt, 1971). Miller, Stock and Stuart (1974) investigated the ability of caffeine to potentiate normal thermic responses and found that it caused a marked increase in peripheral tissue oxygen consumption.

Sutherland, Robinson and Butcher (1968) provided a biochemical explanation for some of the metabolic effects of caffeine and methylxanthines in
general. The enzyme phosphodiesterase, is necessary to convert cyclic 3'5'-AMP adenosine monophosphate (AMP) to 5'AMP. Methylxanthines inhibit phosphodiesterase-controlled breakdown of cyclic 3'5'-AMP which then prolongs its metabolic stimulating action in the cells. However, many of the effects of caffeine are probably mediated through antagonism of the adenosine (Fredholm, 1980) and adenine receptors (McCall, Millington and Wurtman, 1982), but some (at very high doses) derive their action from the inhibition of phosphodiesterase (Beavo, Rogers, Crofford, Hardman, Sutherland and Newman, 1970).

In addition, cyclic 3'5'-AMP has been implicated in the excitatory action of caffeine on gastric acid secretion. The primary effect is believed to result from stimulation of the gastric mesenteric (muscular layer of the intestine) and submucous nerve networks by caffeine (Cohen and Booth, 1975; Roth, Ivy and Atkinson, 1944). A secondary effect is believed to come from CNS stimulation via the cholinergic nerves. Caffeine has been shown to cause an increase in cyclic 3'5'-AMP, which appears to be involved in the stimulation of hydrogen ion secretion by the gastric mucous (Harris and Alonso, 1965; Harris, Nigon and Alonso, 1969).

**The Central Nervous System.** The xanthines can stimulate all parts of the CNS when high enough concentrations are attained; as noted, caffeine is the most potent in this respect. Doses of 50mg to 200mg of caffeine result in increased alertness, decreased drowsiness and lessened fatigue. Doses in the range of 200mg to 500mg may produce headache, tremors, nervousness and irritability. Sleep postponement and hyperesthesia (excessive sensitivity, especially of the skin), pleasant or unpleasant, may occur after excessive coffee intake (Dorfman and Jarvik, 1970; Goldstein, Warren and Kaizer, 1965; Karacan, Thornby, Anch, Booth and Williams, 1976; Ritchie, 1975; Truitt, 1971). Segregating subjects on the basis of personality showed that performance tests of verbal abilities were impaired by caffeine in introverted subjects but improved in extroverted subjects (Revelle, Humphreys, Simon and Gilliland, 1980). These personality types are thought to have basic differences in baseline arousal (Eysenck, 1967).

Goldstein conducted a series of studies (Goldstein and Kaizer, 1969; Goldstein,
Keizer and Warren, 1965; Goldstein, Keizer and Whitby, 1966) on caffeine's psychotropic effects. Caffeine has no demonstratable effect on objectively measured performance, although it made the subjects feel more alert and physically active. In some subjects, caffeine was reported to induce feelings of "nervousness" rather than alertness. Although dysphoric effects are reported, there are both qualitative and quantitative differences in response to caffeine which are related to the degree of habitual consumption (Goldstein, Kaizer and Whitby, 1969; Mitchel, Ross and Hurst, 1974). Heavy users appear to become less nervous and have fewer headaches with increasing doses of caffeine while, in the abstainers, caffeine produces nervousness and gastrointestinal complaints.

The development of caffeine-withdrawal headache is well documented (Burg, 1975; Dews, 1982; Dreisbach and Pfeiffer, 1943; Goldstein and Kaizer, 1969; Harrie, 1970; Miller, 1960; Shorofsky and Lamm, 1977). Goldstein and Kaizer (1969) reported on caffeine withdrawal in a group of home-employed women in the natural surroundings of their homes. Moderate to heavy coffee drinkers described a set of reactions in addition to headache: irritability, nervousness, fatigue, tiredness and an inability to work effectively and to sleep. Blood chemistry studies indicated that serum calcium levels fell (essential for metabolic processes, including nerve function, muscle contraction and blood clotting) and serum phosphorous rose.

Hypertensive headaches have been relieved with the intravenous administration of caffeine. It is suggested that constriction of cerebral arteries decreases the brain swelling caused by hypertension (Harrie, 1970; Shorofsky and Lamm, 1977). Harrie (1970) administered caffeine during the first or prodomal stage of the four phases of migraine headache and found that it blocked further headache development in some subjects.

An intact CNS and its interaction with visceral, olfactory, visual and auditory modalities serves as the basis for our being able to survive and function within the environment. Alterations in either component - CNS or sensory - by the ingestion of food, beverages and chemicals places our internal environment at a disadvantage. The use of dietary control and the maintenance of a careful monitoring system for ingested...
substances by some people may have an effect on their tinnitus. The effect of drug ingestion has to be considered as one of the major agents producing or potentiating tinnitus. Modification of the potentiation through a drug-elimination programme becomes, therefore, a powerful therapeutic tool.

Research in the area of auditory function has been alien to most pharmacologists. Yet, some problems in audition by their nature should have attracted them. For instance, the problem of ototoxicity and the study of drugs used empirically by otolaryngologists (for example, vasodilators) by definition belong to pharmacology, yet have received little or no attention from that science. Little progress has been made toward understanding the mechanisms underlying the actions of either ototoxic drugs or ototherapeutic drugs, and especially their relationship with auditory dysfunctions such as tinnitus. The dearth of empirical, scientific evidence concerning drug potentiation of tinnitus is borne out in the following section of the introduction.

III. Caffeine and Tinnitus

In a review of the status of tinnitus in 1982, McFadden concluded that, although caffeine was frequently mentioned for its ability to produce or exacerbate tinnitus, no systematic studies were found to support these statements. Researchers have commented on the role diet plays in tinnitus management and noted that in their experience coffee, tea, tonic water, red wine, grain-based spirits, cheese and chocolate have been the most common dietary sources or exacerbatory factors of tinnitus (Brown et al., 1981; DeBartolo, 1989; Evans, 1981; Goodey, 1981, 1986; Lechtenberg and Shulman, 1981; Manahan, 1988; Meyerhoff and Mickey, 1988; Pulec, 1979; Pulec et al., 1978; Schleuning, 1981). But beyond comments of this nature, there is no scientific evidence relating to causal links between diet and tinnitus. Seven years later, Manahan in 1988 re-confirmed the statement made by McFadden in 1981 - research has yet to confirm the relationship between tinnitus and caffeine intake.

I have identified sixteen articles which mention or discuss caffeine in relation to tinnitus. A list of the researchers and their corresponding assumptions and
statements made concerning the relationship between caffeine and tinnitus are listed in Table III. Brief details as to data collection and subject population have also been recorded. The reader is referred to Table III for a general overview of the current status of the literature within this field.

It can be seen from Table III that there are three main bases for the caffeine-tinnitus assumption: a) no evidence; b) anecdotal and patient self-report; and c) evidence from other authors. Based on patient self-report and anecdotal evidence, Goodey (1986) and Saunders (1986) suggested that the avoidance of nerve stimulants, including excessive coffee and smoking, may be helpful to tinnitus. Manahan (1988) and Schleuning (1981) report having seen a number of patients where the cessation of coffee, tea and cola beverages resolved tinnitus.

Malatesta et al. (1980) cite Pulec (1979) and Meyerhoff and Mickey (1988) cite Meyerhoff and Cooper (1980) as the reference source for the following statements: "In accord with published data (Pulec, 1979), the subject reported greater awareness of tinnitus following consumption of coffee, cola and other beverages containing caffeine" (Malatesta et al., 1980: p. 315) and, "Although many therapies now exist for nonvibratory tinnitus, few are definitive. Current management includes avoidance of caffeine, nicotine, and salt: factors that are known to have an adverse effect on the symptom of tinnitus (Meyerhoff and Cooper, 1980)" (Meyerhoff and Mickey, 1988: p. 602). Reading Pulec (1979) and also Pulec, Hodell and Anthony (1978) reveals that there is no empirical evidence or anecdotal reports published by these authors which substantiate the claims of Malatesta et al. (1980). Pulec (1979) says: "In addition to mechanical causes for subjective tinnitus within the cochlea, mechanisms acting directly upon the neuro-receptors and the nerves themselves can produce tinnitus. These include...and the effects of certain drugs, e.g., aspirin, caffeine, nicotine and aminoglycosides" (p. 21). Pulec et al. (1978) proposes the inclusion of a subjective assessment measure for tinnitus which should include information regarding the intake of caffeine.

Meyerhoff and Mickey's (1988) reference source, that is, Meyerhoff and Cooper (1980) do not refer to caffeine, coffee, tea, cola or caffeine-containing food and
Table III. A list of the assumptions (A) and findings (F), self-report and anecdotal evidence for the relationship between caffeine and tinnitus. The corresponding author and brief description of the research is also given.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Experimental Research</th>
<th>Form of Data Collection</th>
<th>Number of Subjects:</th>
<th>Assumption (A) or Finding (F):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al. (1981)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>A = Caffeine can produce tinnitus by acting on the CNS.</td>
</tr>
<tr>
<td>DeBartolo (1989)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>A = Basic diet factors that are good for the heart are good for tinnitus. Caffeine should be reduced, at best avoided.</td>
</tr>
<tr>
<td>Evans (1981)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>A = Caffeine exacerbates tinnitus.</td>
</tr>
<tr>
<td>Goodey (1981)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>A = Caffeine aggravates tinnitus.</td>
</tr>
<tr>
<td>Goodey (1986)</td>
<td>No</td>
<td>Anecdotal</td>
<td>Not stated</td>
<td>F = Tinnitus sufferers should avoid the use of nerve stimulants, including caffeine.</td>
</tr>
<tr>
<td>Lechtenberg and Shulman (1984)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>A = Drug reactions (caffeine) have been implicated in cases of subjective tinnitus.</td>
</tr>
<tr>
<td>McFadden (1982)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>A = This agent is frequently mentioned for its ability to produce or exacerbate tinnitus, but no studies have been found in support of caffeine's action on tinnitus.</td>
</tr>
<tr>
<td>Malatesta et al. (1980)</td>
<td>Single case study</td>
<td>Tinnitus intensity after 2 cups of brewed coffee</td>
<td>One</td>
<td>F = Consumption of coffee was associated with a systematic increase in judged tinnitus intensity.</td>
</tr>
<tr>
<td>Manahan (1988)</td>
<td>No</td>
<td>Patient self-report</td>
<td>Not stated</td>
<td>F = Avoidance of caffeine alleviates symptoms of tinnitus although there is no research to confirm this effect.</td>
</tr>
<tr>
<td>Meynholz and Mickey (1988)</td>
<td>No</td>
<td>Evidence from other authors</td>
<td>None</td>
<td>A = Factors that are known to have an adverse effect on tinnitus - caffeine are incorporated as current management techniques.</td>
</tr>
<tr>
<td>Pulec (1979)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>A = It is possible that caffeine aggravates tinnitus. Ingestion of caffeine should be avoided because of caffeine's vasoconstrictive effect.</td>
</tr>
<tr>
<td>Pulec et al. (1978)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>A = Information concerning factors known to aggravate tinnitus, for example, caffeine, smoking and noise exposure should be included in the otolaryngologist's assessment.</td>
</tr>
<tr>
<td>Saunders (1986)</td>
<td>No</td>
<td>Anecdotal</td>
<td>Not stated</td>
<td>F = Caffeine can trigger tinnitus.</td>
</tr>
<tr>
<td>Schleuning (1981)</td>
<td>No</td>
<td>Patient self-report</td>
<td>Not stated</td>
<td>F = Caffeine is a frequent contributor to the severity and degree of tinnitus. Tinnitus was remarkably reduced with the cessation of coffee, tea, and cola.</td>
</tr>
<tr>
<td>Swaine (1988)</td>
<td>No</td>
<td>None</td>
<td>None</td>
<td>A = Avoidance of carbonated beverages and chocolate may minimize symptoms of auditory diseases including tinnitus.</td>
</tr>
</tbody>
</table>
beverages. Statements like: "Additional history should include information regarding aural discharge, head trauma, noise exposure, or exposure to ototoxic drugs" (p. 1864) appear in the article. The use of vitamins, local anaesthetics and medication aimed at increasing blood flow are also discussed but there is no reference to the avoidance of caffeine as a current management technique for tinnitus.

Similarly, Lechtenberg and Shulman (1984) cite Goodey (1981) and Schleuning (1981) as the reference source for the following statements: "Diabetes mellitus, thyroid disease...drug reactions (aspirin, quinine, aminoglycosides, antibiotics, caffeine, and tricyclic antidepressants), poisons...have all been implicated in cases of subjective tinnitus (Goodey, 1981; Schleuning, 1981)", (p. 720). But there is no empirical, patient self-report or anecdotal evidence given by Goodey (1981) to substantiate this statement: "Avoid use of nerve stimulants, including excessive coffee and smoking", (p. 1). Schleuning (1981) states that: "We've all noted that caffeine itself is a frequent contributor to the severity and degree of tinnitus. Most of us have had the experience of having tinnitus which has resolved remarkably with the cessation of coffee and coke and tea, and cigarette smoking as well" (p. 99). Had Lechtenberg and Shulman (1984) been referring to the anecdotal reports in Goodey (1986), there would at least have been some basis for their statement.

It is apparent from the literature and Table III that the unproven assumptions underlying the caffeine and tinnitus relationship are thought of as fact. Malatesta et al. (1980) appears to be the only example of experimental work within this field at the current time. Malatesta et al. assessed the effect of brewed coffee ingested by one male subject on the intensity of his unilateral tinnitus in accordance with the published data of Pulec (1979) which apparently shows a greater awareness of tinnitus after caffeine-containing beverages. The subject was asked to consume approximately 380ml (that is, two cups) of brewed coffee (an amount reported to be consumed consistently by the subject at breakfast) and intensity measurements were recorded immediately following and 45 minutes after consumption. Subsequent to these procedures, the subject was asked to consume a further 190ml of coffee and measurements were again obtained. Results indicated that the consumption of brewed coffee was associated with a
systematic increase in tinnitus intensity peaking at approximately 45 minutes which then returned to normal within 90 minutes. An increase in tinnitus intensity was reinstated with additional consumption of coffee.

The strength or true nature of the relationship between caffeine and tinnitus is difficult to ascertain from Malatesta et al.'s (1980) study due to a number of methodological flaws. Table IV below presents a brief critical description of Malatesta et al.'s research and the corresponding resolutions in the present study.

Overall, it is evident from the literature that no authors have proposed or discussed specific sites or mechanisms of action by which caffeine potentiates tinnitus. With regard to this criticism, the present author would like to propose three models which account for the possible effect of caffeine in the CNS and the inner ear, and hence, on tinnitus. An understanding of inner ear metabolism and oxygen distribution is central to the three models and a general overview of these concepts will be presented as introductory material.

III. Mechanisms of Caffeine Action which Potentiate Tinnitus

In contrast to the number of different forms the sensation takes, there must be a limited number of possible types of tinnitus source. At each stage of the auditory pathway one can only postulate sources of spontaneous activity which are:

1. appropriate to the physiology of that stage, and
2. can be affected by caffeine.

Overall, it is evident from the literature that no authors have proposed or discussed specific sites or mechanisms of action by which caffeine might potentiate or alleviate tinnitus. Hence, I propose three models which account for the possible effect of caffeine on the CNS and the inner ear, and hence, on tinnitus. An understanding of inner ear metabolism and oxygen distribution is central to the three models and a general overview of these concepts will be presented as introductory material.
**Auditory Metabolism.** The functional existence of a living organism is based on the ability of its constituent cells to incorporate simple chemical compounds and transform them into complex molecules necessary for cellular structure and function. The composition of fluids bathing tissue cells must be controlled to provide the body with a degree of functional freedom from the variability of the external environment. It is within these fluids and cells that normal metabolism takes place. Therefore, the internal environment of the body of a cell is maintained at the expense of and dependent upon metabolic energy. Alterations in metabolism result in aberrant normal function.

In humans (as in all higher multi-cellular organisms) metabolism is basically coordinated by two major systems, the endocrine system and the autonomic nervous system (ANS). Hormones and related neural transmitting substances either stimulate or inhibit specific metabolic activities in tissues and organs by acting on cell membranes, enzymes or on genes, directly (Coleman, 1974; Hardman, 1974; Rasmussen, 1974). In these instances the hormone or neural transmitter ( the "first" chemical messenger) transforms information across the cell membrane to cyclic 3'5'-Adenosine Monophosphate (cyclic 3'5'-AMP).

When the circulating hormone (first messenger), released either from an endocrine gland or a neural transmitting substance from a nerve ending, interacts with its receptor on the plasma membrane of the target cell, there is an increase (or in some cases a decrease) in the activity of the enzyme adenylate cyclase. Cyclic 3'5'-AMP has been designated as a "second" messenger and is formed from adenosine triphosphate (ATP) by a reaction catalysed by magnesium and requiring the enzyme adenylate cyclase (Carlson, 1986; Green, 1987). Alterations in this reaction lead to changes in the rate of cyclic 3'5'-AMP synthesis which, in turn, may alter enzyme activity, ion transport and numerous responses (Ahlstromm, Thalmann, Thalmann and Ise, 1975; Coleman, 1974; Hardman, 1974; Rasmussen, 1974). Drugs that inhibit the activity of ATP or the enzyme adenylate cyclase allow cyclic 3'5'-AMP to accumulate and keep the ion gates open for a longer-than-usual time (Hoffer, Siggins, Oliver and Bloom, 1972).

The process of transducing acoustic stimuli into neural excitation is an active
one and requires metabolic energy. The inner ear tissues rely primarily on oxidative tissue which enhances the metabolic energy provided by cyclic 3'5'-AMP for the ionic movements, maintenance of the electrical potential and cell survival. The stria vascularis is the most metabolically active inner ear tissue and represents one of the most metabolically active tissues in the body. It is highly endowed with respiratory enzymes and requires a large oxygen ($O_2$) input and a continuous amount of energy to help maintain the ionic and electrical environment of the inner ear (Bosher, Smith and Warren, 1973; Matschinsky and Thalmann, 1970). The organ of Corti on the other hand, has sufficient glycolytic metabolism with abundant carbohydrate stores and lower energy requirements and, therefore, depends less upon $O_2$ (Bosher, Smith and Warren, 1973; Kaku, Farmer and Hudson, 1973; Matschinsky and Thalmann, 1970; Naftalin, 1976).

ATP provides energy for all active transport across all membranes. The enzyme is found where active transport of electrolytes occur. This enzyme is present on the endolymphatic layer of Reissner's Membrane, abundant in the stria vascularis and spiral ligament, and on the outer surface of the cells of the organ of Corti (Naftalin, 1976; Nakai and Hilding, 1967; Rauch, 1970; Spector and Lucente, 1974; Thalmann, 1971; von Borstel, Wurtman and Conlay, 1982).

The Role Of Oxygen in Auditory Metabolism. The entire auditory system is dependent upon oxidative metabolism and deprivation of oxygen, absolute or effective, will result in aberrations of auditory perception (Hawkins, 1973; Johnson, 1973; Johnson and Hawkins, 1972; Lawrence and Nuttal, 1972; Lawrence, Nuttall and Burgio, 1975; Mishray and Hildreth, 1958; Spector and Carr, 1977; Spector and Lucente, 1974; Thalmann, Matschinsky and Thalmann, 1970; Wever, Bray and Lawrence, 1974). Capillary changes and alterations in inner ear $O_2$ tension have been identified with aging, vascular disorders, and disorders of systemic metabolism, inflammation, toxins and noise exposure (Thalmann, 1971; Thalmann, Kusakari and Myoshi, 1973). These alterations include vasoconstriction, capillary degeneration which affects inner ear blood and $O_2$ supply adversely. Changes in the $O_2$-carrying capacity of the blood causes hypoxia (a condition in which the tissues of the body
receive inadequate amounts of O$_2$) to the end-organ (Gelfand, 1981; Lawrence and Nuttall, 1972; Lawrence Nuttall and Burgio, 1975).

Excellent studies of the vascularisation of the inner ear have been made by Smith (1973) and Axelsson (1968). The reader interested in greater detail should consult these references, particularly Axelsson (1968). Blood is supplied to the inner ear by the labyrinthine artery. As it reaches the inner ear, the labyrinthine artery supplies separate branches to the vestibule and to the cochlea. The second branch of the cochlea artery supplies blood to the capillaries in the spiral border below the basilar membrane and in the area of the inner hair cells and tunnel of Corti. Although a blood vessel runs along the basilar membrane, the main supply of blood-O$_2$ to the cochlea is via the stria vascularis (Guth, Norris and Bobbin, 1976).

With hypoxia, O$_2$ tension in the tunnel of Corti decreases, followed in sequence by a decrease in O$_2$ tension in the cochlea duct, a decrease in the endolymphatic potassium-sodium ratio, and diminished cochlea microphonics. The stria vascularis, due to almost total dependence upon oxidative metabolism, high rate of energy utilisation, and low O$_2$ reserve is affected earlier in hypoxia than the organ of Corti with its efficient anaerobic energy generation and low rate of energy utilisation. The half-time decay for ATP in the stria vascularis is approximately one minute, as compared to 30 minutes in the organ of Corti (Lawrence, Nuttall and Burgio, 1975; Thalmann, 1971; Thalmann, Kusakari and Miyoshi, 1973; Wilmott and Henry, 1976).

Further research has shown that during O$_2$ deprivation the auditory cortex response to acoustic stimuli is the first electrical response to decay, followed by the response at the inferior colliculus (Kusakari and Thalmann, 1976). It has also been noted that during hypoxia, spontaneous and evoked responses to physiologic and electrical stimuli activity in the auditory system are abolished, while nerve fibres remain excitable and able to propagate impulses (Guth, Norris and Bobbin, 1976; Honrubia, Strelioff and Sitko, 1976; Kusakari and Thalmann, 1976; Lawrence and Nuttall, 1972). It is possible that the impulses propagated by the excited nerve fibres may result in, add to, or potentiate tinnitus.

This suggests that at the cochlea level, O$_2$ deprivation initially affects
the electrical transmission at the hair cell-neuron junction. Johnstone (1975) has shown that in the nerve terminals the dendrites under the hair cells are very oxygen sensitive. Diagnostic and therapeutic applications of such findings are frequent as many processes interfere with \( O_2 \) supply and utilisation. The reversible hearing loss seen in aspirin toxicity may be due to aspirin uncoupling oxidative phosphorylation (McCabe and Dey, 1975; Quick, 1980).

**Caffeine, \( O_2 \), Auditory Metabolism and Tinnitus.** The anatomical site(s) of drugs producing or potentiating tinnitus is not known. However, the circumstantial evidence appears to be substantially in favour of most of these drugs producing or potentiating tinnitus by acting within the central nervous system (CNS); alterations in the CNS can in turn result in changes within the peripheral environment of the inner ear. Experimental evidence indicates that drugs which affect biogenic amine transmission in the CNS also affect seizure activity (Jobe, 1981). It is possible that proconvulsant drugs (for example, caffeine) facilitate the development of a sensory seizure (that is, tinnitus) within the auditory pathway by enhancing the excitability of neurons that are already predisposed to abnormal activity because of pre-existing cochlea deficit. The use of anaesthetics and anticonvulsant drugs to suppress or minimise symptoms of tinnitus lends weight to this possibility.

Local anaesthetics, especially derivatives of para-amino benzoic acid (for example, procaine) and the aminoacyl group (for example, lignocaine and tocalaine hydrochloride) have been advocated for use due to their ability to decrease sensory activity at a central level when administered systematically. Anticonvulsive agents such as Tegretol, Mysoline and Premidone have also been used with varying success (Israel, Connelly, McTigue, Brummet and Brown, 1982; Melding and Goodey, 1979; Melding, Goodey and Thorne, 1978; Meyerhoff and Mickey, 1988; Shea, 1984; Shea, Emmett and Mays, 1981; Shea and Harrell, 1978).

Brown, Penny, Henley, Hodges, Kupetz, Glenn and Jobe (1981) listed caffeine as a CNS stimulant and as a central vasoconstrictor, affecting biogenic amines directly or through an effect on folic acid metabolism. By the very nature of this classification, it is probable that in addition to the facilitatory, sensory seizure action of caffeine, it
may produce or potentiate tinnitus through alterations in the cochlea or CNS circulation (Snow and Suga, 1975). Moyer, Tashnek, Millar, Snyder and Bowan (1952) and Weschler, Kleiss and Katy (1950) demonstrated a marked decrease in cerebral blood flow and O2 tension in the brain after administering 200mg and 400mg, respectively, of caffeine. Even if tinnitus is not primarily the result of sensory seizures or abnormal circulation, changes induced in these two factors by caffeine may potentiate or add to the tinnitus. There is evidence which suggests that caffeine can alter these two factors by impacting on: a) the metabolic energy in tissue by changing cyclic 3'5'-AMP through alterations in ATP or glucose concentrations; b) the production of ATP necessary for cyclic 3'5'-AMP to transduce acoustical stimuli by acting on a cyclic 3'5'-AMP precursor, adenine; and c) the distribution of O2 in the CNS by antagonising adenosine.

The Effect of Caffeine on Tinnitus: Model I, Mechanism I.

Site of Operation: Auditory nerve fibres and tissue of the inner ear.

Chemicals Involved: Cyclic 3'5'-AMP, ATP and ATPase.

Graphical Presentation of Model I: Page 30.

Sutherland, Robinson and Butcher (1968) and Robinson, Butcher and Sutherland (1971) have revealed a biochemical mechanism that may underlie certain of the metabolic and physiologic effects of methylxanthines, including caffeine. Having first established the critical role of cyclic 3'5'-AMP in promoting glycogenesis in certain tissues (including the inner ear), they showed that caffeine was a competitive inhibitor of at least certain forms of cyclic nucleotide phosphodiesterase (ATPase), the enzyme that catalyses the conversion of cyclic 3'5'-AMP to 5'-AMP (Butcher and Sutherland, 1962; Galli and Spagnuolo, 1975).

