

**OBJECTIVE ASSESSMENT OF TINNITUS:
THE ROLE OF COCHLEAR EMISSIONS**

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**A thesis presented to the University of London for the degree of
Doctor of Philosophy
September 1998**

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ABSTRACT

Tinnitus is a subjective phenomenon, which remains poorly understood with respect to the underlying mechanism. At present, no objective method for assessment is available. The subject of this thesis is to assess the role of cochlear emissions in objective evaluation of tinnitus.

There is evidence of a bi-directional interaction between the cochlea and the central auditory system, and, assuming that tinnitus is a consequence of altered neural activity due to a lesion or dysfunction at any level in the auditory system, the alteration may be reflected in cochlear mechanics, and therefore, otoacoustic emissions (OAEs).

Cochlear mechanics have been examined in different groups of patients with tinnitus, homogeneous with respect to auditory pathology and/or audiometric thresholds:

(i) normal hearing and tinnitus subsequent to presumed central nervous system pathology consequent upon head injury (ii) those with normal hearing and no identifiable pathology (iii) those with tinnitus following noise exposure and (iv) Menière's disease.

Four separate studies, examining each of these groups, form the integral part of the thesis. The fifth study, including all groups, explored a unique form of spontaneous (mechanical) activity in the cochlea.

OAE were recorded using standard techniques, suitable for the clinical environment, with the Otodynamics ILO88/92 Analyser: Transient click-evoked (TEOAEs) and spontaneous otoacoustic emissions (SOAEs), in order to assess the structural and functional state of the cochlea, and TEOAEs under contralateral acoustic stimulation to assess the function of the medial olivo-cochlear system.

Studying OAEs in different, but aetiologically homogenous, groups of patients with tinnitus has enabled the identification of group-characteristics, consequent upon the particular underlying mechanisms, in the generation of tinnitus. In significant number of patients, an increased variability of SOAEs associated with the complaint of tinnitus, has

been observed. There is evidence to suggest that changes in cochlear mechanics in patients with tinnitus have resulted from dysfunction of efferent control, and reflect hyperexcitability in the auditory pathways.

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STATEMENT OF ORIGINALITY

The studies included in this thesis were carried out at the Neuro-otology department of the Institute of Laryngology and Otology and the National Hospital for Neurology and Neurosurgery.

The systematic application of otoacoustic emissions in aetiologically and audiometrically homogeneous groups of patients with tinnitus, has led to the finding of a significant variability in cochlear mechanics, which appears to be associated with the perception of tinnitus. It also led to a common observation of raised cochlear activity, as objective evidence indicating that tinnitus is an hyperactive auditory dysfunction and that the cochlea and, thus, otoacoustic emissions, reflect alteration of the central mechanisms related to tinnitus. These findings were reported in the literature as original papers.

The candidate was the investigator responsible for the planning and implementation of the studies, as well as being responsible for data collection, storage and analysis, and preparation of publications arising from this work.

PUBLICATIONS AND PRESENTATIONS RESULTING FROM THESIS

PUBLICATIONS:

Josifovic Ceranic B, Prasher DK, Luxon LM Tinnitus and otoacoustic emissions. *Clin Otolaryngol* 1995; 20; 192-200.

Josifovic Ceranic B, Prasher DK, Luxon LM. Changes in cochlear mechanics due to impulse noise. In: Schoonhoven R, Kapteyn TS, de Laat JAPM, eds. *Proceedings of European Conference on Audiology*, Noordwijkerhout, 1995: 89-95.

Espir M, Illingworth R, Ceranic B, Luxon LM. Paroxysmal tinnitus due to meningioma in the cerebellopontine angle. *J Neurol Neurosurg Psych* 1997; 62:401-403.

Ceranic B, Prasher DK, Luxon LM. Presence of tinnitus indicated by variable spontaneous otoacoustic emissions. *Audiol Neuro-Otol* 1998; 3: 332-344.

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Ceranic B, Prasher DK, Raglan E, Luxon LM. Tinnitus following head injury: Evidence from otoacoustic emissions. *J Neurol Neurosurg Psych* 1998; 65: 523-529.

PUBLISHED ABSTRACTS:

Ceranic B, Prasher D, Luxon LM. Does increased variability of spontaneous otoacoustic emissions provide objective evidence of tinnitus? In: Popelka GR, ed. Abstracts of the XIX Midwinter Meeting of the Association for Research in Otolaryngology, St. Petersburg Beach, Florida, 1996. Abstract 384.

Josifovic Ceranic B, Prasher DK, Luxon LM. Endolymphatic hydrops alters cochlear mechanics: evidence from otoacoustic emissions. Book of abstracts, XXIII International Congress of Audiology, Bari