In vitro investigations have shown caffeine to be an inhibitor of ATPase (Beavo et al., 1970; Butcher and Sutherland, 1962; Sutherland and Rall, 1958) thus producing a rise in cyclic 3'5'-AMP by blocking its conversion to 5'-AMP. Since cyclic 3'5'-AMP has been implicated in altering post-synaptic activity (Hoffer, Siggins, Oliver and Bloom, 1972), caffeine's effect on reticular neurones might
operate through a cyclic 3’5’-AMP mechanism. Cyclic 3’5’-AMP concentrations are thus elevated in CNS and peripheral tissue requiring cyclic 3’5’-AMP for metabolism following exposure to caffeine. As previously discussed, this includes tissue within the inner ear. Furthermore, transduction of acoustic stimuli along the auditory nerve requires metabolic energy - cyclic 3’5’-AMP. Accumulation of cyclic 3’5’-AMP prolongs its metabolic, stimulating action within the tissue cells of the auditory nerve and may result in aberrant neural excitation either in the absence of an external sound or after transduction of acoustic stimuli while the cells remain in a state of stimulation. This neural excitation may add to or potentiate tinnitus.

The underlying premise of this mechanism is that there must be a biochemical imbalance in the inner ear or auditory pathway resulting from or affecting cyclic 3’5’-AMP. Caffeine has been demonstrated to inhibit phosphodiesterase at doses well in excess of the caffeine level normally ingested via coffee consumption. However, it is probable that the action of caffeine may well be enhanced within a biochemically sensitive environment and hence, the level of caffeine required to inhibit phosphodiesterase is reduced.

In addition to the direct inhibiting action of caffeine on ATP and ATPase and hence cyclic 3’5’-AMP, caffeine may also act indirectly on ATP through: a) glucose concentrations in the inner ear or; b) a cyclic 3’5’-AMP precursor, adenine.

**The Effect of Caffeine on Tinnitus: Model I, Mechanism II.**

**Site of Operation:** Inner ear, cochlea.

**Chemicals Involved:** Cyclic 3’5’-AMP, ATP and Glucose.

**Graphical Presentation Of Model I:** Page 30.

Glucose is stored in the inner ear in ATP (required for the change of cyclic 3’5’-AMP to 5’-AMP) and it is believed that it is a source of metabolic energy. It is proposed that stimulation of glucose by caffeine results in a hypermetabolic environment within the inner ear. In this case, the metabolic stimulating actions in the cells are prolonged and the transduction of acoustic stimuli may be aberrant or sound may be perceived in the absence of external stimuli. Weight is given to this
proposal by the research which has shown that caffeine increases blood glucose concentration (Bellet, Feinberg, Sandberg and Hirabayashi, 1968; Bellet, Kerschbaum and Aspe, 1965; Butcher and Sutherland, 1962; Nal'smith, Akinyanju, Szanto and Yudkin, 1970; Sasaki, Babitz and Kauer, 1981; Sutherland, Robinson and Butcher, 1968).

Research by Bellet, Kerschbaum and Aspe (1965) and Bellet, Feinberg, Sandberg and Hirabayashi (1968) has shown a prolonged rise in serum free fatty acids and blood glucose concentration after oral ingestion of 1.5mg/kg to 5mg/kg of caffeine. Since Butcher and Sutherland (1962) demonstrated that methylxanthines block the inactivation of cyclic 3'5'-AMP, a ribonucleotide of importance in glycogenesis, the effects of coffee and caffeine on the metabolism of glucose in human subjects has been of interest.

Few quantitative studies have so far been reported concerning the role of glucose in the inner ear and its relationship to ATP and cyclic 3'5'-AMP. A study of these substances promises to be of interest: a) because of the high levels of glycogen in the organ of Corti and a possible role in the regulation of glycogen and cyclic 3'5'-AMP metabolism (Matschinsky and Thalmann, 1970); b) because of glucose's potential role in permeability and transport phenomena in the stria vascularis, which by general consensus is thought to be the primary structure responsible for the maintenance of the unique ionic composition of the endolymph, and the generation of the endolymphatic potential (Ahlstrom, Thalmann, Thalmann and Ise, 1975; Johnstone, 1971); and, c) because it is conceivable that glucose might be involved in cochlea transduction (Bitensky, Gorman and Miller, 1971), in analogy to the reaction of photoreceptors in the retina to light. It is now well established that the responses to light in retinal cells involves cyclic 3'5'-AMP (Bitensky et al., 1971; Marx, 1972; Perkins and Moore, 1973).

Sasaki et al. (1981) examined changes in activity in the guinea pig auditory pathway using an autoradiographic method of functional brain mapping after short-term and long-term cochlea ablations which can, in humans, initiate the occurrence of tinnitus. There was an increase in 14C-2-deoxyglucose uptake in all
Model I: The effect of caffeine on the synthesis of cyclic 3'5'-AMP (inner ear metabolism) through inhibition of ATPase and the effect of caffeine on inner ear glucose concentration and spontaneous neural activity.

Mechanism I: Caffeine inhibits ATPase.
Caffeine prolongs cyclic 3'5'-AMP stimulating metabolic cell action by inhibiting phosphodiesterase (ATPase). Due to excessive metabolic energy, the ion gates are opened for a longer-than-usual time and the stimulatory action of the cell is prolonged. Because of the open, stimulatory action of the cell within the nerve fibres, sensations interpreted as sounds may be perceived in the absence of, or in addition to external stimuli. These sensations may potentiate the symptoms of tinnitus.

Mechanism II:
Increase in glucose due to increase in blood concentration of caffeine.

Caffeine orally ingested
Brain
Auditory Cortex

Mechanism II:
Transduction of acoustic stimuli into neural excitation requires metabolic energy, cyclic 3'5'-AMP.

Cochlea:
Increase in glucose due to increase in blood concentration of caffeine.

Inner Ear

It is possible that Mechanism II impacts on Mechanism I. Glucose is stored in ATP and increases in the amount of glucose as a result of caffeine may alter the status of ATP and hence, the formation of cyclic 3'5'-AMP.

It is also possible that Mechanism II impacts on Mechanism I. Glucose is stored in ATP and increases in the amount of glucose as a result of caffeine may alter the status of ATP and hence, the formation of cyclic 3'5'-AMP.
regions of the pathway. Based on this data, Sasaki et al. (1981) suggested that increased glucose uptake may relate to the appearance of spontaneous neuronal activity along the central auditory pathway and that such aberrant activity occurs in response to cochlea injury but independently of acoustic stimulation. Hence, ingestion of a glucose stimulant - caffeine - may cause a greater change or aberration in spontaneous neuronal activity in the symptoms of tinnitus.

The Effect of Caffeine on Tinnitus: Model II.

Site of Operation: Blood-Brain Barrier, CNS.

Chemicals Involved: Cyclic 3'5'-AMP, ATP and Adenine.

Graphical Presentation of Model II: Page 33.

Drugs acting on the brain must pass through the cerebral capillary endothelial cells, which make up the Blood-Brain Barrier (BBB). Like metabolic substrates, drugs may enter and leave the brain by simple diffusion, facilitated diffusion or active transport. A high degree of lipid solubility predicts ready passage into the brain by simple diffusion. Caffeine is thought to enter the brain readily because of its high degree of lipid solubility. Rapoport (1976) found that caffeine has an olive-oil:water partition coefficient of 1:10 and attributed its penetration into the brain and circulatory system to this high degree of lipid solubility.

Important substrates for brain metabolism which are not very lipid soluble (for example, adenine) may nonetheless enter the brain by facilitated diffusion if transport carriers for them happen to exist - presumably the transport carriers are located within the cerebral endothelial cells. Research shows that caffeine enters the brain by both a carrier-mediated transport mechanism and by simple diffusion (McCall, Millington and Wurtman, 1982; Rapoport, 1976; Robertson et al. 1978). Further research has shown that the macromolecule which mediates its transport may be the same as the adenine carrier, inasmuch as caffeine competes with adenine for brain uptake (Robertson, Johnson, Robertson, Niles, Shand and Oates, 1979; McCall et al., 1982). Thus, caffeine can restrict the entry of adenine into the brain.

Changing blood adenine levels or competition by other compounds for the same
transport carrier would be expected to influence the transport of adenine into the brain and possibly transport of other purines (nitrogen-containing compound with a two-ring molecular structure). This interpretation fits with research which has shown that adenine loading produces increases in ATP pools from which cyclic 3'5'-AMP is generated within the brain. Decreasing adenine transport with the aid of caffeine could then alter the formation of cyclic 3'5'-AMP for which adenine may act as a precursor. Alterations in cyclic 3'5'-AMP would alter its synthesis to 5'-AMP and hence, the transduction of acoustic stimuli. To the author's knowledge, research thus far, has not established how limited adenine brain uptake alters cyclic 3'5'-AMP synthesis. Speculating on the possible effects of alterations in cyclic 3'5'-AMP due to limited adenine brain uptake, it is hypothesised that one or other of the following statements are true:

1. Causes excitation of tissue cells within the auditory nerve which is interpreted as a sound(s) in the absence of an external stimuli. Accumulation of cyclic 3'5'-AMP prolongs its metabolic, stimulating action within the tissue cells of the auditory nerve and may result in aberrant neural excitation either in the absence of an external sound or after transduction of acoustic stimuli while the cells remain in a state of stimulation. This neural excitation may add to or potentiate tinnitus. This hypothesis is dependent on the synthesis of cyclic 3'5'-AMP being rapidly increased as a result of limited adenine brain uptake, or

2. Decreases neural excitation in the cochlea. Based on the work of Kiang et al. (1976) it is possible that reduced cochlea activity may result in the generation of sound sensations in the absence of external stimuli. It is also plausible that a decay in the effect of caffeine will release the suppression of cochlea activity. Response by the cochlea nerve to this release may be to engage in spontaneous hyperactivity corresponding to the central pools of neuronal hyperactivity found with trigeminal neuralgia (Anderson et al., 1971). This hypothesis is dependent on the synthesis of cyclic 3'5'-AMP being rapidly decreased as a result of limited adenine brain uptake.

Whilst research has shown that caffeine can affect the metabolic chemistry of body tissue, further investigations have revealed that caffeine has the ability to alter
Model II: The effect of caffeine on the brain uptake of adenine, a precursor for the synthesis of cyclic 3'5'-AMP.

**Mechanism I:** Altered formation of cyclic 3'5'-AMP necessary for metabolic energy and the transduction of acoustic stimuli. Too much metabolic energy induces a hypermetabolic state where sound sensations may be perceived in addition to, or in the absence of external stimuli. These sound sensations may potentiate tinnitus.

**Mechanism II:** Limited adenine in the brain - precursor for the synthesis of cyclic 3'5'-AMP. Limited adenine may result in decreased cyclic 3'5'-AMP and hence, decreased metabolic energy. Consequently, there is depressed activity in the cochlear nerve which may result in spontaneous neural activity in higher centres.

**Blood-Brain Barrier**

- Caffeine
- Adenine
- Transport Carriers
- Auditory Nerve Fibres
- Acoustic Stimuli
- Inner Ear
- External Stimuli
the distribution of O₂, centrally.

The Effect of Caffeine on Tinnitus: Model III.
Site of Operation: Organ of Corti, Stria Vascularis and CNS.
Chemicals Involved: Adenosine and O₂.

Graphical Presentation of Model IV: Page 36.

It has been observed that caffeine and theophylline, added for the purpose of enhancing cyclic 3'5'-AMP accumulation in brain slices subjected to electrical stimulation, produced marked inhibition of a nucleotide (Kakauichi, Rall and McIlwain, 1969). Subsequently, this inhibition was found to be due to competitive antagonism by caffeine on the actions of adenosine released from brain cells.

Adenosine dilates blood vessels particularly in the coronary and cerebral circulation and slows the rate of discharge of a variety of neurons in the CNS. In addition, it strongly reduces the release of norepinephrine (a hormone released by the medulla of the adrenal glands and also released as a neurotransmitter by sympathetic nerve endings; among its many actions are constriction of small blood vessels leading to an increase in blood pressure) and in some cases probably inhibits the release of excitatory neurotransmitters in the CNS (von Borstel et al., 1982). Adenosine can also augment accumulation of cyclic 3'5'-AMP in brain tissue (von Borstel et al., 1982). Depending on the type of cell involved, activation of receptors for adenosine can lead to either stimulation or inhibition of cyclic 3'5'-AMP synthesis (Ritchie, 1975). Thus, the anti-adenosine affects of methylxanthines must be considered seriously even in those instances where a regulatory function for adenosine has yet to be established.

Adenosine's pharmacological effects can be blocked by caffeine at concentrations likely to occur in plasma after the consumption of coffee or tea (von Borstel et al., 1982). The reduction of basal plasma adenosine levels after caffeine consumption suggests that this drug might modify the physiologic disposition of adenosine in blocking the binding of adenosine to brain membranes (von Borstel et al., 1982) and antagonise the ability of adenosine to activate adenylate cyclase (Bloom, 1980; Rall, 1980; ).
Adenosine is produced in the heart and vasculature in response to hypoxia and may act to attenuate the state of oxygen deprivation by inducing vasodilation (Berne, 1980; Bloom, 1980; Hunter, Barrera, Dohanich and Dunlap, 1990; Truitt, 1971). Adenosine's secondary response by the heart to hypoxia is further inhibited by caffeine because of its circulatory distribution. Deprivation of O₂ by caffeine may result in a state of sensory epilepsy within the inner ear, producing or exacerbating tinnitus through alterations in cochlea function or CNS circulation because of pre-existing cochlea damage (Brown et al., 1981; Melding et al., 1978; Shea, 1983; Shea and Emmett, 1983; Shea and Harrell, 1978).

Weight is given to this line of reasoning by research which has shown that anticonvulsant medications (for example, lignocaine, xylocaine and local anaesthetics) suppress tinnitus as they do to the epileptic state (Israel et al., 1982; Shea, 1984; Shea and Emmett, 1983; Shea and Harrell, 1978). It is believed that these drug agents have a blocking action on abnormal spontaneous hyperactivity in the CNS (Israel et al., 1982).

The potent effect of caffeine as an antagoniser/inhibitor of adenosine is further borne out by the research which has shown that the common sequelae of caffeine withdrawal, such as headache and fatigue (Burg, 1975; Dews, 1982; Driesbach and Pfeiffer, 1943; Harrie, 1970) might reflect enhanced tissue sensitivity to endogenous adenosine. Caffeine itself is used to treat several types of headache, where its beneficial effect is believed to result from its ability to constrict cerebral arteries (Miller, 1960; Shorofsky and Lamm, 1977), combating the potent dilatory action of adenosine on the cerebral vasculature.

During hypoxia in the inner ear, Honrubia, Strellof and Sitko (1976) reported that the spontaneous and evoked response activity to physiological and electrical stimuli were abolished while the nerve fibres remained excitable and able to propagate nerve impulses. It was suggested that the lack of O₂ affected transmission at the hair cell-neuron synapse but not the excitability of the nerve fibre axons. Whitfield (1967) found that inner hair cells, as shown by their behaviour when stained with methylene blue, were more sensitive to hypoxia than outer hair cells and
Model III: The effect of caffeine on tinnitus through an alteration in the tension and distribution of oxygen within the CNS and the inner ear. The proposed mechanism for action is caffeine's antagonistic relationship with adenosine.

Mechanism I: Nerve fibres remain excitable and able to propagate impulses. In the absence of sound production from the Organ of Corti due to oxygen depletion, the nerve fibres enter into a state of hyperexcitability which is perceived as sound. This may potentiate tinnitus.

Mechanism II: Reduction in oxygen may suppress random activity of hair cells. Once the effect of caffeine is in the process of decaying and oxygen is restored to the organ of Corti, the hair-cell neurons may: 1) return to their 'normal' state, or 2) enter into a state of hyperexcitability which potentiates tinnitus.
lost their activity first when the organ of Corti was subjected to a lack of $O_2$.

Changes in CNS $O_2$ distribution resulting from the antagonistic action of caffeine to adenosine affects the inner ear after 1 to 30 minutes. It is proposed that depletion of $O_2$ within the inner ear might exacerbate or potentiate tinnitus in one or both of the following ways:

1. In the absence or reduction of spontaneous random activity by the hair cells, a state of hyperexcitability in the nerve fibre axons may be induced. This is interpreted by the auditory cortex as acoustic stimuli. Johnstone (1975) demonstrated a state of mild hypoxia in an individual nerve fibre of a guinea pig where clicks were presented to the ear and the action potential (AP) was recorded from the round window. At the point where the respiratory system was changed to 5% $O_2$ and nitrogen, AP fell at the end of a few minutes of hypoxia. The single unit nerve fibre lost about 30 dB to 40 dB of sensitivity. The effect was reversible. A point of interest which Johnstone (1975) discusses concerns the production of recruitment with a shift in threshold of some 90 dB. Johnstone concluded that mild hypoxia of 4 minutes duration caused a transient fluctuation in threshold of sensitivity and that the effect was reversible if not continued for too long.

2. A reduction of $O_2$ in the cochlea, resulting from ingestion of caffeine, may suppress random, spontaneous activity by the hair cells and hence, reduce symptoms of tinnitus. As the effect of caffeine begins to decay - between 30 and 90 minutes - the response of hair cell-neuron synapses to the restoration of $O_2$ in the organ of Corti (after severe deprivation) may be: a) a return to the 'normal' hyperexcitable environment which characterises tinnitus; or b) to enter into a state of abnormal hyperactivity which is interpreted by the auditory cortex as acoustic stimuli. This additional activity may potentiate tinnitus.
THE PRESENT STUDY

There were three primary purposes for this study:

I. To establish scientific evidence pertaining to the effect of caffeine on tinnitus. The rationale for predicting that caffeine would potentiate tinnitus was based on the underlying premise that subjective tinnitus results from neural excitation anywhere within the auditory system (Crue, 1970; Harrie, 1968; Hazell, 1978; Melding et al., 1978; Pulec, 1974, 1979; Pulec et al., 1978; Shea, 1983; Shea and Emmett, 1983; Tonndorf, 1976, 1980; Teas et al., 1970) and, hence any factor which alters or affects the degree of neural excitation being elicited would have an effect on tinnitus. Caffeine may alter the temporal pattern and amount of spontaneous activity which is elicited.

In addition, current treatment of tinnitus includes the administration of drugs aimed at increasing blood flow. In light of caffeine's vasoconstrictive capacity (Bunker and McWilliams, 1979; Josephson and Stine, 1976; Truitt, 1971) it was proposed that caffeine would potentiate tinnitus. In discussing the 'potentiating' effect of caffeine, it was speculated that the stimulatory action of caffeine would further exacerbate the hyperactive environment of the auditory cortex, auditory pathway or the inner ear, resulting in:

1. Increases in pitch, threshold of sensitivity, loudness of tinnitus, and the corresponding subjective ratings of these measurements. In relation to subjective measurements, it was predicted that subjects would be able to accurately assess the effect of caffeine on their tinnitus. This was based on the research by Blount and Cox (1983) who demonstrated that people were able to accurately assess the dosage and bodily effects of caffeine.

2. Fluctuations in the above measurements. This prediction was based on the premise that additional hyperactivity, which was induced by caffeine, may result in a suppression or reduction of the activity of the cochlea nerve. In this respect, immediate ingestion of caffeine would result in a depressed state of hyperactivity with a return to the 'normal' hyperactive environment in correspondence with the decaying...
II. To assess the effect of caffeine on unilateral or bilateral or head tinnitus. It was speculated that persons who reported tinnitus as being localised in one ear (unilateral) were describing peripheral tinnitus. Conversely, persons who reported a more general tinnitus may be describing a tinnitus of central origin (Meyerhoff and Cooper, 1980). In this respect, caffeine was expected to differentially affect tinnitus on the basis of the reported sound locations - unilateral or bilateral or head located. On the basis of the proposed models, caffeine should activate or potentiate tinnitus differentially at the level of the cochlea (peripheral) or the CNS (central).

It was predicted that unilateral tinnitus would be affected by caffeine's action at a peripheral level in the tissue of the inner ear by: a) increases in glucose concentration (Model I, Mechanism II); and b) hypoxia (Model II, Mechanism II). If the increase in glucose concentration accounted for the action of caffeine, it was further predicted that caffeine's effect would be heightened at 60 minutes, with evidence of tinnitus potentiation at 30 minutes. The time pattern was expected to mimic the length of time taken to transport caffeine to the peripheral tissue from a CNS site. The underlying premise was that caffeine's stimulatory action on glucose would result in potentiation not alleviation of tinnitus. It was also predicted, however, that if caffeine potentiated unilateral tinnitus through hypoxia, the effect would be seen within 30 to 60 minutes after oral ingestion. This prediction was in line with the research showing that the organ of Corti was affected by O₂ deprivation within 30 minutes. The effect of caffeine on hypoxia was expected to be dose-dependent.

It was proposed that centralised tinnitus (bilateral or head tinnitus) would be affected by caffeine through the following mechanisms: a) inhibition of acoustic transduction due to the inappropriate synthesis of cyclic 3'5'-AMP (Model I, Mechanism II); b) limited adenine brain uptake (Model II, Mechanism I and II); and c) hypoxia (Model II, Mechanism I).

The effect of caffeine on the inappropriate synthesis of cyclic 3'5'-AMP within the auditory nerve would potentiate tinnitus within 30 to 60 minutes. The effect would
be heightened at 60 minutes. This prediction was based on the speculation that ATP inhibition could result in prolonged stimulatory action of the cells at any point along the auditory nerve. If the CNS site of caffeine action can potentiate tinnitus within 30 minutes, then a site of action located between the extreme peripheral and CNS tissue would be expected to be affected within 30 to 60 minutes after oral ingestion of caffeine.

Conversely, limited adenine brain uptake was predicted to occur within a relatively shorter period of time, that is, by 30 minutes the effect of caffeine would be evident because of the CNS site of caffeine action. This prediction was based on the research which showed that caffeine diffuses readily into the CNS (Axelrod and Riechenthal, 1953; Carlson, 1986; Rall, 1980; Ritchie, 1975) and that cerebrospinal fluids reach half plasma levels within 4 to 8 minutes (Teschemacher et al., 1968). The length of time for caffeine to diffuse along the auditory nerve fibre and alter the formation of cyclic 3'5'-AMP was expected to be 60 minutes because of the more peripheral location of caffeine's site of action. Subjects with bilateral or head located tinnitus experiencing hypoxia would follow a similar time sequence. It was speculated, however, that the decay in caffeine's effect on adenine uptake would be more pronounced by 60 minutes when compared with hypoxia. Circumstantial evidence indicates a faster elimination of caffeine from CNS than peripheral tissue.

In addition, this study aimed at assessing the length of time required for alkaloid drugs - caffeine - to impact on the auditory system. To this author's knowledge, there is no published research to date addressing this issue.

III. To address and overcome the methodological flaws associated with Malatesta et al.'s (1980) research. Table IV lists the methodological problems associated with Malatesta et al.'s research and the corresponding resolutions utilised in the present study.
Table IV. Methodological criticisms of Malatesta et al.'s (1980) study and the corresponding methodological resolutions utilised in the present study.

<table>
<thead>
<tr>
<th>Malatesta et al. (1980)</th>
<th>The Present Study</th>
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<tbody>
<tr>
<td><strong>Caffeine Manipulations:</strong></td>
<td><strong>Experimental Design:</strong></td>
</tr>
<tr>
<td>Caffeine was not calculated in accordance with the weight of the individual subject.</td>
<td>Individual weight measurements were recorded for each subject and the percentage of caffeine to be received calculated as a function of milligrams per kilogram of body weight.</td>
</tr>
<tr>
<td>Caffeine was ingested in the form of brewed coffee, not pure caffeine. One or more of the many compounds in coffee - niacin, ammonia, acetone, furfuran, methylamine, trimethylamine, fumaric acid, acetic acid, resorcinol, hydroquinone, pyridine - could have produced the reported increment in intensity.</td>
<td>Pure caffeine was used.</td>
</tr>
<tr>
<td>Caffeine was not administered using a randomised, double-blind procedure.</td>
<td>The randomised, double-blind procedure for drug administration was utilised in the present study. Subjects were not aware of which dosage they received. Taste discrimination pilot study evaluated the ability to discriminate the level of caffeine by olfactory cues.</td>
</tr>
<tr>
<td>There was no control for an expectation effect.</td>
<td>Placebo beverage was used to control for subject expectation.</td>
</tr>
<tr>
<td>No abstinence period from caffeine-containing products prior to the ingestion of the brewed coffee.</td>
<td>Subjects were required to abstain from caffeine-containing food and beverages for 24 hours.</td>
</tr>
<tr>
<td><strong>Experimental Design:</strong></td>
<td></td>
</tr>
<tr>
<td>Subject population = 1</td>
<td>Subject population = 16</td>
</tr>
<tr>
<td>Assessment was made on only one tinnitus characteristic, intensity.</td>
<td>Audiological assessment included monitoring the pitch of tinnitus, threshold of sensitivity and the loudness of tinnitus.</td>
</tr>
<tr>
<td>No subjective ratings were made.</td>
<td>Subjects rated the pitch and loudness tinnitus.</td>
</tr>
<tr>
<td>Only one intensity assessment was made.</td>
<td>Subjects were required for six experimental sessions and a baseline assessment.</td>
</tr>
<tr>
<td>Acoustic stimulus was tonal.</td>
<td>Acoustic stimuli were tones and broadband noise.</td>
</tr>
</tbody>
</table>
METHOD

Subjects

Sixteen subjects participated in this experiment. The subjects (eight males and eight females) ranged in age from 21 to 80 years. Seven subjects were volunteers recruited from the Canterbury Tinnitus and Hearing Association and a further nine subjects were students and staff members from the University of Canterbury.

All subjects reported continuous tinnitus. In addition to ongoing tinnitus, nine subjects reported the occurrence of intermittent monaural tinnitus. The length of time tinnitus had been experienced ranged from less than one year to more than 20 years. Eight subjects reported monaural tinnitus (two in the left ear and six in the right ear) and five subjects reported binaural tinnitus. Two subjects noted tinnitus as originating in the head and one claimed that tinnitus was both binaural and head-located.

No subjects had previous experience with tinnitus research. Participants were evaluated with regard to the following audiometric measurements: pitch match of their tinnitus; threshold of sensitivity and loudness match at the tinnitus frequency; threshold of sensitivity to a broadband noise (200-10000 Hz); and a loudness match of the noise to the subject's tinnitus. Participants were required to attend one training and preliminary assessment session and six experimental sessions. Three subjects (Subjects 3, 10 and 14) attended only three experimental sessions; these subjects performed once as opposed to twice in each experimental condition.

Informed consent was obtained from all participants.

The characteristics of tinnitus across subjects were not uniform. Similarities and differences amongst subjects can be seen from the overall biographical data presented in Table V.

Eight subjects reported a known hearing loss. Subjects 2 and 5 were speech discrimination deaf in the left and right ear, respectively. Subjects 3 and 4 reported low tone discrimination loss in the right and left ear, respectively. Subjects 11 and 15 reported hearing loss in both ears while Subject 15 noted a greater hearing loss in the left than the right ear. Subjects 1 and 12 experienced a known hearing loss in the left ear. One participant (Subject 11) wore a hearing aid
Table V. Biographic and Questionnaire Data for the 16 Subjects (S). The tinnitus location is indicated by R (right), L (left), H (head) and B (both ears). The bracketed letter specifies the preferred ear used for presentation of tones in the pitch match procedure.

<table>
<thead>
<tr>
<th>S</th>
<th>Sex</th>
<th>Tinnitus Description</th>
<th>Tinnitus Location</th>
<th>Suspected Etiology</th>
<th>Pitch Match Frequency (Hz) at Preliminary Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>Hissing/Tone in noise</td>
<td>L (R)</td>
<td>Acoustic Trauma</td>
<td>7073</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Roaring/Tones in noise</td>
<td>L (R)</td>
<td>Cerebral Meningitis</td>
<td>10 560</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Sea-shell sound Tone in noise</td>
<td>R (R)</td>
<td>Viral Illness</td>
<td>2643</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>Ringing/High tension wire</td>
<td>R (R)</td>
<td>Head Injury</td>
<td>1481</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>Crickets</td>
<td>R (L)</td>
<td>Ear Infection</td>
<td>5848</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>Single tone</td>
<td>R (R)</td>
<td>Head Injury</td>
<td>5100</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>High-pitched hissing/Tone in noise</td>
<td>R (R)</td>
<td>Unknown</td>
<td>5135</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>Single tone/ Buzzing</td>
<td>R (L)</td>
<td>Unknown</td>
<td>1051</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Hissing Tone in Noise</td>
<td>H/B (R)</td>
<td>Acoustic Trauma</td>
<td>742</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>One tone in noise</td>
<td>B (R)</td>
<td>Head Injury</td>
<td>720</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>Hissing/ Cicadas</td>
<td>B (R)</td>
<td>Cerebral Malaria</td>
<td>1990</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>Single tone Hissing/ Crickets</td>
<td>B (R &amp; L)</td>
<td>Unknown¹</td>
<td>3591</td>
</tr>
<tr>
<td>13</td>
<td>F</td>
<td>Tone in noise</td>
<td>B (R)</td>
<td>Onset of Menieres Disease</td>
<td>6894</td>
</tr>
<tr>
<td>14</td>
<td>F</td>
<td>Single tone</td>
<td>H (L)</td>
<td>Unknown²</td>
<td>1825</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>Whistling/ Cicadas</td>
<td>B (R)</td>
<td>Acoustic Trauma</td>
<td>2876</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>Hissing/ Whistling</td>
<td>H (R)</td>
<td>Unknown</td>
<td>7046</td>
</tr>
</tbody>
</table>

Note: 1. Possibly genetic - subject reported both Father and two brothers were diagnosed as having tinnitus.
2. Possibly related to Diabetes.
with a tinnitus masker. All subjects underwent a pure tone audiometry test prior to commencement of the experimental sessions. Audiometric data for all subjects are presented in Table VI.

The audiometric data supports the known hearing losses as reported by Subjects 1, 2, 3, 5, 11, 12 and 15 during the preliminary assessment but not the report made by Subject 4. Table VI indicates that the losses were greater in the high frequency region than in the low frequencies (as reported). It is evident from Table IV that seven subjects (6, 7, 8, 10, 13, 14 and 16) did not have a hearing loss; all seven subjects were under the critical sensitivity 20 dB HL threshold. In addition, it can be seen that Subject 9 had a high frequency hearing loss, which was not evident to the subject.

Subjects were identified as habitual or non-habitual caffeine consumers on the basis of the definitive criteria outlined by Colton, Gosselin and Smith (1968). Each subject was assigned to one of the two categories in accordance with the number of caffeine beverages ingested in any one day. A non-habitual user was one who, by his or her own estimation, usually drank no more than one cup of tea, coffee, cocoa or coca-cola per day. The remaining subjects were described as habitual consumers.

In addition, subjects were asked to identify whether the beverages were consumed ritualistically. A ritualistic consumer was one whose consumption of caffeine followed a daily pattern which was strictly adhered to. This categorisation was devised by the experimenter for two purposes: First, to help identify subjects who had difficulty with the required 24 hour abstinence from caffeine prior to each experimental session. Second, to identify a group of consumers more reliant on caffeine among the already-identified habitual users.

Fourteen subjects were identified as habitual users with a daily mean consumption of 2.9 cups (SD = 1.59), ranging from 1 to 8 caffeine containing beverages per day. Two non-habitual users (2 and 15) averaged a daily intake of 1.0 cup (SD = 0.0). Twelve habitual users defined consumption as ritualistic, with a daily mean consumption of 3.1 cups (SD = 1.6), ranging from 3 to 7 caffeine beverages per day. Two subjects (8 and 13) were identified as habitual/non-ritualistic consumers and a further two subjects (2 and 15) as non-habitual/non-ritualistic
Table VI. Audiograms for the 16 Subjects (S). Pure tone air conduction thresholds are shown in dB HL. Data was derived from segmenting the 30 second tone presentations for each frequency into 7.5 second epochs and averaging the threshold result across the four epochs. Data for both the right and left ear are presented. The term CNM indicates that the threshold could not be measured as presentation of pure tones would have exceeded 90 dB HL.

<table>
<thead>
<tr>
<th></th>
<th>Right Ear:</th>
<th>Left Ear:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(in kHz)</td>
<td>(in kHz)</td>
</tr>
<tr>
<td>S</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>11.5</td>
<td>10.0</td>
</tr>
<tr>
<td>2</td>
<td>27.5</td>
<td>12.0</td>
</tr>
<tr>
<td>3</td>
<td>36.0</td>
<td>28.7</td>
</tr>
<tr>
<td>4</td>
<td>-2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>5</td>
<td>42.2</td>
<td>49.2</td>
</tr>
<tr>
<td>6</td>
<td>-2.0</td>
<td>-3.5</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>2.1</td>
</tr>
<tr>
<td>8</td>
<td>-2.0</td>
<td>0.5</td>
</tr>
<tr>
<td>9</td>
<td>1.7</td>
<td>8.7</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
<td>4.0</td>
</tr>
<tr>
<td>11</td>
<td>23.2</td>
<td>33.2</td>
</tr>
<tr>
<td>12</td>
<td>1.0</td>
<td>11.6</td>
</tr>
<tr>
<td>13</td>
<td>3.0</td>
<td>1.5</td>
</tr>
<tr>
<td>14</td>
<td>0.5</td>
<td>-2.0</td>
</tr>
<tr>
<td>15</td>
<td>10.0</td>
<td>12.0</td>
</tr>
<tr>
<td>16</td>
<td>0.5</td>
<td>-1.7</td>
</tr>
</tbody>
</table>
consumers. These four subjects reported consuming an average daily intake of 1.25 cups (SD = 0.5), ranging from 1 to 2 cups per day. Individual caffeine consumption rates are presented in Table VII. Three subjects smoked cigarettes (3, 4 and 7); the daily average was 9.0 (SD = 5.29) with a range of 5 to 15 cigarettes smoked per day. All three participants were identified as habitual caffeine consumers with an average consumption rate of 3.75 cups per day (SD = 1.7), ranging from 2 to 6 cups per day. A further subject (15) was defined as a non-habitual caffeine user but reported periodic stress-related smoking.

Four female participants were currently taking a prescribed course of oral contraceptives. One female subject was on a prescribed course of Oestrogen Replacement Therapy. Two subjects reported occasional ingestion of prescribed medication for tinnitus and associated problems of stress, anxiety and sleeping difficulties. The following drugs were noted as the more commonly ingested - Valium, Nortriptyline and Benzodiazepam. One subject (Subject 3) was on 100mg of Nortriptyline per day. All subjects were asked to inform the experimenter of changes relating to medication. Subject 3 reported a reduction in medication from 100mg to 50mg of Nortriptyline at the first experimental session. A further reduction to 25mg was reported at the second experimental session. No other changes in medication were noted.

Subjects were not included in this experiment if they reported cardiovascular problems, epilepsy, seizures or blackouts, hypertension, diabetes, kidney disorders or allergies to caffeine.

**Materials**

**Questionnaires.** All subjects completed a questionnaire designed to elicit background and tinnitus-related information concerning the characteristics and causes of tinnitus. The questionnaire was adapted from one used by Kemp and George (1991) in a New Zealand survey on tinnitus. The questionnaire can be seen in Appendix I. In addition to this questionnaire, subjects completed a Personal Assessment Form consisting of self-report frequency and loudness rating scales and a sound description check-list. Self-reported frequency of tinnitus was measured on a scale
Table VII. Caffeine consumption quantities for the 16 subjects (S). Subjects estimates were based on the number of average-sized cups of caffeine-containing beverages ingested in any one day.

<table>
<thead>
<tr>
<th>S</th>
<th>COFFEE</th>
<th>TEA</th>
<th>OTHER</th>
<th>HABITUAL CONSUMER</th>
<th>RITUALISTIC CONSUMER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decaff/instant/Percolated</td>
<td>E.g., Cocoa, Coca-cola</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-</td>
<td>3</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>4</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>6¹</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>2</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>4</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>-</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>-</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>2</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>5¹</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>-</td>
<td>2²</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>4</td>
<td>2</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Note: 1. Very Strong  
2. Very Weak

on a scale of 1 to 10, with '1' representing a very low sound and '10' representing a very high sound. For self-reported loudness of tinnitus, '1' represented a very faint sound and '10' represented a very loud sound. The tinnitus sound description checklist comprised adjectives which the subject checked to represent the sound, or
combination of sounds, reflective of their tinnitus. A copy of the Personal Assessment Form can be seen in Appendix II.

**Apparatus.** Pure-tone audiometry tests were generated by a Grason Stadler 1703B Recording Audiometer, with the presentation of a pulsed tone (500ms ON - 500ms OFF), presented to the subject via a TDH-50P earphone. The subject, seated in the sound attenuated chamber, had control of the sound intensity at the earphone, which could be varied between -10 dB HL and 90 dB HL. The intensity decreased while the response button on the handset was depressed and increased when released. Test frequencies followed the sequence of: 1000, 2000, 3000, 4000, 6000, 8000 Hz, with a recording time of 30 seconds per frequency; total recording time for both ears was 7 - 7.5 minutes.

Other tones presented in the experiment were generated by an EE Function Generator (F34) and fed through a variable attenuator (the Grason Stadler 1703B Recording Audiometer with the signal generator disconnected), attenuated to the desired level and presented to the subject via a TDH-50P earphone. Frequency values from pitch match procedures were displayed on a Trio Frequency Counter/DMM DF-760. Tones generated for the matching procedures were presented ipsilaterally or contralaterally.

When experimental assessments required noise to be presented, it was generated by a Lafayette Noise Generator and fed through a Kemo VBF/8/04 Dual Variable Filter to produce a broadband of 200 - 10000 Hz, attenuated and presented as delineated above. Broadband noise was presented for threshold and intensity measures in pulsed and steady forms, respectively. Threshold and intensity measures consisted of three sets of tonal and noise presentations, each for a 30 second duration. All sound was presented to the subjects through the same headphone of the TDH-50P earphone set.

Sound levels were calibrated on each day of experimental assessments and on a four-weekly basis. Daily calibration checks involved assessing the sound pressure level (SPL) of a generated 1000 Hz tone and broadband noise (200-10000 Hz) at 80 dB HL. All levels were measured with the aid of a Bruel and Kjaer Precision Sound
Level Meter (2238) connected to an Artificial Ear (Bruel and Kjaer Type 4152). Measured values were expected to fall within 0.3 dB SPL of the required 80 dB.

Calibration checks were completed prior to the presentation of any sound. During the experimental sessions, calibration checks were made, after the first series of tests, before the second assessment phase and after completion of the second test phase. Every four weeks, calibration checks were made concerning the SPL of tones generated at 1000 Hz, 2000 Hz, 3000 Hz, 4000 Hz, 5000 Hz, 6000 Hz, 7000 Hz, 8000 Hz, 9000 Hz and 10000 Hz at 80 dB. Each SPL recording, associated with the respective frequency, was noted and compared with the previous days/weeks measures; monitoring the stability of the equipment generated sound levels for the duration of the experiment. The checks were carried out during the evening when the Department was subject to less activity to minimise the effects of voice and movement disturbance on the SPL readings.

Aqueous Caffeine Solutions. Caffeine powder was administered orally in a fruit juice-based beverage. Subjects were weighed (kg) at baseline assessment. Each subject received 2.0 ml of fruit juice per kilogram of body weight. This value was decided upon for ease of calculation (as it was a rounded number) and when multiplied by each subject's weight would render a value equivalent to no more than one cup of fruit juice solution to be ingested by all subjects.

Contained in each 2.0 mls of fruit juice was 0.0mg caffeine for the placebo, 1.42mg caffeine (equivalent to the caffeine contained in 1-2 average-sized cups of coffee) for the low dose and 4.24mg caffeine (equivalent to the caffeine contained in 3-4 average-sized cups of coffee) for the high dose. In order to compensate for the slightly bitter taste of caffeine, the placebo beverage contained a small quantity of Bitrex-Denatonium Benzoate at a level insufficient to produce any pharmacological effects. By multiplying the ml/kg of solution by each subject's body weight all participants received a proportion of the caffeine powder relative to their body mass. For example, Subject 9 weighed 80kg and required 160ml (80kg x 2.0ml/kg) of fruit juice solution. The amount of caffeine powder given to subject 9 in the high-caffeine fruit juice solution was 339.2mg (80kg x 4.24mg/kg).
The weight and comparable proportions of caffeine powder each subject received can be seen in Table VIII.

A technician mixed and placed six litres of each fruit juice solution - in containers marked 'A', 'B' and 'C'. These substance codes were for the purpose of the double-blind procedure; the corresponding level of caffeine was unknown to the experimenter until the completion of all experimental work.

To test for taste discrepancies among the Placebo, Low and High fruit juice/caffeine solutions, an evaluatory, pilot study was completed. Twelve subjects volunteered to act as taste assessors. These subjects were not participants in the tinnitus experiment. Subjects were presented with the two levels of caffeine and the placebo and asked to assess each solution, giving a "Yes" or "No" response as to whether the fruit juice contained caffeine. Utilising a test-retest design, subjects were asked to assess the fruit juice beverages one week later. Experimenter bias was eliminated through a double-blind procedure for caffeine administration.

Statistical analysis concerning the frequency of "Yes" and "No" responses (One Group Chi-Square) showed that in Week I subjects were unable to taste a difference between the placebo and low dose (\(\text{chi}^2 (11) = 3.5\), n.s), placebo and high dose (\(\text{chi}^2 (11) = 6.0\), n.s), low and high dose (\(\text{chi}^2 (11) = 2.5\), n.s). The same pattern of results emerged for Week II. There was no taste differentiation between placebo and low dose (\(\text{chi}^2 (11) = 4.0\), n.s), placebo and high dose (\(\text{chi}^2 (11) = 5.0\), n.s), low and high dose (\(\text{chi}^2 (11) = 2.5\), n.s). Comparisons between frequency of responses across the test-retest assessments showed no difference in responses for placebo (\(\text{chi}^2 (11) = 6.0\), n.s), low dose (\(\text{chi}^2 (11) = 8.0\), n.s) and high dose (\(\text{chi}^2 (11) = 5.0\), n.s).

Thus, there were no taste discrepancies associated with the three fruit juice solutions.
Table VIII. Proportions of liquid and caffeine powder received by the 16 subjects (S). The weight of the subject is reported in kilograms. The amount of fruit-juice beverage each subject received is reported as the amount of mls of liquid solution consumed. In addition, the milligrams of caffeine powder contained in high and low doses of the fruit juice are also reported.

<table>
<thead>
<tr>
<th>S</th>
<th>WEIGHT (in kg)</th>
<th>mls OF FRUIT JUICE</th>
<th>LOW DOSE</th>
<th>HIGH DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Subject's weight multiplied by 2.0mls.</td>
<td>Proportion of caffeine contained in low dose solution, Subject's weight multiplied by 1.42mg caffeine.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proportion of caffeine contained in high dose solution, Subject's weight multiplied by 4.24mg caffeine.</td>
</tr>
<tr>
<td>1</td>
<td>79.0</td>
<td>158ml</td>
<td>112.18mg</td>
<td>334.96mg</td>
</tr>
<tr>
<td>2</td>
<td>82.5</td>
<td>165ml</td>
<td>117.15mg</td>
<td>349.80mg</td>
</tr>
<tr>
<td>3</td>
<td>62.0</td>
<td>124ml</td>
<td>88.04mg</td>
<td>262.88mg</td>
</tr>
<tr>
<td>4</td>
<td>65.0</td>
<td>130ml</td>
<td>92.30mg</td>
<td>275.60mg</td>
</tr>
<tr>
<td>5</td>
<td>54.0</td>
<td>108ml</td>
<td>76.68mg</td>
<td>228.96mg</td>
</tr>
<tr>
<td>6</td>
<td>77.0</td>
<td>154ml</td>
<td>109.34mg</td>
<td>326.48mg</td>
</tr>
<tr>
<td>7</td>
<td>70.0</td>
<td>140ml</td>
<td>99.4mg</td>
<td>296.80mg</td>
</tr>
<tr>
<td>8</td>
<td>60.0</td>
<td>120ml</td>
<td>85.2mg</td>
<td>296.80mg</td>
</tr>
<tr>
<td>9</td>
<td>93.5</td>
<td>187ml</td>
<td>132.77mg</td>
<td>396.44mg</td>
</tr>
<tr>
<td>10</td>
<td>80.0</td>
<td>160ml</td>
<td>113.60mg</td>
<td>339.20mg</td>
</tr>
<tr>
<td>11</td>
<td>76.5</td>
<td>153ml</td>
<td>108.63mg</td>
<td>324.36mg</td>
</tr>
<tr>
<td>12</td>
<td>82.0</td>
<td>164ml</td>
<td>116.44mg</td>
<td>347.68mg</td>
</tr>
<tr>
<td>13</td>
<td>74.0</td>
<td>148ml</td>
<td>105.08mg</td>
<td>313.76mg</td>
</tr>
<tr>
<td>14</td>
<td>52.0</td>
<td>104ml</td>
<td>73.84mg</td>
<td>220.48mg</td>
</tr>
<tr>
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<td>95.0</td>
<td>190ml</td>
<td>134.90mg</td>
<td>402.80mg</td>
</tr>
<tr>
<td>16</td>
<td>73.0</td>
<td>146ml</td>
<td>103.66mg</td>
<td>309.52mg</td>
</tr>
</tbody>
</table>
Procedure

Preliminary Assessment

Subjects were required to attend one session of approximately 60 to 90 minutes duration prior to commencement of the experimental sessions. The purposes of this session were to:

1. Interview Each Participant. Subjects completed a 20-item questionnaire interview. The content of the questions ranged from the length of time the subject had experienced tinnitus, the development of coping strategies, smoking habits, to the experiencing of vertigo. Prior to commencement of the interview, subjects were weighed and the measure recorded on the questionnaire-interview sheet. In addition, subjects were required to complete a Consent Form and a Personal Assessment Form.

2. Assign Subjects to a Time Condition Group. Subjects were assigned to wait either 30 or 60 minutes after oral ingestion of caffeine prior to completion of the second test phase. Assignment to one of the time conditions was not random. Rather, it was based on the subject's personal preference stated in consultation with the experimenter. Eight subjects (Subjects 1, 2, 3, 9, 10, 11, 12 and 15) waited 30 minutes. Eight subjects (Subjects 4, 5, 6, 7, 8, 13, 14 and 16) waited 60 minutes.

3. Introduce Subjects to the Equipment and Provide Basic Training. The aim of this procedure was twofold: First, to familiarise each subject with the experimental stimuli. Subjects were told that the stimuli they would hear would be tones and white noise. The experimenter then generated a 1000 Hz tone at 50 dB HL and presented it to the subject, via a set of headphones, in a pulsed and steady form, respectively. A broadband white noise (200-10000 Hz) was also presented to the subject in the same manner. Subjects were warned that the quality of the experimental stimuli might be grossly different to the sound component(s) each participant perceived as being his/her tinnitus.

Second, to show subjects the appropriate handset manipulations which
corresponded to a given task. Subjects responded to matched-frequency threshold assessments (pulsed tone presentations) by depressing the switch on the handset attached to the variable attenuator when the tone was perceived and releasing the switch when the tone was no longer heard. Responses to loudness matching procedures (steady tone presentation) required the subjects to depress the switch to decrease loudness and release the switch to increase the loudness of the tone. Using the handset in this manner meant that the subject could track the loudness level of his/her tinnitus by matching the level of an adjustable comparison tone (delivered to the left or right ear) to the level of the loudness of their tinnitus. Subjects responded to the noise by using the handset as for pulsed and steady tonal presentations.

4. Establish the Subject's Ear of Preference for the Matching Procedures. A subject's ability to monitor simultaneously an external sound and the tinnitus was used as the basis for the participant's selection of 'ear of preference' to be used in the matching procedures. Subjects were presented with the broadband noise (200-10000 Hz) and tonal stimuli at four different frequencies: 500 Hz, 2000 Hz, 4000 Hz and 8000 Hz at 50 dB HL.

Subjects were given thirty seconds within which to attempt to discriminate their tinnitus from either a tone or noise in the left ear. This procedure was repeated with the right ear. The ear of preference was taken to be the one in which participants were able to 'consistently distinguish' the tone and noise from their tinnitus. 'Consistently distinguish' was defined as a report rate equal to or in excess of 75% for a particular ear. One subject (Subject 12) reported equal consistency across both ears. No other subjects reported a consistency rate of less than 75%.

5. Establish Baseline Assessment Data. Evaluation of each subject began with the determination of the subject's auditory threshold for pure tones by Békésy audiometry. This was followed by baseline data measurements. These tests were the same as those given in the experimental sessions - pitch match, threshold of sensitivity and loudness matches at the tinnitus frequency, threshold of sensitivity and loudness matches to noise. Subjects did not, however, receive any caffeine solutions.
Experimental Assessment

An overview of the experimental design has been charted on Table IX. This can be seen on the next page. Reference will be made to this table in the following procedural sections.

**General.** Subjects were required to attend six sessions of either 60 or 90 minutes duration. As can be seen from Table IX, within each experimental session subjects received two sets of tests - one set prior to the ingestion of caffeine (Phase I) and one set after the ingestion of caffeine (Phase II). Commencement of Phase I and II sessions were marked by subjects completing the Personal Assessment Form (frequency and loudness rating scales and a sound description checklist) followed by a discussion period. Table IX outlines the aims of these procedures. Phase I and II were separated by a time delay of either 30 or 60 minutes (dependent upon which time condition the subject had been assigned to), termed 'Experimental Manipulation'.

**Experimental Manipulation.** All subjects were required to abstain from all caffeine-containing foods and beverages for 24 hours prior to each experimental session. It was emphasised that this abstention was a central requirement to the study. Subjects were given a list of the beverages and foods to avoid. This abstinence procedure was similar to those employed by Blount and Cox (1985; 8 hour abstinence), Parsons and Neims (1978; 24 hour abstinence), Robertson, Wade, Workman, Woosley and Oates (1981; 24 hour abstinence) and Sved, Hossie and McGilveray (1976; overnight abstinence). All subjects acknowledged having fulfilled the abstinence requirement.

A randomised, double-blind procedure was employed for the administration of the caffeine solutions. On completion of the test series for Phase I, subjects were given the fruit juice solution to drink prior to the waiting period. Subjects were reminded that during the waiting period no consumption of caffeine and additional foods and beverages were allowed. The solution each subject received was determined randomly. Over the course of the six experimental sessions, subjects received each fruit juice solution (A, B and C) twice.

**Appointments.** Session times were established one week in advance. In deciding on appointment times, subjects were asked to choose a time they would be
Table IX. Overview of the experimental design. This table illustrates the procedure that each subject received for each of the six experimental sessions.

**START**

<table>
<thead>
<tr>
<th>SUBJECT ARRIVED: at the auditory laboratory.</th>
<th>PERSONAL ASSESSMENT FORM:</th>
<th>DISCUSSION: Subjects reported ed changes in tinnitus and well-being over the previous week. Noted in experimental diary.</th>
</tr>
</thead>
</table>

**PHASE I BEGINS**

<table>
<thead>
<tr>
<th>4. THRESHOLD OF SENSITIVITY FOR WHITE NOISE: Subjects received a threshold test component. Matched.</th>
<th>5. LOUDNESS MATCH TO WHITE NOISE: Subjects received a loudness match component. Matched.</th>
<th>INGESTION OF CAFFEINE: Subjects received a fruit juice solution coded 'A', 'B', and 'C'.</th>
</tr>
</thead>
</table>

**PHASE I ENDS**

**EXPERIMENTAL MANIPULATION**

<table>
<thead>
<tr>
<th>1. PITCH MATCH TASK: Same procedure as in Phase I.</th>
<th>2. THRESHOLD AT TINNITUS FREQUENCY: Same procedure as in Phase I.</th>
<th>3. LOUDNESS MATCH AT TINNITUS FREQUENCY: Same procedure as in Phase I.</th>
</tr>
</thead>
</table>

**PHASE II BEGINS**

<table>
<thead>
<tr>
<th>4. THRESHOLD OF SENSITIVITY TO WHITE NOISE: Subjects received a threshold test component. Matched.</th>
<th>5. LOUDNESS MATCH TO WHITE NOISE: Subjects received a loudness match component. Matched.</th>
<th>APPOINTMENTS: An appointment for the following week was made.</th>
</tr>
</thead>
</table>

**PHASE II ENDS**

**FINISH**
consistently available for the following six weeks. This procedure ensured that probable physiological changes caused by factors dependent on the time-of-day (circadian rhythms, food consumption, activity and mood) would be relatively constant at one point in time, increasing the likelihood that changes in tinnitus were attributable to caffeine.

Subjects had a minimum of seven days between each experimental session. This requirement was based on the findings of classical research concerned with the recall and recognition aspects of memory. Ebbinghaus (1885; cited Woodworth and Schlosberg, 1955), Strong (1913) found that a person's ability to recall or recognise stimuli was greatly reduced after having a seven day time delay. In addition, this procedure ensured that any changes in tinnitus attributed by the subject to the ingestion of caffeine, would have little or no effect on the measurements recorded one week later.

Results from the taste discrimination test also indicated that subjects were unable to discern taste differences among the caffeine solutions seven days after the initial test. In this manner, the experimenter was assured that the audiological measurements would not be affected by a subject's ability to recognise a particular taste sensation if session times were posted one week apart.

Phase I and II Tests

The order of tests completed at each phase of the experimental session can be seen from Table IX. This order corresponds with the order of tests discussed in this section. Three of the five tasks (numbers 1, 3 and 5) involved a psychophysical matching procedure which was employed throughout the study. For all matching tasks, subjects were instructed to match for each sound which was invariable, that is, consistently perceived for the past six months. This procedure ensured that all tinnitus components were monitored across the six-week period of assessment so that the selective action of caffeine on one component, but not another, would be measured. All trials were conducted in a sound attenuated chamber. The response of the subjects for test numbers 2, 3, 4 and 5 were recorded by the automatic recording device of the
Pitch Matches to a Tone. To estimate the pitch of the tinnitus a method of adjustment was employed. A comparison tone (steady presentation) was adjusted in frequency by the experimenter until the subject reported that it matched the tinnitus. Pitch matches were made in the subject's ear of preference as listed on Table I.

Subjects who reported complex tinnitus (3 and 12), that is, a sound description which delineated two or more distinct sound components, for example, ringing and high tension wire sound (Subject 3) or single tone and hissing-crickets (Subject 12) pitch matched for each sound. For subjects with complex tinnitus, the first match was made to the sound subjects identified as being the loudest. To determine the loudest tinnitus sound component, subjects were asked to sit in the anechoic chamber and, "organise the differing sound descriptions into a loudness order from the loudest to the softest sound". Once the participant had completed and reported the loudness order to the experimenter, the pitch match task commenced.

The purpose of this loudness-assigning procedure was twofold: First, to provide the participant with a point of comparison, that is, the pitch of the loudest sound component against which to assess the relative pitch of the other sound components. Second, to validate the verbal order against the number and order of complex sounds that were rated on the Personal Assessment Form thereby, ensuring that what the subject said corresponded with what the subject had rated.

Subjects with tinnitus represented by one sound (5, 6, 10 and 14) or a combination of sounds which were perceived as 'fused together', completed one pitch match per experimental phase. Subjects with a 'fused sound' combination (1, 2, 4, 7, 8, 9, 11, 13, 15 and 16), for example, single tone with buzzing (Subject 3) or seashell sounds with tones and noise (subject 8) reported extreme difficulty when attempting to distinguish and match each sound at the preliminary assessment. Subjects were able to complete consistently the task when matching the entire sound combination to one stimulus presentation.

The subject sat in the doorway of the anechoic chamber so that he or she could communicate with the experimenter. From this vantage point, however, the subject
could see neither how nor when the experimenter changed the stimulus settings. The experimenter generated a 1000 Hz tone at an intensity of 50 dB SPL. The test tone was approximately 10 dB to 30 dB SPL above the subjects absolute detection threshold, so that subjects had no difficulty in hearing the tone clearly.

Sounds were turned on before subjects donned the headphones. This procedure was used to eliminate the possibility of inadvertently presenting a too-intense sound produced by, for example, equipment malfunction.

Subjects were given the following instructions:

"The aim of this task is to match a tonal sound presented to you with how high or low, in sound, you perceive your tinnitus to be. There is no correct or incorrect response to this task. I am only interested in assigning a frequency or numerical value to the sound you hear. This task requires you to respond verbally to me so that I can adjust the tone being presented to you.

You will hear a tone in the headphones as you place them on your head. Try to hear both the tinnitus and the comparison tone. When you are ready to begin the task, say to me, 'I am ready'.

The matching procedure will begin with you listening to a 'frequency sweep'. What you will hear is the tone slowly getting higher and higher (ascending from 1000 Hz to 12000 Hz) and then at some point, it will begin to decrease in frequency, that is, get lower (descending from 12000 Hz to 50 Hz). The sweeping procedure will be slow so that you will have a rough estimate of the frequency range within which to match your tinnitus. When the sweeping procedure is finished, you will hear the same tone you heard before it commenced (1000 Hz).

At this point, your task is to respond verbally to me by saying, for example, 'this tone is too low, could you make it higher'. I will then, very slowly, begin to make the tone higher. If at any point you wish me to stop, just say 'stop'.

When you feel that the comparison tone is similar to your tinnitus say
something like, 'this is similar but not quite the same'. Please be specific when you indicate whether the tone should be higher or lower. At this point I will be making very small adjustments to the tone until you indicate that the comparison tone is as similar to your tinnitus as you can get it. Please match as precisely as possible".

Subjects were also asked to 'talk-through' the pitch match procedure. This required the subject to verbalise problems, ideas and thoughts related to the task at hand. All the comments made by the subjects were noted.

A check for possible octave confusion followed each match. Subjects were presented with a tone one octave above and one octave below the matched frequency. After the subjects had completed an initial match, the participant was instructed to, "listen to this other tone and tell me if it is a closer match to your tinnitus". The participant was then presented a tone one octave above and one octave below the matched frequency, respectively. If the subject indicated that the tone was dissimilar to their tinnitus, he or she was instructed to rematch their tinnitus. Each subject was told, "From this point, please rematch your tinnitus to the tone you perceive as most similar". Subjects pitch matched, therefore, three times: 1) the initial match; 2) the match after one octave above; and 3) the match after one octave below.

All three matched frequencies were noted by the experimenter. If the second and third matches fell within five percent of the first match, the average of the three matches was taken and presented to the subject as the pitch of the tinnitus sound component. Adjustments made to this tone were expected to fall within 5% of the averaged stimuli.

This set of procedures was based on the method reported by Graham and Newby (1962), where subjects continued to pitch match until three consecutive matches, within five percent of the central frequency, had occurred. Graham and Newby (1962) reported this method within the context of a pitch matching task as opposed to checking for octave confusion. The aim of applying this method here was to validate the initial match as the pitch most representative of a subject's tinnitus.

No subjects reported octave confusion.
On identification of the pitch of the tinnitus, a match for loudness was made and compared with the threshold of sensitivity at that frequency.

**Threshold of Sensitivity at the Tinnitus Frequency.** Subjects received three sets of tonal presentations at the tinnitus frequency. Tones were presented in a pulsed form (500ms ON, 500ms OFF). The aim of this procedure was to assess the subject's ability to detect tonal stimuli at the frequency of his or her tinnitus.

Subjects completed a threshold of sensitivity test for each tinnitus sound component that was pitch matched. For subjects with a single or fused sound tinnitus, each participant received one threshold test per ear. For subjects with complex tinnitus, each participant received one threshold test per sound component. For example, Subject 12 completed two pitch matches corresponding to sound descriptions of, 'single tone/hissing' and 'crickets'. Subject 12 was given, therefore, two threshold tests - one at the frequency level at the single tone/hissing and one at the frequency level for crickets. Both the left and right ear were tested with regard to each frequency level. Subjects received the stimuli first to the ear opposite to the one used in the pitch match procedure.

**Loudness Match at the Tinnitus Frequency.** Subjects performed a dichotic loudness matching task which required participants to match the level of sound representative of their tinnitus. The steady comparison tone was presented at the frequency reported to match the tinnitus.

All subjects received three sets of 30 second tone presentations, monaurally.

Subjects completed a loudness match for each frequency reported to match a tinnitus sound component. Subjects with complex tinnitus were told the sound description they were matching prior to the commencement of each trial. The order of sounds to be matched for loudness corresponded to the order established for the pitch match task. Participants received the test stimuli used in the pitch match procedure. For example, Subject 12 pitch matched both sound components using the right ear. Loudness matches were completed, therefore, by presenting a comparison tone to this ear.
Threshold of Sensitivity for a Broadband of Noise. Subjects received three sets of 30 second broadband noise (200-10000 Hz) presentations. Noise was presented in a pulsed form (500ms ON, 500ms OFF) with a HL selection rate of 2.5 Hz per second. The aim of this procedure was to establish for each subject an absolute detection threshold for white noise. The procedure followed a similar pattern to that of threshold of sensitivity at the tinnitus frequency. Participants received one threshold test per ear.

Loudness Match to the Tinnitus for a Broadband of Noise. Subjects performed a dichotic loudness match of the tinnitus to the steady, broadband noise.

Subjects matched the loudness of each sound component to the noise by reception of the stimuli to the ear of preference as established in the preliminary assessment/training session. Subjects with complex tinnitus completed a loudness match to noise for each sound component which had been pitch matched; the order of sounds for loudness matching followed the order as given in the pitch match procedure. Subjects were instructed as to which sound description they were matching prior to the commencement of each test.

Completion of the loudness match to noise marked the conclusion of the testing at Phase I and Phase II for each experimental session.
RESULTS

General. In each of the following subsections, the findings are arranged so that the reader is presented, first with a brief overview of the tinnitus characteristic prior to the ingestion of caffeine and, second the effect of caffeine on tinnitus. The data for the Phase I/before caffeine overviews were derived from the Phase I testing sessions. All data concerning Phase II/after caffeine measurements were derived by subtracting Phase I measures from those at Phase II. In this manner, the effect of caffeine was assessed in terms of increasing or decreasing a specified tinnitus characteristic from Phase I to Phase II.

Analyses of Phase I and II results were undertaken with Three-way Analyses of Variance. The different variables analysed in these tests have been outlined in Table X. This table describes each factor and explains its statistical purpose. The ANOVA used for each statistical analysis followed a similar design: Phase I data was analysed using the time condition and tinnitus location (between-subject factors) together with the week-by-week changes in tinnitus (within-group factor). Phase II data was analysed using the two between-subject factors together with caffeine condition (within-group factor). Details of the associated dependent variables are given in each subsection of the results.

The results are presented in the same order as the auditory tests outlined on the Experimental Design Overview - Table IX. A summary of the findings presented in each results subsection is presented in the table following its conclusion.

For noise and tone thresholds and loudness matches to a tone at the matched tinnitus frequency (referred to as 'T/F') and to noise, the 1.5 minutes of testing for each ear were averaged using 15-second epochs, which represented approximately six reversals of the attenuator direction. One mean value was derived by averaging each resulting score across both ears for each subject. The sensation level of loudness matches as calculated relative to the noise and tone thresholds of each subject. Pitch matches and subjective ratings were averaged across each experimental session.

Table XI presents a detailed breakdown of the individual results for all subjects investigated. The data for this table were derived by averaging the auditory measurements across the six Phase I testing sessions. The aim of this table is to
Table X. Detailed breakdown of the factors analysed in the statistical tests.

<table>
<thead>
<tr>
<th>FACTOR:</th>
<th>USED IN PHASE I/ BEFORE CAFFEINE TO ASSESS:</th>
<th>USED IN PHASE II/ AFTER CAFFEINE TO ASSESS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. <strong>Time Condition</strong></td>
<td>Differences between subjects on the basis of time condition assignment, prior to caffeine.</td>
<td>a) The patterns of change in tinnitus pitch, threshold and loudness matches within a 30 and 60 minute time span = used to monitor changes (increase or decrease) in tinnitus during sessions from Phase I to Phase II. b) Whether the physiological effect of caffeine on the auditory system peaked 30 or 60 minutes after ingestion.</td>
</tr>
<tr>
<td>30 minute versus 60 minute duration group.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between-group factor: 2 levels = 2 duration conditions. Used in Phase I and II ANOVA’s.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Tinnitus Location**

Unilateral versus Bilateral or head located tinnitus.

Differences between subjects on the basis of the reported location of tinnitus prior to caffeine.

Differences between auditory measures based on tinnitus location after caffeine.

Between-group factor: 2 levels = 2 locations. Used in Phase I and II ANOVA’s.

3. **Week-by-Week Changes in Tinnitus**

Weekly measures taken across the six, Phase I testing sessions.

Monitor changes in tinnitus from Week 1, 2, 3, 4, 5 to 6. Used to assess changes in tinnitus (increase or decrease) between each Phase I session, i.e., prior to caffeine.

Not measured at Phase II.

Within-group factor: 6 levels = 6 weekly measurements. Used in Phase I ANOVA’s only.

4. **Caffeine Condition**

Placebo beverages versus low doses versus high doses of caffeine.

Not assessed at Phase I.

The effect of caffeine on tinnitus. Placebo beverage was used to check for expectation effects and provide a baseline level of change from which the caffeine effects were interpreted.

Within-group factor: 3 levels = 3 caffeine conditions. Used in Phase II ANOVA’s only.
Table XI. Individual results for all subjects (S) investigated. The mean result of the pitch matches (in Hz) and the associated threshold (dB SPL) and loudness matches (dB SPL) at the matched tinnitus frequency are presented. Mean results for noise thresholds and loudness matches to noise are also presented. Associated sensation levels for loudness matches to noise and tones are shown. Subjective ratings of tinnitus frequency and loudness on scales of 1 to 10 are also given. Location (L) is indicated by M (monaural), B (binaural), H (head) or B/H (binaural and head). The range of values recorded beneath the main table were derived from the raw data set.

<table>
<thead>
<tr>
<th>S</th>
<th>L</th>
<th>FREQ. (%)</th>
<th>FREQ. RATINGS</th>
<th>THRESHOLDS MATCHES</th>
<th>LOUDNESS MATCHES</th>
<th>LOUDNESS RATINGS</th>
<th>SENSATION LEVELS</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tone Noise</td>
<td>Tone Noise</td>
<td>Tone Noise</td>
<td>Tone Noise</td>
<td>Tone Noise</td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>4237</td>
<td>5.3</td>
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<td>4.3</td>
<td>18.9  29.1</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>3546</td>
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<td>8.0  12.5</td>
</tr>
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<tr>
<td></td>
<td></td>
<td>595</td>
<td>3.3</td>
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<td>20.4  17.5</td>
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<td>6.1  2.9</td>
</tr>
<tr>
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<td>M</td>
<td>4802</td>
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<td>2.8</td>
<td>37.8 25.5</td>
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<td>M</td>
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<td>10.4 10.2</td>
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<td>9</td>
<td>B/H</td>
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<td>28.0  38.4</td>
<td>4.6</td>
<td>26.9 23.7</td>
</tr>
<tr>
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<td>B</td>
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<td>7.0</td>
<td>10.3 11.2</td>
</tr>
<tr>
<td>11</td>
<td>B</td>
<td>733</td>
<td>5.6</td>
<td>53.6  33.0</td>
<td>58.1  52.3</td>
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<td>5.1  5.2</td>
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<td>12</td>
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<td>3007</td>
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<tr>
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</tr>
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<tr>
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<td>H</td>
<td>2085</td>
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<td>25.4 14.1</td>
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<td>11.0 9.8</td>
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<tr>
<td>16</td>
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<td>2288</td>
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<td>17.1  8.9</td>
<td>36.7  21.2</td>
<td>1.0</td>
<td>19.7 12.2</td>
</tr>
</tbody>
</table>

**MEAN:** 2061 5.9 24.8 17.6 37.7 33.9 4.9 13.9 12.6

**RANGE:** 398 2.3 3.0 4.8 16.7 15.2 1.0 4.9 3.1

**SD:** 1644 2.07 16.1 14.5 15.3 16.2 2.3 8.5 6.9

1. For subjects 3 and 12 two lines of data are presented. Subjects 3 and 12 were classified as having complex tinnitus, i.e., 2 or more distinct sounds which could be consistently matched. Each line of data is in reference to the sound being measured.

2. Threshold measures for noise were not recorded for each sound component. All subjects were given a noise threshold test; data was averaged across both left and right ears.
provide an overview of the subject population with regard to each of the auditory measures prior to caffeine. Reference will be made to the table throughout the course of the results.

Subjects described their tinnitus with, for example, the following adjectives: one predominant tone in noise, sizzling, buzzing, a single musical note or tone, crickets, cicadas and hissing. The incidence of various types of tinnitus sounds from the Personal Assessment Form (Appendix II) and their relation to the matched frequency of tinnitus are shown in Figure 1.

Figure 1 shows a correspondence between the different types of sound and its pitch characteristic. Subjects who reported 'a single tone or musical note' all matched their tinnitus pitch to frequencies on or below 3000 Hz, whereas checking 'a predominant tone in noise' indicated either a low frequency (0-2000 Hz) or a high frequency (5000 - 9000 Hz) match. Sounds like ringing, crickets, humming, buzzing, high tension wire noise and cicadas were not matched above 3000 Hz whilst transformer noises and whistling were associated with matches on or above 5000 Hz. Hissing was matched across the frequency spectrum.
Figure 1. Incidence of types of tinnitus sounds averaged across the Phase I testing sessions and the relation between the type of sound and the frequency of the external sound matched to the tinnitus.
Pitch Matches to a Tone

The mean pitch of tinnitus prior to caffeine was matched at 2601 Hz (standard deviation (SD) = 1644 Hz), ranging from 398 Hz to 10789 Hz. Eighty-nine percent, that is, 16 of the 18 matches, were made within a frequency range of 0 Hz to 5000 Hz. Of these matches, 61% (11 of the 18 matches) were no higher in frequency than 3000 Hz.

Data from Phase I before caffeine were subjected to a three-way analysis of variance with time condition and tinnitus location as the between-subject factors and between session assessments as the within-subject variable. The dependent measure was the frequency of the six pitch matches completed across the six Phase I testing sessions. While Table XI attests to individual differences in the pitch of tinnitus, there were no significant differences between subjects assigned to the 30 versus 60 minute time condition (F(1, 14)=4.1, n.s) and those with unilateral versus bilateral or head tinnitus (F(1, 14)=3.8, n.s) prior to caffeine. The associated interaction was not significant (time condition by tinnitus location: F<1). In addition, the ANOVA showed no significant differences in the week-by-week frequency matches of tinnitus pitch (F(2, 28)=1.9, n.s). The following interactions were not significant: tinnitus location by week-by-week variability (F(2, 28)=1.71, n.s); time condition by week-by-week variability (F<1); and tinnitus location by time condition by week-by-week variability (F<1).

Data from the Phase II pitch matches were also subjected to ANOVA. The within-group factor was caffeine condition and the dependent measure was the difference in frequency between Phase I and II after each of the three caffeine solutions. There were no significant main effects for tinnitus location (F(1, 14)=1.3, n.s) or caffeine condition (F<1) and this factor did not significantly interact with tinnitus location (F<1), time condition (F<1) or tinnitus location by time condition (F<1). There was no evidence, therefore, that caffeine altered the pitch of tinnitus. There were, however, significant changes in the pitch of tinnitus during each session (F(1, 14)=4.9, p<.05). There was a greater increase in tinnitus pitch after 60 (403.3 Hz) than 30 minutes (309.7 Hz).
The relationship between the frequency at which hearing loss was most severe and the frequency of tinnitus was examined. There was no association between the two variables as Table XII indicates. The frequency of hearing loss did not correspond to the matched tinnitus frequency.

Table XII. Association between frequency at which hearing loss was most severe and the frequency of the matched tinnitus.

<table>
<thead>
<tr>
<th>Frequency of Severe Hearing Loss (in Hz)</th>
<th>Matched Tinnitus Frequency (in Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4000</td>
<td>1</td>
</tr>
<tr>
<td>5000</td>
<td></td>
</tr>
<tr>
<td>6000</td>
<td>1 1 2</td>
</tr>
<tr>
<td>8000</td>
<td>1 1 2</td>
</tr>
</tbody>
</table>

Note: Subjects 6, 8 and 16 were not included in this distribution as their pure tone thresholds did not exceed 5.0 dB HL at any of the tested frequencies.

**Subjective Reports** how 'low' and 'high' in sound tinnitus was (judged on a 10-point rating scale: '1' = very low sound; '10' = very high sound) at Phase I showed that there were significant changes in week-by-week ratings ($F_{92, 28}= 6.6, p<.005$). The pitch of tinnitus was rated as a higher sound in weeks 5 and 6 (mean = 6.24) versus weeks 1 and 2 (mean = 5.4) and weeks 3 and 4 (mean = 5.5). *A posteriori* comparison showed that rated frequency at weeks 5 and 6 was significantly higher than in weeks 1 and 2 ($q(3, 26)=0.77, p<.05$; Tukey) and 3 and 4 ($q(3, 26)= 0.71, p<.05$; Tukey). There was no difference between the mean ratings at week 1 and 2 versus 3 and 4 ($q (3, 26)=0.1$, n.s.; Tukey).

Analysis of Phase II data, with the difference between Phase I and II ratings as the dependent variable showed that there were no significant increases or decreases in frequency ratings during each session ($F<1$). Subjects rated the frequency of their tinnitus to fall on or about, consistently, a particular numerical value on the scale.
Table XIII attests to this finding by demonstrating the limited range of ratings made at Phase I and II of the assessment sessions.

The ANOVA also showed no significant main effect for caffeine ($F<1$) or the related interactions: caffeine condition by tinnitus location ($F(2, 28)=1.28$, n.s); caffeine condition by time condition ($F<1$); and caffeine condition by tinnitus location by time condition ($F<1$). Frequency ratings were not, therefore, affected by caffeine. This finding was in line with the results from the pitch match tests at Phase II - caffeine did not alter the perceived pitch of tinnitus.

Subjective ratings significantly correlated with the frequency values corresponding to the pitch of tinnitus both before and after caffeine. The correlations are reported in Table XIV. Pitch matches to a tone were a relatively good measure of subject's perceptions of tinnitus pitch (or vice versa).

A summary of the findings from this subsection of the results is presented in Table XV.
Table XIII. Mean subjective ratings of tinnitus frequency made by each subject during each testing session, that is, at Phases I and II. The mean values were derived by averaging the Phase I and II ratings, respectively.

<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Rating at Phase I:</td>
<td>5.0</td>
<td>6.4</td>
<td>7.5</td>
<td>3.2</td>
<td>5.3</td>
<td>8.5</td>
<td>5.2</td>
<td>8.2</td>
<td>2.3</td>
<td>6.8</td>
<td>2.6</td>
<td>5.6</td>
<td>7.3</td>
<td>3.5</td>
<td>7.3</td>
<td>5.0</td>
</tr>
<tr>
<td>Mean Rating at Phase II:</td>
<td>5.0</td>
<td>6.5</td>
<td>6.1</td>
<td>3.3</td>
<td>5.6</td>
<td>8.3</td>
<td>4.6</td>
<td>7.8</td>
<td>2.6</td>
<td>7.3</td>
<td>2.8</td>
<td>5.6</td>
<td>6.7</td>
<td>3.3</td>
<td>6.8</td>
<td>5.0</td>
</tr>
</tbody>
</table>

1. For Subjects 3 and 12 two columns of data are presented. Subjects 3 and 12 were classified as having complex tinnitus, i.e., two or more sounds which could be consistently matched and rated. Each column of data refers to each sound, respectively. The predominant sound is reported in the first of the two columns.
Table XIV. Correlations between subjective frequency ratings and the frequency value representative of the pitch of tinnitus before and after caffeine.

<table>
<thead>
<tr>
<th>OBJECTIVE MEASURE</th>
<th>SUBJECTIVE FREQUENCY RATINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior Pla-</td>
</tr>
<tr>
<td></td>
<td>cebo</td>
</tr>
</tbody>
</table>

Pitch Matches to a Tone: 0.51* 0.47* 0.57^ 0.59^ 0.59^ 0.56^  

Key: * p< .05    ^ p< .02

Table XV. Summary of the findings for pitch matches to tinnitus and subjective frequency ratings.

<table>
<thead>
<tr>
<th>EFFECT OF CAFFEINE</th>
<th>VARIABILITY OF TINNITUS PITCH</th>
</tr>
</thead>
</table>

Pitch Matches:
Low and high doses of caffeine did not affect the pitch of tinnitus.  
Additional Points:
There was no correspondence between frequency level of hearing loss and matched T/F.

Subjective Ratings:
Low and high doses of caffeine did not alter subjective frequency ratings of tinnitus pitch.

Correlation Findings:
Frequency ratings correlated with pitch matches - pitch match tests were relatively good measures of subjective perceptions of tinnitus frequency both before and after caffeine.
Tone and Noise Thresholds

The overall mean threshold for a tone at the matched tinnitus frequency (referred to as 'T/F') was 24.8 dB SPL with a standard deviation of 16.2 dB SPL. Thresholds at T/F ranged from 3.0 dB SPL to 81.7 dB SPL. The range of thresholds for noise was 4.8 dB SPL to 72.8 dB SPL with an overall lower mean of 17.6 dB SPL (SD=17.6 dB SPL). Plotting the threshold at T/F against the noise threshold (Figure 2) suggests that there was a difference in the distribution of threshold responses to the two stimuli. Eighty-one percent of the noise thresholds were below 21 dB SPL, but only 44% of the tone thresholds fell within this range. Eighty-eight percent of the thresholds at T/F fell within a 0 dB SPL to 41 dB SPL range, comparable to 94% of the noise thresholds.

A planned t-test (for related measures) showed that tone and noise thresholds were significantly different prior to the ingestion of caffeine (t(15)=2.1, p<.05). Noise thresholds (mean=17.6 dB SPL) were comparable to the mean response of subjects to the pure tone audiometry test (mean = 18.1 dB HL; t(15)=0.74, n.s). This was not found for threshold measures at the matched tinnitus frequency (mean= 24.8 dB SPL; t(15)=1.85, p<.05). Subject's thresholds for a tone at matched T/F were higher than the mean responses to the pure tone audiometry test. Individual differences across the tone and noise thresholds can be seen from Table XI.

Analysis of Phase I results showed that there was no significant difference in week-by-week threshold measures (threshold at T/F, F<1; noise threshold, F<1). There were no significant differences between subjects on the basis of tinnitus location (threshold at T/F, F<1; noise threshold, F<1) and time condition assignment (threshold at T/F, F<1; noise threshold, F<1). The related interactions were also not significant: tinnitus location by time condition (threshold at T/F, F<1; noise threshold, F<1).

Analysis of the Phase II measures using the difference in threshold between Phase I and II as the dependent variable, showed a significant increase in tone threshold at 60 minutes (mean = 9.4 dB SPL) but not 30 minutes (mean = 0.5dB SPL; F(1, 14) =19.7, p<.001). This was not found for noise thresholds (F<1). Caffeine did not affect the threshold at T/F (F (2, 28) = 1.18, n.s). The related interactions were not
Figure 2. Frequency distribution of threshold responses to a tone at the matched tinnitus frequency and to a broadband of noise. The range of threshold categories were established from the mean values (as seen on Table XI) derived from the six, Phase I/before caffeine testing sessions.

significant: caffeine condition by tinnitus location (F<1); caffeine condition by time condition (F<1); and caffeine condition by tinnitus location by time condition (F(2, 28)=1.5, n.s). Caffeine did affect, however, the threshold for noise (F(2, 24)= 3.7, p<.05). The related interactions were not significant: caffeine condition by tinnitus location (F(2, 24) = 2.81, n.s); caffeine condition by time condition (F(2, 24)=2.32, n.s); and caffeine condition by tinnitus location by time condition (F<1). Overall mean values for the caffeine effects are presented in Table XVI.

Low doses of caffeine elevated the noise threshold. A planned t-test supported this result by showing that there was no difference between noise thresholds prior to and after the placebo (t<1). A posteriori pairwise comparison of the caffeine means revealed that low doses of caffeine produced a mean increase in threshold which was significantly different from the placebo value (q(3, 24)=4.66, p<.05 and high doses of caffeine q(3,24)=5.67, p<.01, respectively; Tukey). There was no significant difference between the increases in noise thresholds after placebo and high doses of caffeine (q(3, 24)=0.71, n.s; Tukey).
A summary of the results for this subsection is presented in Table XVII.

Table XVI. Mean increase (+) or decrease (-) in threshold (in dB SPL) at the matched tinnitus frequency and for noise after caffeine. Standard errors are recorded in brackets beneath the corresponding mean value.

<table>
<thead>
<tr>
<th>Caffeine Condition</th>
<th>Threshold at T/F</th>
<th>Threshold for Noise</th>
</tr>
</thead>
<tbody>
<tr>
<td>After Placebo</td>
<td>+0.91 dB SPL</td>
<td>+0.15 dB SPL</td>
</tr>
<tr>
<td></td>
<td>(4.86)</td>
<td>(4.18)</td>
</tr>
<tr>
<td>After Low Doses of Caffeine</td>
<td>+1.98 dB SPL</td>
<td>+4.81 dB SPL</td>
</tr>
<tr>
<td></td>
<td>(7.90)</td>
<td>(4.51)</td>
</tr>
<tr>
<td>After High Doses of Caffeine</td>
<td>-0.59 dB SPL</td>
<td>-0.86 dB SPL</td>
</tr>
<tr>
<td></td>
<td>(8.82)</td>
<td>(6.28)</td>
</tr>
</tbody>
</table>

Table XVII. Summary table for the results presented in the tone and noise thresholds subsection.

**EFFECT OF CAFFEINE**

**Thresholds at T/F:**
Low and high doses of caffeine did not affect thresholds at T/F.

**VARIABILITY OF THRESHOLDS**

Threshold responses to a tone at T/F did not significantly change week-by-week.
Threshold at T/F were significantly different at Phase I versus Phase II of each testing session. Thresholds were elevated after 60 minutes.

**Noise Thresholds:**
Low doses of caffeine elevated the noise threshold. High doses did not affect noise thresholds.

Noise thresholds did not change week-by-week. Responses at Phase I versus II of each session were not significantly different.
Loudness Matches at the Frequency of Tinnitus Pitch

The overall mean for loudness matches at T/F in Phase I was 37.7 dB SPL (SD=15.3 dB), ranging from 16.7 dB to 80.4 dB SPL. A frequency distribution of loudness matches at T/F and to noise can be seen in Figure 3. The majority of loudness matches were on or below 50 dB SPL: 33% (that is, 6 of the 18 matches) fell within a loudness range of 11 dB to 30 dB SPL with a further 55% (10 of the 18 matches) falling within a loudness range of 31 dB to 50 dB SPL. No subject had a mean loudness match below 10 dB SPL.

![Figure 3. Distribution of loudness matches to noise plotted against loudness matches at the frequency of the tinnitus pitch. The mean loudness for each subject was calculated from the six, Phase I testing sessions. The range and categories of tinnitus loudness were established from these mean values.]

Analyses of the Phase I data showed that there were no significant differences in week-by-week loudness matches to a tone at T/F (F<1). There were no significant differences between the subjects on the basis of tinnitus location (F<1) and time condition assignment (F<1). The associated interactions were not significant: week-by-week variability by tinnitus location (F<1); week-by-week variability by time...
condition (F<1); and week-by-week variability by tinnitus location by time condition (F(2, 28)=1.38, n.s).

Loudness matches to a tone at T/F from Phase II were subject to ANOVA with caffeine condition as the within-subject factor. The dependent variable was the difference in loudness matches between Phases I and II. The ANOVA showed significant changes in loudness matches during each session (F(1, 14)=11.7, p<.01). Tinnitus was matched to a more intense tone after 60 minutes but not after 30 minutes. Table XVIII presents the corresponding mean values.

<table>
<thead>
<tr>
<th>TIME CONDITION</th>
<th>MEAN INCREASE OR DECREASE</th>
<th>SD</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 30 minutes</td>
<td>-0.61 dB SPL</td>
<td>6.63</td>
<td>-13.5dB to +13.2dB</td>
</tr>
<tr>
<td>After 60 minutes</td>
<td>+5.3 dB SPL</td>
<td>7.74</td>
<td>-13.5dB to +16.7dB</td>
</tr>
</tbody>
</table>

The ANOVA further showed that the predicted effect of caffeine on the loudness of tinnitus was significant (F(2, 28)=3.64, p<.05). There were no interaction effects between caffeine condition by time condition (F(2, 28)=2.59, n.s) and, caffeine condition by tinnitus location (F(2, 28)=2.63, n.s). There was, however, a significant three-way interaction of caffeine condition by time condition by tinnitus location (F(2, 28)=4.14, p<.025).

A planned t-test showed that there was no significant difference in loudness matches to a tone at T/F prior to and after the placebo (t<1). A posteriori pairwise comparison of the main effect for caffeine showed that changes in the loudness matches at T/F were significantly higher after low doses (mean = 5.6 dB) versus placebo (mean = 1.24 dB, q(3, 28)=4.38, p<.05; Tukey) and high doses of caffeine (mean = 0.17 dB, q(3, 28)=5.43, p<.05; Tukey). There was no significant difference between loudness matches after placebo and high doses of caffeine (q(3, 28)=0.67, n.s; Tukey).

With regard to the caffeine condition by tinnitus location by time condition
interaction, a planned t-test (for related measures) showed that there were no differences in loudness matches between Phase I/before caffeine and Phase II/after placebo measures for subjects with unilateral tinnitus in the 30 minute ($t(3)=0.25$, n.s) and 60 minute time conditions ($t(4)=0.63$, n.s.), and for subjects with bilateral or head tinnitus in the 30 ($t(4)=1.5$, n.s) and 60 minute time conditions ($t(2)=1.48$, n.s). Increases or decreases in loudness as a result of low and high doses of caffeine have been given in terms of deviation from the placebo value which has been taken as a standard baseline level. Graphical presentations of the interactions are shown in Figures 4 and 5.

It can be seen from Figure 4 that changes in loudness matched to a tone at T/F were similar for subjects with unilateral tinnitus in both the 30 and 60 minute time conditions. Low doses of caffeine had no effect on loudness matches at T/F 30 and 60 minutes after ingestion. High doses of caffeine decreased the loudness of tinnitus. After 30 and 60 minutes the loudness of tinnitus significantly decreased below the standard/placebo level.

Comparison of Figure 4 with Figure 5 shows that 30 minutes after the ingestion of caffeine subjects with bilateral or head located tinnitus experienced similar changes in loudness to subjects with unilateral tinnitus. Low doses of caffeine had no effect on loudness matches to a tone at T/F. High doses of caffeine decreased the intensity. An F-test for simple effects supported these findings by showing that the effect of caffeine 30 minutes after ingestion was dose-dependent for unilateral tinnitus ($F(2, 9)=11.39$, $p<.005$) and bilateral or head tinnitus ($F(2, 15)=8.48$, $p<.025$). The F-test for simple effects further showed that the decrease in loudness 30 minutes after the ingestion of a high dose was greatest for subjects with bilateral or head tinnitus versus unilateral tinnitus ($F(1, 8)=64.01$, $p<.001$).

There was, however, a different set of results for subjects with bilateral or head tinnitus who waited 60 minutes after the ingestion of high doses of caffeine. Low and high doses of caffeine both increased the loudness of tinnitus (Figure 5). An F-test for simple effects supported this finding: the degree of increase in loudness was dose-dependent ($F(2,6)=8.43$, $p<.025$).
Figure 4. Changes in loudness at T/F as a function of caffeine dose based on subjects with unilaterally-located tinnitus who waited 30 and 60 minutes after ingestion.

Figure 5. Changes in loudness at T/F as a function of caffeine dose based on subjects with bilaterally or head-located tinnitus who waited 30 and 60 minutes after ingesting caffeine.
The test for simple effects further showed that the length of time waited after the ingestion of low and high doses of caffeine for subjects with bilateral or head tinnitus was an important factor ($F(1, 7)=7.65, p<.05$, Figure 6; $F(1, 7)= 8.6, p<.025$, Figure 7). Low doses of caffeine increased the loudness of bilateral or head tinnitus after 60 minutes but not after 30 minutes. Figure 6 supports the established finding that low doses of caffeine had no effect on the loudness of unilateral tinnitus matched to a tone at T/F.

Thirty minutes after high doses of caffeine the intensity of bilateral or head tinnitus matched to a tone at T/F decreased. After 60 minutes, however, loudness had increased. High doses of caffeine caused the loudness of bilateral or head tinnitus to decrease then increase. Furthermore, it can be seen from Figure 7 that both 30 and 60 minutes after high doses of caffeine there was a significant decrease in the loudness of unilateral tinnitus. The F-test for simple effects showed no significant difference in loudness after high doses of caffeine versus the initial effect after low doses of caffeine ($F(1, 7)=1.48$, n.s).

A summary of the findings reported in this subsection of the results is presented in Table XIX.
Figure 6. The patterns of loudness change 30 and 60 minutes after ingesting low doses of caffeine for both location groups.

Figure 7. The patterns of loudness change 30 and 60 minutes after ingesting high doses of caffeine for both location groups.
Table XIX. Summary of the overall findings for loudness matches to a tone at the tinnitus frequency.

<table>
<thead>
<tr>
<th>EFFECT OF CAFFEINE</th>
<th>VARIABILITY OF LOUDNESS MATCHES AT TINNITUS FREQUENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low Doses:</strong></td>
<td></td>
</tr>
<tr>
<td>Low doses did not affect the loudness</td>
<td>There were differences in loudness matched to a tone at T/F within each session. Tinnitus was matched to a more intense tone after 60 minutes but not after 30 minutes. Loudness matches did not change significantly week-by-week.</td>
</tr>
<tr>
<td>of unilateral tinnitus up to 60 minutes after ingestion. Low doses increased loudness of bilaterally- or head-located tinnitus. This effect was heightened on or about 60 minutes after ingestion. There was no significant effect after 30 minutes.</td>
<td></td>
</tr>
<tr>
<td><strong>High Doses:</strong></td>
<td></td>
</tr>
<tr>
<td>High doses decreased loudness for sub-</td>
<td></td>
</tr>
<tr>
<td>jects with unilateral tinnitus. This effect was heightened on or about 60 minutes after ingestion. High doses decreased bilateral tinnitus after 30 minutes, but increased it after 60 minutes.</td>
<td></td>
</tr>
<tr>
<td><strong>Additional Points:</strong></td>
<td></td>
</tr>
<tr>
<td>When high doses decreased loudness,</td>
<td></td>
</tr>
<tr>
<td>the loudness level was either comparable</td>
<td></td>
</tr>
<tr>
<td>to or lower than the Phase 1/before</td>
<td></td>
</tr>
<tr>
<td>caffeine loudness measure.</td>
<td></td>
</tr>
</tbody>
</table>
Loudness Matches to Noise

The overall mean of the loudness matches to noise at Phase I was 33.9 dB SPL (SD=16.2 dB SPL), ranging from 15.2 dB to 80.5 dB SPL. Eleven subjects (61%) matched the loudness of their tinnitus to a noise level ranging from 31 dB to 50 dB SPL, with 22% (4 subjects) and 16% (3 subjects) falling within a range of 11 dB to 30 dB SPL and 61 dB to 80 dB SPL, respectively. No subjects matched below 10 dB SPL. A comparison between the frequency distributions of loudness matches to noise and to a tone at the T/F (see Figure 3) suggests that noise matches were comparable in range to those completed at the matched tinnitus frequency. A planned t-test (for related measures) found that there was no difference between subjects loudness matches to noise and T/F (t(17)=0.68, n.s). Viewing Table XI in the General Results section, the similarities between subjects loudness matches to noise and at T/F are evident.

Analysis of Phase I data showed no significant difference in loudness matches to noise between subjects assigned to the 30 versus 60 minute time condition (F(1, 14)=1.7, n.s) and unilateral versus bilateral or head tinnitus (F<1). Loudness matches to noise did not significantly alter week-by-week (F(2, 28)=1.7, n.s). The related interactions were not significant: time condition by tinnitus location (F<1); week-by-week variability by time condition (F<1); week-by-week variability by tinnitus location (F<1); and week-by-week variability by time condition by tinnitus location (F<1). The results of this ANOVA followed the same pattern established for loudness matches to a tone at T/F.

The Phase II data were subjected to the three-way ANOVA with the dependent measure being the difference in matched noise level between testing at Phase I and Phase II. The ANOVA showed a significant main effect for caffeine condition (F(2, 28)=50.77, p<.001) but no significant interaction effects: caffeine condition by tinnitus location (F(2, 28)=1.69, n.s); caffeine condition by time condition (F(2, 28)= 2.15, n.s); and caffeine condition by tinnitus location by time condition (F(2, 28)=1.7, n.s). The mean values for the caffeine conditions are presented in Table XX. Table XX also presents the mean values from the significant main effect of caffeine on loudness matches to a tone at T/F.
**Table XX.** Mean increases (+) or decreases (-) in the loudness of tinnitus (in dB SPL) matched to broadband noise (200 Hz to 10000 Hz) after low and high doses of caffeine. Standard deviations are presented in brackets beneath the corresponding mean. The mean increases or decreases in loudness matches for a tone at the tinnitus frequency as a result of caffeine are also reported.

<table>
<thead>
<tr>
<th>CAFFEINE CONDITION</th>
<th>LOUDNESS MATCH TO NOISE</th>
<th>LOUDNESS MATCH AT T/F</th>
</tr>
</thead>
<tbody>
<tr>
<td>After Placebo</td>
<td>-0.52 dB SPL (1.65)</td>
<td>+1.24 dB SPL (6.90)</td>
</tr>
<tr>
<td>After Low Doses of Caffeine</td>
<td>+5.07 dB SPL (2.82)</td>
<td>+5.6 dB SPL (6.13)</td>
</tr>
<tr>
<td>After High Doses of Caffeine</td>
<td>+7.24 dB SPL (2.44)</td>
<td>+0.17 dB SPL (8.45)</td>
</tr>
</tbody>
</table>

Placebo beverages had no effect on loudness matches to noise across Phase I and II, decreasing Phase II loudness by (-)0.52 dB SPL below the Phase I level. A planned t-test (for related measures) showed that loudness matches to noise prior to caffeine and after placebo were not significantly different (t(17)=1.46, n.s). A posteriori pairwise comparison of the caffeine condition means showed that increases in loudness after low and high doses of caffeine were significantly higher than after the placebo (low versus placebo: q(3, 28)=5.58, p<.01; high versus placebo: q(3, 28)=7.75, p<.01; Tukey). Increases in loudness after high doses of caffeine were significantly higher than after low doses of caffeine (q(3, 28)=2.2, p<.05; Tukey). The distribution of tinnitus loudness after low and high doses of caffeine has been plotted together with the distribution of loudness matches to noise prior to caffeine (as shown in Figure 8). The distribution of loudness matches to noise after low and high doses of caffeine shows a marked increase in the number of loudness matches falling within 21 dB to 30 dB SPL after low doses and 31 dB to 40 dB SPL after high doses compared with Phase I levels, whereas, prior to caffeine, matches commenced at 10 dB SPL.

Caffeine's effect on loudness matches to noise was not dependent on the time condition or tinnitus location, hence a less complex pattern of results emerged when compared with loudness matches to a tone at T/F. Tinnitus location and time condition interacted with the caffeine manipulation to affect the intensity of a tone.
**Figure 8.** Distribution of loudness matches to noise after high and low doses of caffeine plotted against the distribution prior to the ingestion of caffeine.

matched to the tinnitus. In addition, Table XX raises the issue of differences in standard deviation (SD) between loudness matches to a tone at T/F and to noise. Greater variance was associated with loudness matches to a tone at T/F than to noise.

A summary of the overall results is presented in Table XXI.

<table>
<thead>
<tr>
<th>Table XXI. Summary of the overall findings for loudness matches to noise.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFECT OF CAFFEINE</strong></td>
</tr>
<tr>
<td><strong>Low Doses:</strong></td>
</tr>
<tr>
<td>Low doses of caffeine increased the intensity of noise matched to tinnitus.</td>
</tr>
<tr>
<td><strong>High Doses:</strong></td>
</tr>
<tr>
<td>High doses of caffeine increased the intensity of noise matched to tinnitus.</td>
</tr>
<tr>
<td><strong>Additional Points:</strong></td>
</tr>
<tr>
<td>Increases in loudness were dose-dependent - the higher the dose, the greater the increment in loudness.</td>
</tr>
<tr>
<td>Effect of caffeine on tinnitus followed the same pattern for noise thresholds and loudness matches to noise.</td>
</tr>
</tbody>
</table>
Subjective Ratings of Loudness

The overall mean rating of loudness (on a scale of 1 to 10: 1=very soft; 10=very loud) was 4.96 (SD=2.3), with a range from 1.0 to 10. Whilst Table XI in the General Results section attests to the individual differences in loudness ratings, analysis of the Phase I values indicated that subjects grouped on the basis of time condition and reported tinnitus location did not significantly differ on loudness ratings (F<1; F(1, 14)=2.51, n.s, respectively). There were also no significant differences in week-by-week loudness ratings (F<1).

Subjective loudness ratings from Phase II were subjected to ANOVA with caffeine condition as the within-subject variable. The dependent variable was the difference in ratings between Phase I and II. The ANOVA showed no significant changes in loudness ratings during each session (F<1). The ANOVA showed a significant main effect for caffeine (F(2, 28)=34.5, p<.001) and a significant three-way interaction for caffeine condition by time condition by tinnitus location (F(2, 28)=4.45, p<.05). No significant interactions were found for caffeine condition by time condition (F(2, 28)=2.78, n.s) and caffeine condition by tinnitus location (F(2, 28)=1.17, n.s).

A posteriori pairwise comparison of the means for the significant caffeine main effect showed that loudness ratings after low and high doses of caffeine were significantly higher than those made after the placebo (low dose: q(3, 28)=0.81, p<.01; high dose: q(3, 28)=1.14, p<.01; Tukey). There was no difference in subjective ratings after high and low doses of caffeine (q(3, 28)=0.14, n.s; Tukey). These findings parallel the results found for loudness matches to noise but not to a tone at the matched T/F. Low and high doses of caffeine increased the intensity of noise matched to tinnitus but loudness matches to a tone at T/F were only elevated after low doses.

Figures 9 and 10 show the effect of time condition and tinnitus location on the subjective ratings of loudness after low and high doses of caffeine (F(2, 28)=4.45, p<.05). An F-test for simple effects showed that caffeine produced significant increments in loudness ratings for both subject groups and time conditions: Unilateral tinnitus after 30 minutes (F(2, 9)=5.46, p<.05) and 60 minutes (F(2, 12)=24.6, p<.001); Bilateral or head tinnitus after 30 minutes (F(2, 15)=16.04, p<.001)
Figure 9. Changes in subjective ratings of loudness after caffeine ingestion based on subjects with unilateral tinnitus after 30 and 60 minutes duration.

Figure 10. Changes in subjective ratings of loudness after caffeine ingestion based on subjects with bilateral or head tinnitus after 30 and 60 minutes duration.
and 60 minutes \((F(2, 6)=6)=10.94, p<.025\).

The F-test for simple effects further showed that the location of tinnitus for subjects who waited 30 minutes after the ingestion of low and high doses of caffeine was an important factor. Subjects with unilaterally-located tinnitus rated loudness as increasing more after low doses of caffeine than bilateral or head tinnitus \((F(1, 8)=8.59, p<.025\). Similarly, 30 minutes after high doses of caffeine subjects with unilateral tinnitus rated loudness as increasing more than bilateral or head located tinnitus \((F(1, 8)=7.0, p<.025\). Loudness ratings 30 minutes after low and high doses of caffeine were, however, higher than the ratings made at 60 minutes for unilateral tinnitus \((F(1, 7)=4.8, p<.05\); \(F(1, 7)=8.4, p<.025\), respectively). Subjects with bilateral or head tinnitus rated the effect of high doses of caffeine as greater after 60 than 30 minutes \((F(1, 7)=8.89, p<.025\;\text{Means }= 1.5 \text{ and } 0.83\), respectively).

Caffeine, time condition and tinnitus location differentially affected subjective ratings of loudness and loudness matches to a tone at T/F. Subjects with unilateral tinnitus rated its loudness as increasing 30 and 60 minutes after low and high doses of caffeine. There was no corresponding increase in loudness matches to a tone at T/F. Low doses of caffeine did not affect the loudness of unilateral tinnitus but high doses decreased the loudness after both 30 and 60 minutes. Subjects with bilateral or head tinnitus rated loudness as increasing 60 minutes after low and high doses of caffeine but decreasing 30 minutes after high doses. Loudness matches to a tone at T/F similarly decreased 30 minutes after high doses of caffeine with increases in loudness 60 minutes after low and high doses. The loudness ratings completed by subjects with bilateral or head tinnitus paralleled the results from the loudness matches at T/F. No comparison can be drawn with loudness matches to noise as analysis of this data did not yield a caffeine condition by time condition by tinnitus location interaction.

Loudness matches to a tone at T/F were not correlated with subjective ratings of loudness either before or after caffeine. There was, however, a significant correlation between loudness ratings and matches to broadband noise both before and after caffeine. Correlations between loudness ratings and loudness matches are shown in Table XXII.
A summary of the overall results presented in the Subjective Ratings subsection is shown in Table XXIII.

### Table XXII. Correlation between subjective loudness ratings and loudness matches to a tone at the matched tinnitus frequency and to noise.

<table>
<thead>
<tr>
<th>OBJECTIVE MEASURES</th>
<th>SUBJECTIVE LOUDNESS RATINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior Placebo</td>
</tr>
<tr>
<td>Loudness Matches to Noise</td>
<td>0.59^</td>
</tr>
<tr>
<td>Loudness Matches at T/F</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Key: ^ p < .02 * p < .05

### Table XXIII. Summary of the overall findings for subjective ratings of loudness.

<table>
<thead>
<tr>
<th>EFFECT OF CAFFEINE</th>
<th>VARIABILITY OF LOUDNESS MATCHES TO NOISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loudness ratings increased after low and high doses of caffeine.</td>
<td>Loudness ratings did not significantly increase or decrease week-by-week. Ratings completed during each session, at Phases I and II were not significantly different.</td>
</tr>
<tr>
<td><strong>Low Doses:</strong> 30 minutes after ingestion, subjects with unilateral tinnitus rated tinnitus louder than those with bilateral or head tinnitus. Similarly, 60 minutes after ingestion, unilateral tinnitus was rated louder than bilateral or head tinnitus.</td>
<td></td>
</tr>
<tr>
<td><strong>High Doses:</strong> 60 minutes after ingestion, bilateral or head tinnitus was rated as louder than after 30 minutes. Unilateral tinnitus was rated louder after 30 minutes than 60 minutes.</td>
<td></td>
</tr>
<tr>
<td><strong>Correlation Findings:</strong> Loudness matches to noise were significantly correlated with subjective ratings of loudness prior to and after caffeine. Loudness matches at T/F did not correlate with loudness ratings.</td>
<td></td>
</tr>
</tbody>
</table>
Sensation Level of Loudness Matches

The sensation level of loudness matches to a tone at T/F and to noise were analysed to check that differences in loudness matches expressed in SPL could not be traced to difference in tone and noise thresholds, but reflected changes in loudness per se.

The sensation levels (SL) of loudness matches to noise and tone stimulus were calculated for each subject. The overall mean for loudness matches at T/F and to noise prior to caffeine were, 13.9 dB SL (SD= 8.5; Range = 4.9 dB - 37.8 dB SL) and 12.6 dB SL (SD= 6.9; Range= 3.1 dB to 29.1 dB SL), respectively. It is evident that sensation levels of tinnitus for loudness matches at T/F and to noise were similar. A t-test for related measures further confirmed that there was no significant difference between sensation levels for loudness matches to a tone at T/F and to noise (t(17) =2.34, n.s). Frequency distributions of sensation levels are presented in Figure 11.

### Figure 11. Distribution of the sensation levels for loudness matches to noise and to a tone at the matched tinnitus frequency.

Analyses of sensation level data from Phase I showed that there was no significant difference in week-by-week loudness matches at T/F (F<1) and to noise (F<1). In addition, there were no main effects for time condition (loudness match at T/F: F(1, 14)=3.29, n.s; loudness matches to noise: F<1) and tinnitus location (loudness match at T/F: F<1; loudness match at T/F: F<1). The related interactions were not significant.
These results were expected as there were no differences between subjects on the basis of time condition or tinnitus location for threshold and loudness matches expressed in SPL.

The Phase II ANOVA showed significant differences between loudness matches to a tone at T/F (dB SL) during each session ($F(1, 14)= 5.43, p<.05$). Sensation level increased after 60 minutes (mean = 6.5 dB SL) but not after 30 minutes (mean = -0.92 dB SL). There were no significant changes in sensation level of loudness matches to noise during each session ($F(1, 14)=2.93, n.s$). These findings were expected as loudness matches to noise (dB SPL) were not significantly different at Phase I and II of each testing session whereas tone thresholds and loudness matches to a tone at T/F (dB SPL) increased after 60 but not 30 minutes.

The ANOVA also showed a significant main effect of caffeine condition on sensation level of loudness matches to noise ($F(2, 28)=5.84, p<.01$) but not to a tone at T/F ($F(2, 28)=1.7, n.s$). There were no significant interactions: caffeine condition by tinnitus location (loudness match at T/F: $F<1$; loudness match to noise: $F<1$); caffeine condition by time duration (loudness match at T/F: $F<1$; loudness match to noise: $F<1$); and caffeine condition by tinnitus location by time condition (loudness match at T/F: $F(2, 28)=1.64, n.s$; loudness match to noise: $F<1$). Mean values for the caffeine conditions are presented in Table XXIV.

A posteriori pairwise comparison of the caffeine condition means for loudness matches to noise showed that increases in sensation level after high doses of caffeine were significantly higher than the changes incurred after low doses of caffeine ($q(3, 28)=7.67, p<.01$; Tukey) and the placebo ($q(3, 28)=7.36, p<.01$; Tukey). There was no difference between Phase I and II sensation level after the placebo and low doses of caffeine ($q(3, 28)=0.31, n.s$; Tukey).

Figure 12 compares the sensation level results with the SPL results for the loudness matches at T/F and tone thresholds. Figure 13 compares the sensation level results with the SPL loudness matches to noise and noise thresholds. Changes in sensation level corresponded with changes in threshold and loudness matches to a tone at T/F and to noise, respectively.
Table XXIV. Mean increase (+) or decrease (-) in sensation level (dB) for loudness matches. Standard deviations are presented in brackets below the corresponding mean.

<table>
<thead>
<tr>
<th>CAFFEINE CONDITION</th>
<th>LOUDNESS MATCH AT T/F (SL)</th>
<th>LOUDNESS MATCH TO NOISE (SL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After Placebo</td>
<td>+0.31 dB SL (4.65)</td>
<td>+0.54 dB SL (4.64)</td>
</tr>
<tr>
<td>After Low Dose of Caffeine</td>
<td>+3.3 dB SL (7.41)</td>
<td>+0.23 dB SL (4.96)</td>
</tr>
<tr>
<td>After High Doses of Caffeine</td>
<td>+0.81 dB SL (4.16)</td>
<td>+7.92 dB SL (6.06)</td>
</tr>
</tbody>
</table>

Loudness matches (dB SL) to a tone at T/F and to noise were not significantly correlated with subjective ratings of loudness before and after caffeine. Table XXV presents the associated correlations.

Table XXVI summarises the findings presented in this subsection of the results.
Figure 12. Comparison of loudness matches and threshold increases or decreases at T/F (dB SPL) with the changes in sensation level after caffeine. The data points represent the mean difference in responses to caffeine between Phases I and II.

Figure 13. Comparison of loudness matches and threshold (dB SPL) increases or decreases to noise with changes in sensation level after caffeine. The data points represent the mean difference in response to caffeine between Phases I and II.
Table XXV. Correlation between subjective loudness ratings and the sensation level of loudness matches to a tone at the matched tinnitus frequency and to noise.

<table>
<thead>
<tr>
<th>OBJECTIVE MEASURES</th>
<th>SUBJECTIVE LOUDNESS RATINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior Placebo</td>
<td>After Placebo</td>
</tr>
<tr>
<td>Prior Low Dose</td>
<td>After Low Dose</td>
</tr>
<tr>
<td>Prior High Dose</td>
<td>After High Dose</td>
</tr>
</tbody>
</table>

| Sensation Level for Noise | -0.0 | -0.1 | 0.23 | 0.15 | -0.1 | -0.2 |
| Sensation Level at T/F   | -0.3 | -0.2 | -0.2 | -0.2 | -0.1 | 0.0  |

Key: ^ p < .02 * p < .05

Table XXVI. A summary of the findings concerning the sensation level (SL) of tinnitus for loudness matches to a tone at the matched tinnitus frequency and to noise.

EFFECTS OF CAFFEINE

Loudness Matches at T/F (dB SL):
Low and high doses of caffeine had no effect on sensation level for loudness matches to a tone at T/F.

Loudness Matches to Noise (dB SL):
High doses of caffeine increased the sensation level of tinnitus for loudness matches to noise.

Additional Points:
Sensation level of loudness matches to noise and to a tone at T/F (dB SL) corresponded with changes in threshold and loudness matches expressed in SPL.

Correlation Findings:
Sensation level of loudness matches to a tone at the T/F and to noise did not correlate with subjective ratings of loudness.

VARIABILITY OF SL

Loudness matches at T/F (dB SL) did not significantly change week-by-week. The SL of loudness matches at T/F increased after 60 but not 30 minutes during each session.

Loudness matches to noise (dB SL) did not significantly change week-by-week or during each session.
Individual Differences

Inherent in drug-related research is the expectation that certain individuals will not be affected by the drug manipulation. The results thus far have provided an overall understanding of the action of caffeine with regard to the entire subject population. In this subsection of the results, the individuals and the audiometric measurements not affected by caffeine will be addressed, briefly. Caffeine was defined as having no effect on a specified measure if the difference between tests at Phase I and Phase II did not exceed or was within 2.0 measurement units of the difference between Phases I and II after placebo. Pitch match and tone thresholds are not addressed as these measurements were found not to be affected by caffeine.

The results are presented in Table XXVII where the subject, audiometric test and corresponding caffeine doses are listed.

Subjects categorised as having complex tinnitus (Subjects 3 and 12 who heard two or more distinct sounds which could be consistently matched) found low doses of caffeine produced different effects on the two sounds. Low doses of caffeine had no effect on noise threshold and loudness matches to noise (dB SPL) for Subject 3's dominant (loudest) sound (sea-shells). This sound was affected by high doses of caffeine on all measures. Low and high doses of caffeine impacted on the less dominant sound (tone in noise) for all audiological measures.

For Subject 12 low doses of caffeine had no effect on the less dominant of the two tinnitus sounds (hissing-cricket). Low doses of caffeine did not affect loudness matches to noise (dB SPL) and the corresponding sensation level. High and low doses of caffeine did, however, affect the dominant sound (a single tone) on all measures.

The noise thresholds for Subjects 4, 7, 9, 11 and 16 were not affected by either low or high doses of caffeine. The noise threshold for Subject 8 was not affected by high doses of caffeine. High doses of caffeine had no effect on noise threshold for Subject 4, subsequent loudness matches to noise (dB SPL) remained unaffected. Loudness matches to a tone at T/F and to noise were not affected by low doses of caffeine for Subject 14. For Subject 2, neither high nor low doses of caffeine affected loudness matches to a tone at T/F (dB SPL) or the corresponding subjective ratings.
Ten subjects were not affected by low or high doses of caffeine or both on a number of different measures. The other subjects (1, 5, 6, 10, 13 and 15) were affected consistently by both low and high doses of caffeine on all audiometric tests.
Table XXVII. An overview of the subjects (S) not affected by low and/or high doses of caffeine. The differences in results between Phases I and II for the associated audiometric test are presented for placebo, low and high doses of caffeine. The data were derived from the raw data sets utilised for the ANOVAs. A minus sign (-) indicates a decrease in the corresponding stimulus characteristic from Phase I to II.

<table>
<thead>
<tr>
<th>S</th>
<th>Noise Threshold (dB SPL):</th>
<th>Loudness Matched to a tone at T/F (dB SPL):</th>
<th>Sensation Level of Loudness Matches at T/F:</th>
<th>Subjective Ratings of Loudness:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Not affected by low and high doses:</td>
<td>Not affected by low doses:</td>
<td>Not affected by low doses:</td>
<td>Not affected by low doses:</td>
</tr>
<tr>
<td></td>
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<td>Placebo: 1.5dB</td>
<td>Placebo: 0.7dB SL</td>
<td>Placebo: 0.0</td>
</tr>
<tr>
<td></td>
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<td>Low Dose: 1.4dB</td>
<td>Low Dose: 0.4dB SL</td>
<td>Low Dose: 0.03</td>
</tr>
<tr>
<td></td>
<td>High Dose: 1.4dB</td>
<td>High Dose: 9.0dB</td>
<td>High Dose: 11.4dB SL</td>
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<td>Not affected by low doses:</td>
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</tr>
<tr>
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<td>Low Dose: 1.05dB</td>
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<td>Low Dose: 0.4dB SL</td>
<td>Low Dose: 0.4dB</td>
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<tr>
<td></td>
<td>High Dose: 11.35dB</td>
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<td>High Dose: 11.4dB SL</td>
<td></td>
</tr>
<tr>
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<td>Not affected by high doses:</td>
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<td>Not affected by high doses:</td>
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<td>Low Dose: 0.4dB SL</td>
<td>Low Dose: 0.4dB</td>
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<td>High Dose: 11.4dB SL</td>
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<tr>
<td></td>
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<td></td>
<td>High Dose: -1.86dB</td>
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<td>Not affected by high doses:</td>
<td>Not affected by high doses:</td>
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<td>Placebo: 0.7dB SL</td>
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<tr>
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<td>Low Dose: -3.5dB</td>
<td>Low Dose: -1.3dB</td>
<td>Low Dose: 11.8dB</td>
<td></td>
</tr>
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<td>High Dose: -0.4dB</td>
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<tr>
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</tr>
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<tr>
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<td>High Doses: 0.1dB</td>
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</tr>
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<td>Not affected by low doses:</td>
<td>Not affected by low doses:</td>
</tr>
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<tr>
<td></td>
<td>Low Dose: 3.2dB</td>
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</tr>
<tr>
<td></td>
<td>High Dose: -10.3dB</td>
<td>High Dose: 8.4dB</td>
<td>High Dose: 4.0dB</td>
<td></td>
</tr>
<tr>
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<td>Low Dose: -1.3dB</td>
<td>Low Dose: 11.8dB</td>
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<td>High Dose: 11.8dB</td>
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</tr>
<tr>
<td>16</td>
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<td>Not affected by low and high doses:</td>
<td>Not affected by low and high doses:</td>
<td>Not affected by low and high doses:</td>
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<tr>
<td></td>
<td>Placebo: -0.2dB</td>
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<td>Placebo: -0.2dB</td>
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<tr>
<td></td>
<td>Low Dose: -0.15dB</td>
<td>Low Dose: -0.15dB</td>
<td>Low Dose: -0.15dB</td>
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</tr>
<tr>
<td></td>
<td>High Dose: -0.2dB</td>
<td>High Dose: -0.2dB</td>
<td>High Dose: -0.2dB</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

The present study aimed to determine the true nature of the relation between caffeine and tinnitus. Previous articles and authors have discussed the probable and anecdotal effects of caffeine on the disorder. The relation between the drug and the dysfunction has been seen as both simplistic and linear - caffeine is a stimulant and must, therefore, exacerbate the symptoms and sensation of tinnitus (Brown et al., 1981; DeBartolo, 1989; Evans, 1981; Goodey, 1981, 1986; Lechtenberg and Shulman, 1984; Manahan, 1980; Meyerhoff and Mickey, 1988; Pulec, 1979; Pulec et al., 1978; Saunders, 1986; Schleuning, 1981; Swaine, 1988). Statements such as: "Caffeine is a frequent contributor to the severity and degree of tinnitus" (Schleuning, 1981; p. 100) and, "The commonest drinks to cause trouble have been coffee and strong tea..." (Goodey, 1981; p. 263) imply a generalised and systemic action of caffeine. The results of the present study show, however, that the connection between caffeine and tinnitus is neither as simple nor as easily understood as implied by the current state of the literature. The effects of caffeine are not only dose-, time- and tinnitus location-dependent, but also differ with the type of stimulus presentation as well as individual reactions to the drug manipulation. One is reminded that:

The truth is rarely pure and never simple

(Wilde, 1964; p. 72).

In the following discussion interpretation of the results pertaining to the effect of caffeine on tinnitus will refer to the models and mechanisms of action postulated in the Introduction. The discussion contains only limited comparison with previous work in this field as there are no studies to date which have postulated or identified mechanisms or sites of action by which caffeine affects tinnitus.

The underlying premise of this experiment was that the stimulatory action of caffeine would affect tinnitus by exacerbating the hyperactive environment of the inner ear, auditory pathway and auditory cortex. The effect of caffeine on one area of the auditory system or CNS was predicted to affect tinnitus via a multiplicity of cellular,
and biochemical interconnections. The action of caffeine would either potentiate or suppress symptoms of tinnitus. A differential action for caffeine on the basis of reported tinnitus location was also postulated.

The results showed that subjective ratings of tinnitus pitch, the matched frequency of tinnitus pitch and tone thresholds were not affected by caffeine. Noise threshold and loudness matches to noise increased after caffeine. Caffeine increased the loudness level of bilateral or head tinnitus but decreased the loudness of unilateral tinnitus. Subjective ratings of tinnitus loudness mirrored the overall increase in loudness matches to noise after caffeine. Tinnitus pitch, tone thresholds and loudness matches to a tone at T/F increased during each session, irrespective of caffeine.

**Variation in Measures Associated with a Tonal Stimulus**

**Discussion of Results.** Pitch matches, tone thresholds, loudness matches to a tone at T/F (dB SPL) and the sensation level of the loudness matches increased during each testing session, independent of the drug manipulation. Tinnitus pitch increased 30 and 60 minutes after testing at Phase I. The increase at 60 minutes was greater than the increase at 30 minutes. Tone thresholds, loudness matches and the sensation level of loudness matches to a tone at T/F were elevated after 60 but not 30 minutes. The increase in these audiometric measures was not attributable to differences between subjects on the basis of their assignment to different time conditions. Analysis of tinnitus pitch, tone threshold, loudness matches to a tone at T/F and sensation level of the loudness matches in Phase I showed no significant difference between subjects assigned to wait 30 or 60 minutes.

However, the results showed no increase or decrease in the corresponding measures using broadband noise. There was no daily or weekly variation with these tests. Although tone thresholds were elevated when compared with noise thresholds at Phase I, the responses at Phase II showed a greater elevation in response to tone threshold. The results suggest, therefore, that tone stimuli may interfere with tinnitus, varying the responses on tonal measures irrespective of caffeine. Two explanations are tentatively proposed to account for this variation:
I. Suppression of Tinnitus by a Tone. Auditory nerve responses to two tones have been investigated by Sachs and Kiang (1968) who found that tone-driven activity of a single-fibre in response to one tone can be suppressed by the presence of a second tone. This phenomenon is termed two-tone suppression. The suppressing tone usually has its greatest effect at frequencies slightly above or below the area of the units excitatory response to a single tone. Thus, the dominant tone appears to 'capture' the response of the neurone. However, suppression is normally seen only when the suppressor is outside or at the edges of the response area.

Presenting a matching tone at, or approximating the frequency of tinnitus pitch may suppress or mask the tinnitus. If this were so, measures of tinnitus at Phase I using a tone at T/F may 'capture' the frequency of the suppressor tone because the external sound masks the tinnitus. Following a period of suppression the tinnitus may compete with the external tone attempting to rise above the tonal stimulus at T/F. The increase in response at Phase II is consistent with this theory. The results tentatively suggest that tinnitus begins to compete with the tone after 30 minutes.

Subject's verbal reports also give weight to this theory. Nine subjects (1, 5, 7, 10, 11, 12, 13, 15 and 16) reported difficulty in matching their tinnitus pitch consistently, because they were unable to perceive their tinnitus. Complaints such as: "I can't hear my tinnitus anymore" (Subject 1) and "I can't distinguish the tone from my tinnitus anymore" (Subject 7) were common. Five subjects (Subjects 1, 3, 11, 12 and 16) reported that following the matching procedures the sound of their tinnitus had altered. Comments like: "My tinnitus is ringing now, it doesn't usually do this" (Subject 1) and "I'm sure I've got more cicadas than I started with" (Subject 11) were reported. The prominent tinnitus location of subjects who reported suppression of and competition by the tinnitus, was bilateral or head located. Overall, it is possible that a tone at T/F is able to induce a shift in the symptoms of tinnitus. Furthermore, subjects' verbal reports suggest that steady but not pulsed tones induce this shift. The comments associated with pulsed tone presentations used during tone thresholds suggest that tone threshold stimulus was difficult to detect because of the presence of tinnitus, rather than its suppression by or competition with the external stimulus.
II. Tinnitus Interference with Detection of a Tonal Stimulus. The tinnitus may interfere with perception of a tone at the matched T/F (Penner, 1983, 1984, 1986) thus making the external tone more difficult to detect. In order to discriminate the external signal from the tinnitus, the detection signal may have to be increased to the point where the subject perceives the external tone and the tinnitus as distinct. The results showed that tone thresholds were elevated at both Phase I and II. Levi and Chisin (1987) found that all patients with tinnitus reported its interference with pure tone audiometric thresholds but their control group reported no difficulty in detecting the tone. Levi and Chisin argued that this effect was due to the existence of tinnitus rather than hearing loss as the control and tinnitus groups were matched on this factor.

The results from this experiment support Levi and Chisin's argument. The present study found no association between frequency of tinnitus pitch and the frequency of severest hearing loss. It is tentatively suggested that the elevation in tone threshold response in this sample population may not result from hearing loss. Levi and Chisin's argument is further supported by the present finding that there was no significant increase or decrease in responses to noise threshold during each session or week-by-week. Subjects' verbal reports confirmed that broadband noise did not interfere or fuse with tinnitus. Thus, a noise stimulus appears to minimise variation in response induced by a tone stimulus.

Overall, these results bring into question the validity and reliability of tinnitus matching procedures which rely on presentation of an external tone at the matched T/F. As this procedure is used frequently (Bailey, 1979; Burns, 1984; Graham and Newby, 1962; Hazell, 1981; Man and Naggin, 1981; Penner, 1983, 1986, 1988, 1989; Reed, 1960; Tyler and Conrad-Armes, 1983; Vernon, 1979) the results from this experiment suggest that its application and interpretation should be approached with caution.
Discussion of Results. Subjective ratings and the matched frequency of tinnitus pitch were not affected by caffeine. These results do not support the prediction that caffeine would increase tinnitus pitch. There were, however, significant increases in the matched tinnitus pitch during each testing session but not week-by-week. The increases in tinnitus pitch were independent of the drug manipulation. Tinnitus pitch increased within both 30 and 60 minutes and the increases at 60 minutes were greater than the increases recorded at 30 minutes. This result implies the escalation of tinnitus pitch over a relatively short period of time.

Subjective ratings, however, did not mirror the increases in tinnitus pitch matches within 60 minutes. Tinnitus pitch was rated as increasing on a week-by-week basis but not during each testing session. There was never a great disparity in the ratings made during each session. The mean difference in ratings of tinnitus pitch between Phase I and II was 0.3. The discrepancy between the subjective ratings and matched frequency of tinnitus pitch may be indicative of the unreliability of the measures employed. Jakes et al. (1986) reported high correlations between self-report and matching techniques when the following conditions were used: a) the exclusion of subjects who admitted to having difficulty with the self-report measures; and b) the exclusion of subjects who were rated by the audiological technician as having difficulty with any of the procedures. In addition an accurate match may involve the presentation of a large number of different sounds. A single tone may not adequately represent the frequency of the tinnitus pitch.

The present results suggest that subjects were aware of tinnitus pitch changing week-by-week rather than during each day. This finding is contrary to the significant correlation between subjective ratings and the matched frequency of tinnitus pitch prior to and after caffeine. The significant correlation between tinnitus pitch and the ratings appears to suggest that subjects were able to judge accurately the matched frequency of tinnitus pitch. Note also that ratings were made prior to each match rather than after. The significance of this correlation may be due to the limited frequency range of tinnitus pitches. Eleven subjects matched below 3000 Hz at Phase
1. Correlating the ratings of tinnitus pitch with a narrow frequency distribution may have overestimated the significance of this relationship. In addition, the tendency for subjects to rate tinnitus pitch as falling consistently on or about a particular numerical value on the scale may have increased the level of significance.

The results of the pitch matching to an external tone at the equivalent frequency suggests that the lack of pitch salience is not the result of general degradation in the perception of pitch associated with the impairment which led to the tinnitus. The increase in tinnitus pitch, however, suggests that the pitch perception associated with tinnitus is variable.

**Caffeine and Tinnitus Pitch.** There are three possible explanations for the non-significant effect of caffeine on tinnitus pitch.

1. Caffeine simply does not affect the pitch of tinnitus.

2. Damaged tissue causing the tinnitus is not sensitive to the action of caffeine and the external stimulus. Auditory pathology causing tinnitus may be characterised by a certain degree of tissue damage. Presenting a tone at a frequency approximating the tinnitus pitch may require a portion of, or the entire area generating tinnitus to be operational. The degree of damage will limit the effective response of the auditory tissue to the external stimulus (which involves functioning of the damaged area to enable perception) and the stimulatory action of caffeine.

3. The external stimulus may interfere with the tinnitus (Penner, 1983, 1984, 1986) and mask the effect of caffeine on tinnitus pitch. Presenting a matching tone at, or approximating the frequency of tinnitus may suppress or mask the tinnitus. If this were so, the effect of caffeine may be secondary to the competition between the tinnitus and the external tone, resulting from initial suppression of tinnitus. The possible suppression of tinnitus by an external tone may also account for the discrepancy in results between subjective ratings and tinnitus pitch. Subjects rated the tinnitus pitch as increasing weekly but pitch matches varied within a session. If the matched frequency of tinnitus pitch was suppressed, subjective ratings made prior to the pitch match test may be more representative of the actual tinnitus pitch.

The results from the present study suggest that tinnitus may be variable in
frequency and possibly inter-active with external tones which repress the action of caffeine.

**Measuring Tinnitus Pitch.** The constancy in tinnitus pitch between weekly testing sessions did not support the results from previous research. Man and Naggin (1981), Penner (1983, 1986, 1988) and Tyler and Conrad-Armes (1983) reported changes in tinnitus pitch between each testing session. The discrepancy between the results from this experiment and these researchers may be attributable to differences in the methodological procedures. This experiment differs from Man and Naggin (1981), Penner (1983, 1986, 1988) and Tyler and Conrad-Armes (1983) in the following matching techniques:

1. In this experiment all tinnitus sound components were matched, attempting to control for shifts in the characteristics of tinnitus, for example, the lowest or highest, the mean, median or modal component the subject chose to match. Penner (1983, 1986, 1988) and Tyler and Conrad-Armes (1983), who adopted the technique of matching to the prominent tinnitus pitch, reported week-by-week changes in response. In addition, the variability in their matches during the sessions exceeded the values reported in the present study (Table XXVIII).

2. Subjects in this experiment were tested for their ability to consistently perceive in the left or right ear (that is, for 75% or more of the trials) the tonal stimulus and broadband noise as distinct from the tinnitus. This ear was then used for all matching procedures across the six experimental sessions. Burns (1984), Man and Naggin (1981) and Penner (1983, 1986, 1988) on the suggestion of Tyler and Conrad-Armes (1983), matched the frequency of tinnitus pitch in the ear ipsilateral to the tinnitus or the louder tinnitus. However, these researchers continue to report gross changes in tinnitus pitch on a daily and weekly basis. Testing for the ear best able to discriminate external sound from the tinnitus may limit the changeable nature of tinnitus as suggested by the figures in Table XXVIII.
Table XXVIII. Comparison of changes in tinnitus pitch between this experiment and the work of Penner (1983, 1986, 1988). The values (given in Hz) represent the average of the differences between matching trials during a testing session. These values have been calculated on the basis of the published data.

<table>
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<tbody>
<tr>
<td>403.3 Hz</td>
<td>2000 Hz</td>
<td>2573 Hz</td>
<td>697 Hz</td>
</tr>
</tbody>
</table>

Threshold Effects

Discussion of Results. Noise thresholds increased after low but not high doses of caffeine. Tone thresholds were unresponsive to the action of caffeine. The effect of caffeine on noise threshold supported the prediction that caffeine would raise thresholds. This prediction was not upheld for tone thresholds. Noise thresholds did not vary on a daily or weekly basis. Tone thresholds, however, increased after 60 but not 30 minutes, irrespective of the caffeine manipulation. Tone thresholds were also significantly elevated at Phase I compared with noise thresholds and the mean response of subjects to pure tone audiometry corresponding to the matched frequency. This result suggests that detection of a tone at the matched frequency of tinnitus pitch was difficult. The results also suggest that the difficulty associated with detection of a tonal stimulus at T/F may not result from hearing loss. There was no association between frequency of tinnitus pitch and frequency of severe hearing loss. It is possible that the area of severe tissue damage on the basilar membrane causing hearing loss does not produce tinnitus. However, this does not necessarily imply that there is no widespread or general hearing loss associated with tinnitus. Nine of the sixteen subjects exhibited a hearing loss of 20 dB HL or more across at least two pure tone audiometry frequencies, and six of these subjects showed hearing loss across four or more of the test frequencies.

Overall, the discrepancy in results between the noise and tone threshold measures imply differential levels of functional ability within the auditory system. The elevation of tone thresholds compared with noise threshold and pure tone
audiometry suggests that a tone stimulus at a frequency approximating the tinnitus pitch engages a response from the highly localised lesions which produce tinnitus. The wide spectral frequency of broadband noise may, however, reflect the functional level of non-damaged tissue. In this respect, results from noise threshold tests may represent a measure of the overall functional ability of the auditory network. The results suggest that noise stimuli should be used to measure the overall general level of auditory system functioning. A tone at the matched T/F may supply information about a specific site of damage.

Meyerhoff and Cooper (1980) suggested that some people with narrowband or tonal tinnitus have highly localised lesions, while some of those with broadband and complex tinnitus have numerous or widespread sites of tinnitus origin. Tinnitus sound descriptions may yield information concerning the number of lesions or damaged tissue sites. For example, one tone in noise (Subjects 3, 10 and 13) and a single tone (Subjects 6 and 14) would indicate a single area of highly localised lesions; single tone/buzzing (Subject 8) and hissing/tone in noise (Subjects 1, 7 and 9), two areas; while hissing/crickets/single tone (Subject 11) might imply multiple sites of damage. The relation between tinnitus sound description and the number of localised lesions or damaged areas producing tinnitus is currently a matter of speculation and requires further research.

Caffeine and Noise Threshold. In reference to an earlier consideration - that audiometric responses to broadband noise may represent the functional ability of auditory tissue - the generalised and systemic action of caffeine on non-damaged tissue anywhere in the auditory system or higher CNS pathways may be reflected in the measures associated with noise stimulus. The action of caffeine on highly localised lesions may be reflected by tonal measures. Caffeine's lack of effect on the tone threshold thus suggests that caffeine does not alter the discrimination ability of highly localised lesions producing tinnitus. Once the tissue damage has occurred and is 'fixed' into the feedback system of the afferent-efferent pathway and the memory loop (Meyerhoff and Cooper, 1980) the functional ability of the damaged area may be set unless it either heals or deteriorates further.
Caffeine did affect noise threshold. Low doses of caffeine increased the threshold by 4.81 dB SPL from Phase I to Phase II. High doses of caffeine did not affect noise threshold. Caffeine's effect on noise threshold was dependent on neither the length of time waited for caffeine ingestion nor the tinnitus location - again implying a more generalised action of caffeine on the auditory system as a whole. The finding that high doses of caffeine did not affect noise threshold suggests that the caffeine effect was dose-dependent particularly as loudness matches to noise were affected by both low and high doses of caffeine. The discrepancy in caffeine's action between threshold and loudness matches to noise may indicate the involvement of another mechanism which is capable of altering tinnitus loudness and is sensitive to both 100mg and 300mg of caffeine. Moreover, results from the individual differences analysis show that six of the sixteen subjects were insensitive to the action of 300mg of caffeine on noise threshold.

The possibility remains, however, that the present study did not incorporate enough time conditions within which to monitor the action of high doses of caffeine. Bonati et al. (1981), Robertson et al. (1978) and Robertson et al. (1981) found substantial levels of caffeine in the blood by 15 minutes and after 120 minutes, while Blount and Cox (1985) and Patwardhan et al. (1980) reported peak plasma levels by 90 minutes. The emphasis here on caffeine-plasma levels may be erroneous for auditory research. The peak level of caffeine in the cochlea or the auditory system and not the plasma is likely to be an important factor in tinnitus. The time period associated with the caffeine-cochlea interaction has yet to be established.

Measuring Thresholds. There are a number of methodological problems associated with the threshold measurement technique which explain further the discrepancy between noise and tone thresholds: a) The rate at which the stimulus is presented affects detection - 500ms ON/500ms OFF may have been too fast to enable accurate detection of tones; b) Research has shown that the description of the stimulus given to the subject can affect his or her response to the audiometric test. Gerber (1974) reported that instructing subjects to identify a 'clear and obvious tone' rather than 'only distinguish if something occurs' resulted in a marked increase in threshold; and c) Subjects reported what Gerber (1974) classified as an 'OFF' response.
Subjects realised the stimulus had occurred only when it stopped occurring, bringing into question the relative accuracy of threshold measures. The results suggest that procedural differences (for example, the number of judgements, stimulus timing, or the training of listeners), and individual differences may play a role in the variation observed in this experiment.

Objective measures do not require such participation by the subject and usually merely require him or her to cooperate by keeping still and tolerating any measurement apparatus which is attached to him or her. In addition, objective measures such as the acoustic mobility of the tympanic membrane (including measurement of acoustic reflexes) and the changes in electrical potentials at the cochlea or on the surface of the scalp elicited by sound stimulation, are time-consuming and tedious for the subject. However, in recent years it has been proposed that acoustic reflex measures may be used to predict auditory threshold (Popelka, 1982) and the techniques proposed make use of the fact that acoustic reflex threshold for broadband noise is lower than for a tone (Jerge, Burney, Maudlin, Crump, 1974; Neismeyer and Sesterhenn, 1974). The discrepancy between the more subjective tests of threshold assessment suggest that objective techniques should be seen as adjuncts useful for certain aspects of assessment and as an alternative not a substitute where subjective method fails.

Tinnitus Loudness

Discussion of Results. Loudness matches to noise increased after low and high doses of caffeine. The increase in tinnitus loudness after high doses was greater than the increase after low doses of caffeine. When matching to noise was performed, loudness expressed in dB sensation level increased after high but not low doses of caffeine. The sensation level was responsive to low doses of caffeine as both threshold and loudness matches (dB SPL) were comparably affected by low doses. Similarly, the differential effect of high doses of caffeine on noise threshold (no effect) and loudness matches to noise (increased above the low dose level) accounted for the corresponding increase in sensation level. The overall increase in matched tinnitus loudness (dB
SPL) and sensation level of loudness matches to noise after caffeine parallels the general assumptions in much of the anecdotal literature. Caffeine is stated to increase, exacerbate and aggravate tinnitus, with tinnitus loudness believed to be a frequent recipient of caffeine's potentiating action (Brown et al., 1981; Evans, 1981; Goodey, 1981, 1986; Malatesta et al., 1980; Manahan, 1980; Pulec, 1979; Saunders, 1986; Schleuning, 1981).

The present study found that in addition to a generalised and systemic action, caffeine's effect on tinnitus was highly localised and dependent on:

1. The site of the reported tinnitus sound
2. The length of time allocated for drug ingestion
3. The amount of caffeine ingested, and
4. The external stimulus presented for the loudness matches, that is broadband noise or a tone at the matched T/F.

Analysis of loudness matches to a tone at T/F showed that the loudness level of unilateral tinnitus decreased after high doses of caffeine. The decrease in loudness was greater after 60 minutes than the decrease after 30 minutes. Low doses of caffeine did not affect the loudness of unilateral tinnitus matched to a tone at T/F. The loudness level of bilateral or head tinnitus decreased then increased, 30 and 60 minutes, respectively, after high doses of caffeine. Low doses of caffeine increased the loudness of bilateral or head tinnitus after 60 but not 30 minutes.

The effect of caffeine on the loudness level of unilateral tinnitus in this study is not supported by Malatesta et al. (1980). Malatesta et al.'s investigation into the effect of two cups of brewed coffee on one male's unilateral tinnitus showed an increase in intensity after 40 minutes. Subjects with unilateral tinnitus in the present study showed a decrease in tinnitus loudness. The discrepancy in results between this experiment and Malatesta et al.'s may be attributable to: a) The size of Malatesta et al.'s sample population. It is possible that in the present study some individuals experienced an increase in the loudness of unilateral tinnitus. However, the overall effect of caffeine on the loudness level of unilateral tinnitus, taken across sixteen subjects, suggests a decremental effect; and b) A difference in the administration form
of caffeine. Malatesta et al. used brewed coffee which in addition to caffeine contains, niacin, acetone, furfuran, ammonia, methylamine, trimethylamines, tumaric acid, artic acid, resorcinol, hydroquinone and pyridine. These compounds may have masked the effect of caffeine on tinnitus loudness.

The increases in the loudness level of unilateral tinnitus in Malatesta et al.'s (1980) study are similar to the results for subjects with bilateral or head tinnitus in this experiment.

In the present study low doses of caffeine affected neither unilateral nor bilateral or head tinnitus after 30 minutes. While the loudness level of unilateral tinnitus continued to be unresponsive to the effect of low doses of caffeine after 60 minutes, the loudness level of bilateral or head tinnitus increased. High doses of caffeine decreased both unilateral and bilateral or head tinnitus after 30 minutes. However, after 60 minutes the loudness level of unilateral tinnitus continued to decrease while the loudness of bilateral or head tinnitus increased. The decrease in loudness after 30 minutes was found to be dependent on the location of tinnitus - subjects with bilateral or head tinnitus showed the greater decrease in tinnitus loudness.

These results suggest that for unilateral tinnitus the action of caffeine is dose-dependent. In addition, the results argue against caffeine's effect being time-dependent because both 30 and 60 minutes after high doses of caffeine, the loudness of unilateral tinnitus decreased. It is possible that the damaged tissue producing tinnitus is insensitive to a low but not high level of drug action. Similarly, the effect of the low doses of caffeine on the loudness level of bilateral or head tinnitus after 60 but not 30 minutes suggests that a period of time greater than 30 minutes is necessary for caffeine to affect the loudness of bilateral or head tinnitus. Subjective ratings of loudness further suggest that the effect of caffeine is heightened at 30 minutes for subjects with unilateral tinnitus but 60 minutes for subjects with bilateral or head tinnitus. Subjects with bilateral or head tinnitus rated the effect of caffeine on tinnitus loudness greater at 60 minutes but subjects with unilateral tinnitus rated caffeine's effect greater at 30 minutes.
Based on the findings from this experiment, the timing of caffeine ingestion in relation to audiometric loudness tests has been set out in Table XXIX.

**Table XXIX.** Times for caffeine ingestion on the basis of testing for generalised/systemic or localised action.

<table>
<thead>
<tr>
<th>Tinnitus Location:</th>
<th>Caffeine Dosage:</th>
<th>Loudness Matched to a Tone at the Tinnitus Frequency (Localised Lesions):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral</td>
<td>100mg 300mg</td>
<td>Has no effect 30 - 60 Minutes</td>
</tr>
<tr>
<td>Bilateral or Head</td>
<td>100mg 300mg</td>
<td>60 Minutes</td>
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</table>

<table>
<thead>
<tr>
<th>Caffeine Dosage:</th>
<th>Loudness Matched to Broadband Noise (Generalised Effect):</th>
</tr>
</thead>
<tbody>
<tr>
<td>100mg 300mg</td>
<td>30 - 60 Minutes</td>
</tr>
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</table>

The discrepancy in the action of high doses of caffeine after 30 and 60 minutes between unilateral and bilateral or head tinnitus suggests that highly localised lesions producing tinnitus are responding differently to the drug manipulation. While the results from the loudness matches to noise suggest that caffeine has a systemic effect on the auditory system, the results from the loudness matches to a tone at T/F suggest that highly localised lesions respond in a different manner than non-damaged tissue to high doses of caffeine. Moreover, the results showed that low doses of caffeine affected the loudness level of bilateral or head tinnitus after 60 but not 30 minutes. High doses of caffeine, however, affected tinnitus loudness by 30 minutes. The difference in time parameters suggests a more peripheral site of action for low doses of caffeine but a CNS site of action for high doses. Thus, it is speculated that the site of tinnitus aggravation for subjects with bilateral or head tinnitus may be peripheral, central or both. The results from the individual differences analysis agree with this contention, as subjects with complex tinnitus were affected differently by caffeine. Subject 12's less prominent sound was affected by high but not low doses of caffeine but the prominent
sound was affected by both doses of caffeine suggesting different sites of aggravation for each sound. The difference in loudness measures between the tinnitus location groups may reflect a difference in the symptomatology and etiological basis of the disorder.

The sensation level of loudness matches to a tone at T/F were not affected by low or high doses of caffeine. The sensation level measure did not show the differential effects of caffeine on unilateral and bilateral or head tinnitus across the 30 and 60 minute time periods. The results suggest, therefore, that the sensation levels of loudness matches to a tone at T/F were not sensitive to the localised changes in tinnitus loudness induced by caffeine. The sensation level of loudness matches to noise, however, was sensitive to caffeine. Therefore, the sensation level measure may be applicable in assessing only the overall effect of the drug manipulation on the auditory system as a whole. Similarly, the subjective ratings of loudness also reflect a generalised action of caffeine on tinnitus.

Subjective ratings of tinnitus loudness increased after low and high doses of caffeine. A significant relationship was established between loudness matches to noise and subjective ratings of loudness. The significance of the relationship was not a function of the caffeine manipulation as subjects were accurately judging the loudness of their tinnitus matched to noise before and after the placebo and caffeine administrations. Loudness ratings were also affected by time condition, tinnitus location and caffeine. A similar effect was found for loudness matches to a tone at T/F. There was, however, no significant correlation between the loudness ratings and loudness matches to a tone at T/F, or loudness ratings and the sensation level of loudness matches to a tone at T/F. Loudness matches to noise but not a tone at T/F (dB SPL) were reliable predictors of subjective loudness. The discrepancy in the results may arise from the methods used to measure loudness.

Overall, these findings support the idea that subjective ratings of loudness and loudness matches to noise reflect the generalised and systemic action of caffeine on tinnitus.

Subjects with unilateral tinnitus rated the loudness level as increasing 30 and 60 minutes after low and high doses of caffeine but loudness matches to a tone at T/F
decreased with high doses and low doses did not affect the loudness match. Subjects with bilateral or head tinnitus rated the loudness as increasing 30 and 60 minutes after low and high doses of caffeine. Loudness matches to a tone at T/F showed, however, that low doses of caffeine increased the loudness level after 60 but not 30 minutes. The increase in loudness ratings after high doses reflected accurately the increase in loudness matches to a tone at T/F after 60 minutes but not the decrease after 30 minutes. Although subjects uniformly rated loudness as increasing after caffeine, subjects with unilateral tinnitus rated this tinnitus to have increased in loudness more than subjects with bilateral or head tinnitus after 30 minutes. Conversely, subjects with bilateral or head tinnitus rated their tinnitus to have increased in loudness more than subjects with unilateral tinnitus after 60 minutes. The increases in loudness ratings from Phase I to II mirror the increases which occurred in the loudness matches to a tone at T/F during each session but independent of the caffeine manipulation.

These results suggest that subjects had an idea of 'when' the effect of caffeine had heightened. The discrepancy with the loudness matches to a tone at T/F suggest that subjects may have judged caffeine's effect by some physiological change other than tinnitus. Research by Blount and Cox (1985) has shown that untrained subjects can discern the amount of caffeine ingested on the basis of bodily and arousal effects. It is possible that subjects judged the increase in tinnitus as synonymous with an increase in physiological or arousal functions in the body. This contention is, however, speculative as this study did not include physiological measures of caffeine's action.

Discrepancies in Loudness Measures. From the results it appears to be a misconception that the loudness of tinnitus is related to its matched sensation or sound pressure level. Subjects in this experiment who described themselves as having 'very loud tinnitus' (for example rating 8 to 10 on the loudness scale) often commented that their tinnitus did not seem loud to them, rather that its constant and unremitting nature was the problem. Also, when the loudness of tinnitus was matched to an external sound, 83% of the loudness matches were obtained at sensation levels below 20 dB. This finding is comparable to the sensation levels reported by previous research. Reed (1960) reported that 87% of his 91 subjects experienced tinnitus of 20 dB SL or
less, and 95% experienced tinnitus of 30 dB SL or less. Vernon (1976) reported that all of his patients suffered from severe tinnitus but none experienced tinnitus of more than 20 dB SL. Hazell (1979), Jakes et al. (1986) and Man and Naggin (1981) reported no significant relationship between the subjective description of tinnitus and its intensity. Meikle et al. (1984) found that ratings of severity were not related to the type, quality or pitch of the tinnitus heard. Jakes et al. (1986) suggested that emotional factors influenced loudness judgements and hence their low correlation with matched sensation and sound pressure level.

The following considerations may be important in explaining the discrepancy:

1. Subjects may have been rating from expectation. Subjects' attitudes toward the drug rather than the drug itself could have affected the loudness ratings. Therefore, it is possible that subjects were rating in a manner consistent with their personal expectation that caffeine would 'worsen' tinnitus.

2. Self-report scales may be invalid. Jakes et al. (1986) suggested that: a) measurement errors attributed to poor self-report scales; and b) subjects not understanding the procedure could account for the low correlation between the loudness match and the subjective rating. This criticism, however, does not explain the significant relationship between loudness matches to noise and loudness ratings found in this experiment. Subjective ratings correlated well with tinnitus loudness matched to broadband noise.

3. Loudness ratings may have been influenced by the variations in loudness matches during each session. Loudness matches to a tone at T/F increased during each session. Tinnitus was matched to a more intense tone after 60 but not 30 minutes. Subjects with bilateral or head tinnitus rated the loudness level greater at 60 than 30 minutes.

4. Subjects were habituated to the loudness of their tinnitus and any alteration in this level - an increase or decrease - may have been automatically judged as 'bad'. Hence, a subject's cognitive reaction to changes in tinnitus loudness may affect the associated ratings. In addition there may be a physiological basis to this cognitive reaction. Interference by the external stimulus with the tinnitus may bring the
tinnitus to the attention of certain neural mechanisms that persist in unsuccessful attempts to force the tinnitus to conform to the behaviour of the external stimulus. The competition between the external tone and the tinnitus may reach a conscious level where the loudness level is perceived as worsening with increasing exposure to the sound. Although such a connection is only speculative, a shift in some aspect of the intensive dimension of subjective experience brought about by previous stimulation may be a factor involved in understanding the difference between subjective and objective measures of tinnitus.

5. Loudness matches to a tone at T/F may be an invalid measure of the loudness level of tinnitus because: a) Tinnitus may be suppressed and induced into competition by a tone at T/F. Subjective ratings were made prior to the loudness matches and may not have reflected the interference of, or suppression by the tone at the matched T/F. The discrepancy between these measures may be a function of the type of auditory stimulus presented for the loudness matching procedure. This contention is supported by the significant correlation between subjective ratings of loudness and loudness matches to broadband noise; b) Loudness matches to a tone at T/F simply do not measure the same facet of tinnitus loudness judged by the tinnitus sufferer; and c) Recruitment may have affected the loudness matching procedure. It is unlikely, however, that recruitment accounts for the discrepancy between loudness matches to a tone at T/F and loudness ratings. There was no significant difference between the loudness matches (dB SPL and dB SL) to broadband noise and a tone at T/F for Phase I. Had recruitment been a significant factor in this subject population, loudness matches to a tone at T/F should have been significantly elevated compared with loudness matches to noise. White noise by its nature is less susceptible to recruitment than a tone at T/F. Although a more direct test was not undertaken, recruitment appears to be substantially absent in this experiment.

Overall, the results suggest that caffeine increases the loudness of bilateral or head tinnitus. The decrease in loudness of unilateral tinnitus is not supported by the subjective ratings - all subjects rated caffeine as increasing the loudness level of tinnitus. The results from the loudness matches to noise and the matched sensation
levels suggest that, overall, caffeine increases the loudness level of tinnitus. The results also suggest that caffeine requires a different length of ingestion time on the basis of tinnitus location. Furthermore, the effect of caffeine itself is dose-dependent. Measures of tinnitus loudness using noise stimuli appear to reflect the overall effect of caffeine on non-damaged tissue in the auditory system while those with a tone stimulus at T/F appear to reflect the operative level of the highly localised lesions which produce tinnitus. The results for sensation level of loudness matches to noise appear to support this contention. Sensation levels matched to noise appear to monitor the generalised and systemic action of caffeine on tinnitus, while at the same time, raising the question of discrepancies in measures between subjective and objective tests of tinnitus loudness.

Caffeine's Systemic Action on Tinnitus Loudness. Caffeine's effect on the loudness of tinnitus matched to noise implies a mechanism of generalised and systemic action anywhere within the higher regions of the auditory pathway and cortex - cyclic 3′5′-AMP (Mechanism I, Model I). Hoffer et al. (1972) have shown that alterations in the synthesis of cyclic 3′5′-AMP via the inhibiting action of caffeine on phosphodiesterase allows cyclic 3′5′-AMP to accumulate, resulting in a prolonged, stimulatory action of metabolising cells. The speculative link at present, however, is that the hyperstimulatory action of metabolising cells (due to caffeine) may transduce acoustic stimuli in an aberrant manner. The results show that caffeine's generalised action occurs within 60 minutes. This result follows the prediction that the potentiation of tinnitus by caffeine at a site between the CNS and inner ear would occur within 60 minutes. The comparability between the established findings from cyclic 3′5′-AMP research (Beavo et al., 1970; Butcher and Sutherland, 1962; Sutherland and Rall, 1958) and the results from the present study tentatively suggest that caffeine may affect the loudness of tinnitus by altering the synthesis of cyclic 3′5′-AMP.

Although inhibition of phosphodiesterase will only occur at doses well in excess of what would be ingested in normal coffee consumption, a pre-existing biochemical sensitivity in the auditory tissue which causes or potentiates tinnitus may be affected by a less-than-normal dosage level. If this were so, the ingestion of 100mg or 300mg
of caffeine into a hypersensitive environment may be adequate to elicit an effect comparable to, for example, 600mg of caffeine within a normal and balanced milieu.

Current drug treatment for tinnitus is aimed at suppressing its symptoms by altering or disrupting the rhythmic hyperactivity of the reflex arc (Brown et al., 1981; Engelsson et al., 1976; Fowler, 1953; Gejrot, 1963, 1976; Melding et al., 1978; Sakarta and Umeda, 1976; Shea and Harrell, 1971). The hyperactivity may be induced by changes in the biochemical structures of the auditory pathway (Pulec, 1974; Pulec et al., 1978). Gelfand (1981) has shown that a stable chemical environment is necessary for the transfer of acoustic energy from a vibratory stimulus to a neural signal. The cyclic 3'5'-AMP model tentatively suggests that alterations in this chemical transmitter could result in or potentiate tinnitus. The temporary suppression of tinnitus symptoms by anti-convulsant drugs such as lignocaine and procaine may result from the transient nature of their action on the reflex arc instead of acting to normalise or equalise the biochemical state of the inner ear. This, however, is currently a matter of speculation.

The general pattern of results for the sensation level of loudness matches to noise are in accordance with the cyclic 3'5'-AMP model. Sensation level of loudness matches to noise increased within 60 minutes. This finding was in line with the theory that caffeine inhibits phosphodiesterase within 60 minutes of ingestion.

**Caffeine and Unilateral Tinnitus.** Unilateral tinnitus was expected to be affected by caffeine mechanisms and sites of action at the peripheral level. It was hypothesised that the highly localised lesions giving rise to tinnitus in one ear would be affected by either: a) an increase in glucose concentration due to high caffeine blood levels; or b) hypoxia. Caffeine was hypothesised to decrease $O_2$ distribution which in turn was predicted to suppress or exacerbate tinnitus. The results showed that high doses of caffeine decreased the loudness of unilateral tinnitus after 30 and 60 minutes. Low doses of caffeine did not affect the loudness of unilateral tinnitus. The reduction in tinnitus loudness below the baseline placebo level tentatively suggests the involvement of $O_2$ deprivation via hypoxia (Mechanism II, Model II). The results showed that the reduction in loudness occurred within the predicted time frame - 30 to 60 minutes -
and that it was dose-dependent.

Three hundred mg but not 100mg of caffeine affected the loudness level of unilateral tinnitus suggesting that the physiological disposition of adenosine binding to brain membranes might be affected by doses of caffeine in excess of 100mg. It was predicted that changes in CNS O_2 distribution due to limited adenosine binding would occur rapidly, within 30 minutes. The results showed that a decrease in the loudness of unilateral tinnitus occurred immediately after 30 minutes. This speculation is supported by Lawrence et al. (1971), Thalmann (1971), Thalmann et al. (1973) and Wilmott and Henry (1973) who found that the organ of Corti is affected within 30 minutes following O_2 deprivation.

The use of anti-convulsants in the treatment of tinnitus has shown temporary decreases or suppression of the symptoms of tinnitus (Donaldson, 1978; Israel et al., 1982; Melding and Goodey, 1979; Shea and Harrell, 1979). McFadden (1982) cites a study by Martin and Coleman (1980) who used a double-blind procedure randomly administering an intravenous dosage of lignocaine (1.5mg/kg of body weight). Subjects matched the frequency and intensity of their tinnitus before and after drug administration. Subjects in the lignocaine condition matched their tinnitus to intensities lower than those before the injection. Martin and Coleman reported the decrease in intensity to be 7.5 dB or more. Subjects with unilateral tinnitus in the present study matched their tinnitus to intensities lower than those before low doses (1.42mg/kg of body weight) and high doses (4.24mg/kg of body weight) of caffeine by 4.47 dB and 7.39 dB, respectively. If caffeine does affect the loudness level of unilateral tinnitus via hypoxia, the comparability between the results from the present study and Martin and Coleman (1980) suggests that the site of caffeine action associated with hypoxia may be synonymous with the site of action for anti-convulsant drugs.

Caffeine and Bilateral or Head Tinnitus. The results from the loudness measures are consistent with two mechanisms of caffeine action hypothesised to affect bilateral or head tinnitus: a) the glucose model. It was hypothesised that caffeine's action in the auditory system would alter the glucose level of the inner ear. It was
further hypothesised that the peripheral site of action would result in potentiation of tinnitus within 60 minutes. The results showed that low doses of caffeine increased the loudness level of bilateral or head tinnitus after 60 but not 30 minutes; or b) the adenine model. The adenine model speculated that caffeine may compete for adenine transport carriers in order to move across the blood brain barrier. Research has shown that a decrease in the presence of adenine in the brain can alter the formation of cyclic 3'5'-AMP. The model further hypothesised that a decrease in adenine could reduce the formation of cyclic 3'5'-AMP and hence decrease the amount of metabolic energy available to cells responsible for the transduction of acoustic stimuli. Conversely, if limited adenine-brain uptake resulted in an increase in synthesis of cyclic 3'5'-AMP, an increase in the aberrant transduction of acoustic stimuli was postulated. The results of this study showed that 30 minutes after high doses of caffeine the loudness of bilateral or head tinnitus decreased but then increased after 60 minutes. It is speculated, therefore, that high doses of caffeine may compete with adenine for brain uptake decreasing then increasing the stores of cyclic 3'5'-AMP.

Although it was hypothesised that caffeine had two sites of action - adenosine and glucose - it was further speculated that the resulting effect ultimately impacted on the state of one biochemical agent, that is, the availability of cyclic 3'5'-AMP along the auditory pathway. It is tentatively suggested that cyclic 3'5'-AMP may act as a mechanism or site of action for caffeine's effect on tinnitus loudness. The results from the present study, however, do not yield evidence to support this theory and it is thus a matter of speculation. The effect of caffeine on loudness matches to noise may, therefore, represent caffeine’s direct action on auditory system tissue via cyclic 3'5'-AMP. Caffeine's effect on damaged tissue (highly localised lesions) may operate through a secondary structure or substance which may elicit an effect that otherwise may not have occurred because severely damaged tissue is possibly insensitive to caffeine’s direct but not indirect action. These intermediary mechanisms may be useful in identifying subjects who may or may not be affected by caffeine.
Individual Differences in Response to Caffeine

Discussion of Results. The results from this experiment suggest that research using drug manipulations must take account of subjects who are insensitive to the drug's action. The present study showed that ten subjects were not affected by low doses or high doses of caffeine or both. Six subjects were unresponsive to the action of low or high doses of caffeine or both on the matched sensation level and sound pressure level of tinnitus loudness. Three subjects were unresponsive to the effect of low dose or low and high doses of caffeine on loudness matches to noise. The discrepancies among individual's insensitivity to caffeine as a function of the external stimulus is consistent with two earlier considerations:

1. The insensitivity of subjects to noise stimuli may represent the insensitivity of non-damaged tissue in the auditory system to caffeine; and

2. The insensitivity of subjects to caffeine's effect on a tone at T/F suggests that the degree of tissue damage associated with the tinnitus is too severe and thus lacks the ability to respond to the stimulatory action of caffeine.

The individual differences data support these contentions. Subjects who were unresponsive to caffeine on noise and tonal stimulus or both, reported complex tinnitus (Subject 12), fused tinnitus (Subjects 3, 4, 7, 8, 9 and 11) and, bilateral or head tinnitus (Subjects 9, 11, 12, 14 and 16), which may reflect a greater number of damage sites in the auditory network giving rise to multiple tinnitus sounds. Multiple sites of tinnitus aggravation may: a) decrease the amount of non-damaged tissue which may respond to caffeine; and b) increase the amount of tissue which is not responsive to caffeine.

Furthermore, subjects were not differentially sensitive to high or low doses of caffeine, or both. For example, Subject 3 was not affected by low doses of caffeine on noise threshold and loudness matches to noise. Subject 12 was not affected by low doses of caffeine on loudness matches to a tone at T/F and to noise and the sensation level of loudness matches to noise. Subjects were, therefore, consistently insensitive to the same dosage level of caffeine. This result agrees with the earlier contention that once the auditory tissue is damaged, the severity of tissue damage remains fixed and thus,
remains unresponsive consistently to specific dosage levels of caffeine.

**Caffeine and Drug Metabolism.** One of the primary causes underlying this insensitivity may be an acquired tolerance to caffeine associated with frequent and repetitive exposure to the alkaloid. Eight subjects were habitual and ritualistic caffeine consumers and a further subject ingested caffeine in a habitual manner. If this tolerance is not caused by an enhanced metabolism or excretion of caffeine, the relative insensitivity of persons to this alkaloid probably reflects a true tissue or cellular tolerance. The results suggest that this tolerance is uniform and fixed to a certain degree once it has been established. Subjects were consistently unaffected by the same dosage level(s) of caffeine. Drug metabolism can also be affected by: a) environmental or genetic differences between individuals (Dews, 1982); or b) the interference of foodstuffs consumed directly before, after or during the drug-ingestion time and their influence on the rate of metabolism uptake or excretion. Thus, if additional studies on the effect of caffeine on tinnitus were performed, it would be wise to involve larger populations, more stringent dietary controls and exploration of 'background values' in order to determine what factors are responsible for inter-individual differences.

A summary of the limitations associated with this experiment are presented in Table XXX. Suggestions for their resolution in future research have also been stated.

**Suggestions for Future Research**

The relation between caffeine and tinnitus would benefit from further research. One suggestion is that the present study be replicated using 15, 90 and 120 minute time delays for the ingestion of caffeine. The research should aim at identifying the time parameters within which caffeine's effect heightens and then decays. Similarly, future research is required to resolve the discrepancy in results between subjective and objective tests concerning the effect of 300mg of caffeine on unilateral tinnitus. The question is no longer whether caffeine does or does not affect the loudness level of unilateral tinnitus but whether the decrease (seen in the audiometric loudness tests) or the increase (in subjective loudness ratings) reflects accurately the true nature of caffeine's action. It is suggested that a large sample population should be used in this
Table XXX. Methodological limitations of the present study and suggestions for their resolution in future research.

<table>
<thead>
<tr>
<th>Limitations in the Present Study:</th>
<th>Resolutions for Future Research:</th>
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<tr>
<td><strong>ORAL INGESTION OF CAFFEINE:</strong></td>
<td>Intravenous injections provide complete absorption. Subjects should abstain from food consumption for 3-5 hours prior to drug administration or the type of food consumed should be administered and monitored by the researcher, keeping the quantity and type constant across all subjects.</td>
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<td>Inefficient in terms of amount of drug that reaches the blood brain barrier because of its interaction with digestive enzymes in the gut. The contents of the gut also affects the rate of absorption.</td>
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<td><strong>INDIVIDUAL DIFFERENCES IN DRUG TOLERANCE:</strong></td>
<td>Subject population should be larger than required because a number of subjects in the population who will be totally or partially insensitive to the drug manipulation. Future research should use the habitual/ritualistic categories used in this experiment to identify subjects with a tolerance to caffeine. Screening these subjects for a pre-determined degree of tolerance may limit the number of subjects excluded from the subject pool. Screening procedure should also include identifying subjects who are hyper-sensitive to the action of drugs.</td>
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<td>Ten of the sixteen subjects displayed differing levels of insensitivity to the action of low or high doses of caffeine or both across different audiometric measures.</td>
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<td><strong>24 HOUR CAFFEINE ABSTINENCE - QUESTIONABLE:</strong></td>
<td>Abstinence period should be greater than one day. Bonali et al. (1982) had subjects abstain from coffee, tea, chocolate and cola beverages for 10 days prior to their investigation. There should also be an increase in the abstinence time period for subjects identified as habitual or ritualistic caffeine consumers or both.</td>
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<td>Subjects were asked to abstain from caffeine-containing food and beverages for 24 hours prior to each testing session. Research by Robertson et al. (1981) found that baseline plasma caffeine levels were still present in the blood after 24 hours.</td>
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<tr>
<td><strong>CAFFEINE INGESTION TIME:</strong></td>
<td>Include 15, 30 and 120 minute time conditions in addition to 30 and 60 minutes.</td>
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<td>Thirty and sixty minute time delays for the ingestion of caffeine were not adequate to assess the time course of caffeine's effect, from its initial action to the time of decay.</td>
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<td><strong>NO PHYSIOLOGICAL MEASURES OF CAFFEINE'S ACTION:</strong></td>
<td>Blood pressure and heart rate should be monitored before and after drug administration and on completion of each time condition. If possible, blood and urinary caffeine-concentrations should be monitored. These tests will enable the researcher to establish the point at which the effect of caffeine is heightened and decays.</td>
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<tr>
<td>Research indicates that the actions of caffeine are associated with changes in blood pressure, increased concentration in plasma, plasma renin activity and the rate of urinary excretion.</td>
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<td><strong>INTERFERENCE WITH CAFFEINE UPTAKE BY NICOTINE:</strong></td>
<td>Subjects who smoke should be either excluded from experimental work involving alkaloid drugs or blocked into a subgroup of the population in order to assess the degree of interference nicotine has on caffeine's action. If a small proportion of subjects smoke, a period of nicotine abstinence, comparable to the abstinence period for caffeine should be employed.</td>
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<tr>
<td>Four subjects in this experiment smoked. Research indicates that nicotine increases the clearance rate of caffeine, contributing to the need for higher doses of caffeine for the person to be exposed to the drugs normal, physiological action (Belle, Roman, Sandberg and Kostis, 1970; Gilbert, 1979; Parson and Neims, 1978).</td>
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study. This would accommodate subjects who are insensitive to the action of caffeine (unless a tolerance screening procedure is employed) or who respond aberrantly to either the audiometric or subjective measures of tinnitus.

Future research should also consider addressing the finding that 100mg of caffeine does not affect the loudness level of unilateral tinnitus. Tinnitus by its very nature is a disorder which impacts on differing facets of the sufferer's life and the identification of food and beverage substances which can be enjoyed without potentiating tinnitus should be explored. Conversely, a longitudinal study concerned with assessing the full implication of caffeine cessation might ask the following questions: 'If caffeine ingestion results in an increase in tinnitus loudness, does caffeine cessation necessarily result in a loudness reduction?' and, 'If this is so, does the reductionary action of caffeine have a long- or short-term effect on the loudness of tinnitus?'.

The differential effects of caffeine on the basis of tinnitus location suggest that caffeine could be used as a biological marker to differentiate between tinnitus that is thought to be of peripheral or central origin. In this respect, future investigations may consider mapping the changes in tinnitus before and after caffeine with the differing reported location of tinnitus sounds. Consistent patterns between changes in tinnitus symptoms and tinnitus location or sound descriptions may emerge. In terms of actually measuring the tinnitus, investigations into the efficacy of the matching procedures used in this experiment (ear of preference test and matching all tinnitus sound components) together with the procedures established by Penner (1983) and Tyler and Conrad-Armes (1983) would be of interest. Moreover, an important area of investigation confronting this field is to determine the most appropriate methods for evaluating both the subjective and objective measures of tinnitus.

Implications of the Present Study

Caffeine as a Management Technique for Tinnitus. The results of this experiment have some implications for the clinical management of tinnitus. The cessation of caffeine-containing food and beverages may be a possible tinnitus management technique. The results showed that the loudness level of bilateral or head
tinnitus decreased then increased after caffeine. Subjective ratings of loudness also increased after caffeine. One of the major difficulties in coping with tinnitus, reported in much of the literature, is its ability to alter in pitch, loudness and sound description within a relatively short period of time. Although the unremitting nature of tinnitus is also a problem, reducing the increases or variations in tinnitus experienced after caffeine is a probable adjunct to current treatment programmes. The audiometric tests for loudness further showed that unilateral tinnitus decreased with caffeine. However, the subjective ratings of loudness supported caffeine's stimulatory action. Although there is a discrepancy in these results they imply that persons who report tinnitus sounds in one ear should be encouraged to test the effect of caffeine - exacerbation or reduction - on the loudness of their own tinnitus. The inter-individual differences regarding caffeine's effect on tinnitus suggest that the possible therapeutic effect of caffeine should be assessed on an individual basis.

Findings from the research using anti-convulsant drugs to control or suppress the symptoms of tinnitus parallel the results found in this present study in relation to caffeine and unilateral tinnitus. Understanding the physiological nature of anti-convulsant drugs may enhance understanding of the action of caffeine. Moreover, the correspondence between the results of this experiment and those of other research implies a differential drug action on the basis of tinnitus location. The results from the present study imply that persons with unilateral tinnitus but not bilateral or head tinnitus may ingest up to 100mg of caffeine without experiencing any increase or decrease in tinnitus loudness.

The effect of caffeine on tinnitus is dependent on the dosage level and the length of time for drug ingestion. The results from this study imply that 60 minutes is an adequate time frame within which to monitor the effects of high doses of caffeine on the auditory system. Low doses of caffeine may, however, require shorter or longer periods of time than 30 and 60 minutes, respectively. With regard to the ingestion of caffeine in the form of food and beverages, the results imply, for example, that 3-4 cups of coffee consumed within a short space of time elicit an effect on tinnitus within 60 minutes. For tinnitus sufferers who are habitual or ritualistic caffeine consumers
or both, the ingestion of a further 3-4 cups of coffee prior to the end of the 60 minute time period may have a drug-accumulative effect.

**Caffeine as a Marker for the Auditory System's Differential Response to External Stimuli.** The results suggested that different external stimuli presented to the subject measures different facets of caffeine's action on damaged and non-damaged tissue. This result implies that caffeine has a differential action on the basis of whether the auditory tissue under assessment is damaged or not. In addition the severity of the damage appears to produce differential responses to caffeine. When research is performed using drug manipulations, the following question should be asked: 'Is a greater concentration of the drug required to elicit a response comparable to the effect of caffeine on non-damaged tissue?', because: a) as the differential response of auditory tissue to the noise and a tone at T/F implies, the area of normal absorbing tissue surface may be reduced; and b) as the differential action of caffeine on the basis of dosage level implies, there may be an alteration in the normal route of caffeine's systemic or localised action because of the damaged tissue. It has already been speculated that caffeine's action may be mediated through secondary structures or substances.

The increase in tinnitus pitch, tone threshold and loudness matches after exposure to a tone at T/F implies the need for an external stimulus which is not capable of suppressing, competing or interfering with the tinnitus. Although the results from this research suggest that tinnitus by nature is variable, the findings also suggest that the variability can be minimised by using the ear of preference test and matching for all tinnitus sound components. The results also showed that independent of the drug manipulation there were changes in tinnitus measures when a tone at the matched T/F but not broadband noise was presented. This suggests that research may reduce the degree of variation associated with tinnitus measures by presenting only broadband noise. However, auditory research assessing the effect of drugs on tinnitus should consider using a tone at the matched T/F in order to assess the effect of the drug on the highly localised lesions in the auditory system which produce tinnitus. In using a tone at T/F researchers must realise the degree of variation associated with this measure.
irregardless of the actual drug administration.

**Subjective and Objective Measures of Tinnitus.** The sensation level of tinnitus matched to a tone at T/F was not a good measure of caffeine's effect on highly localised lesions, rather it reflected the generalised and systemic action of caffeine on the auditory system as a whole. The results from this study imply that loudness matches expressed in dB SPL rather than sensation level may be more sensitive to drug-induced changes in tinnitus. Similarly, the discrepancy in results between tone and noise thresholds suggests that noise but not tone thresholds are affected by drug administration. This finding supports the implication that noise stimulus produces a consistent measure of the functional ability of the auditory system. There was also a discrepancy between the subjective ratings of tinnitus loudness and tinnitus pitch and the more objective audiometric tests, implying that subjective rating scales may not measure the same aspect of tinnitus as the objective tests. Thus, attempts to use the rating scales as adjuncts with the results from the tinnitus pitch and loudness matches may be erroneous. It is suggested that a subjective scale be considered a valid test of tinnitus in itself.
CONCLUSION

The inner ear and its central auditory and vestibular projections represent one of the most highly complex and integrated metabolic systems in the body, and its proper function is dependent upon metabolic homeostasis. The peripheral auditory system is activated by a combination of mechanical, hydraulic, electrical and biochemical processes. It is the most complex sense organ in that it must integrate the widest variety of physical processes. It has been speculated that caffeine's action alters the biochemical state of the inner ear and auditory pathway which may affect the metabolic homeostasis of the auditory milieu. The present study has shown that caffeine affects tinnitus, a disorder originating within the auditory system and believed at times to result from biochemical alterations in the auditory network (Pulec, 1979; Pulec et al., 1978). Research in the past has tended to state merely that caffeine may exacerbate tinnitus without attempting to explain how the drug produces the morphologic changes and how these changes may affect tinnitus. The models of caffeine action proposed in the present study, albeit speculative and conjectural in nature, provide a theoretical framework from which future research can prove or disprove the associated hypotheses.

In general, tinnitus sufferers should consider the cessation of caffeine containing foods and beverages as a form of treatment for the disorder. The tinnitus sufferer must decide whether the olfactory, behavioural and physiological effects of caffeine are worth its effect on tinnitus. For people in whom caffeine may reduce symptoms of tinnitus, it must be decided whether it is worth ingesting a sometimes noxious stimulant.

The ultimate conclusion is that tinnitus is a symptom for which there appears to be no universal cure only therapeutic management. The cessation of caffeine or, conversely, for some individuals its ingestion may not be a panacea, but it does offer some relief and should be offered as a possible adjunct to the treatment of tinnitus.
REFERENCES


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## Appendix I. Demographic Questionnaire

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<thead>
<tr>
<th>Name</th>
<th>Weight</th>
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<th>Sex</th>
<th>Age</th>
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<td>[ ] female</td>
<td>[ ] 0-20</td>
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<td>[ ] male</td>
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<td>[ ] 51-60</td>
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<td>[ ] 61-70</td>
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<td>[ ] 70+</td>
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1. How long have you been experiencing tinnitus?
   - [ ] Less than one year
   - [ ] One to five years
   - [ ] Six to twenty years
   - [ ] More than twenty years

2. In which ear does your tinnitus occur?
   - [ ] Left ear only
   - [ ] Right ear only
   - [ ] Mostly in the left ear
   - [ ] Mostly in the right ear
   - [ ] Both ears
   - [ ] Tinnitus occurs in the head, rather than in the ear(s)

3. If you experience tinnitus in both ears please indicate whether it is of the:
   - [ ] Same type in each ear, and these are of equal loudness
   - [ ] Same type in each ear, but these are of unequal loudness
   - [ ] Different types in each ear, and these are of equal loudness
   - [ ] Different types in each ear, but these are of unequal loudness
4. How long does your tinnitus typically last?

[ ] Less than 1 minute
[ ] To 5 minutes
[ ] To 10 minutes
[ ] More than 10 minutes
[ ] Constant

5. How loud do you judge your tinnitus to be?

1 2 3 4 5 6 7 8 9 10
Very faint Very loud

6. When does your tinnitus occur?

[ ] Only after exposure to loud noise
[ ] After loud noise, but also occasionally for no apparent reason
[ ] After loud noise, and frequently for no apparent reason
[ ] Occasionally occurs, but not at all after loud noise
[ ] Frequently occurs, but not at all after loud noise
[ ] Tinnitus is constant

7. When did you first notice your tinnitus?

[ ] Cannot remember
[ ] Seems to have always been there
[ ] During childhood (no known reason)
[ ] During adolescence (no known reason)
[ ] After adolescence (no known reason)
[ ] After an ear infection or sinus
[ ] After taking a course of prescribed drugs
[ ] After brief exposure to intense noise
[ ] Gradually, after prolonged exposure to a noisy environment
[ ] After a head injury or severe blow to the head
[ ] After some specific incident or illness (please specify on following page)
8. What do you believe caused your tinnitus?

9. Is this belief concurrent with medical opinion?

[ ] Yes
[ ] No (please state the medical diagnosis)

10. Check any items below which describe your tinnitus.

[ ] A single musical note or tone
[ ] Several low tones
[ ] Several high tones
[ ] One predominant tone in noise
[ ] Several prominent tones in noise
[ ] Ringing
[ ] Hissing
[ ] Roaring
[ ] Whistling
[ ] Sizzling
[ ] Crickets
[ ] Hum
[ ] Buzzing
[ ] Pounding
[ ] Bells
[ ] Sea-shell sound
[ ] Transformer noise
[ ] High tension wire noise
[ ] Other - please describe in your own words the noise that you hear

11. Does your tinnitus ever seem to pulse?

[ ] Yes constantly
[ ] Yes frequently
[ ] Yes occasionally
[ ] No

12. How do you cope with your tinnitus? (tick all appropriate boxes)

[ ] By ignoring it
[ ] By concentrating on some other activity
[ ] Seek loud noises to cover it
[ ] Take prescribed drugs for it
  (what are these?) ________________________________

[ ] Acupuncture/acupressure
[ ] Relaxation therapy
[ ] Biofeedback
[ ] Hypnotherapy
[ ] By exercising
[ ] By using a tinnitus masking device
[ ] By using a hearing aid, or radio to cover it
[ ] By avoiding certain foods or drinks
  (what are these?) ________________________________

[ ] By eating or drinking certain foods or refreshments
  (what are these?) ________________________________
13. Do you smoke cigarettes or tobacco?

[ ] Yes
[ ] No

14. If you answered yes, please approximate the number of

[ ] Cigarettes/tobacco smoked in a day
[ ] Packets smoked in a week

15. How much effect does tinnitus have on your life, with respect to the following? (tick one box on each scale)

**Personal Relationships**
None [ ] [ ] [ ] [ ] [ ] [ ] [ ] Pronounced

**Family Relationships**
None [ ] [ ] [ ] [ ] [ ] [ ] [ ] Pronounced

**Concentration**
None [ ] [ ] [ ] [ ] [ ] [ ] [ ] Pronounced

**Ability to Sleep**
None [ ] [ ] [ ] [ ] [ ] [ ] [ ] Pronounced

**Driving Ability**
None [ ] [ ] [ ] [ ] [ ] [ ] [ ] Pronounced
16. Do you experience dizziness (vertigo) in addition to your tinnitus?
   [ ] Yes
   [ ] No

17. Do you suffer from Menieres Disease?
   [ ] Yes
   [ ] No

18. How would you rate your hearing level?

   1 2 3 4 5 6 7 8 9 10
   Excellent   Poor

19. Do you have a known hearing loss?
   [ ] Yes
   [ ] No

20. Do you wear a hearing aid?
   [ ] Yes in the left ear only
   [ ] Yes in the right ear only
   [ ] Yes in both ears
   [ ] No

Experimenter's Additional Notes:
Appendix II. Personal Assessment Form

1. How loud do you judge your tinnitus to be?

1  2  3  4  5  6  7  8  9  10
Very faint  Very loud

2. At what frequency do you judge your tinnitus to be?

1  2  3  4  5  6  7  8  9  10
Low sound  High sound

3. Check any items below which describe your tinnitus.

[ ] A single musical note or tone
[ ] Several low tones
[ ] Several high tones
[ ] One predominant tone in noise
[ ] Several prominent tones in noise
[ ] Ringing
[ ] Hissing
[ ] Roaring
[ ] Whistling
[ ] Sizzling
[ ] Crickets
[ ] Hum
[ ] Buzzing
[ ] Pounding
[ ] Bells
[ ] Sea-shell sound
[ ] Transformer noise
[ ] High tension wire noise
[ ] Other - please describe in your own words the noise that you hear

______________________________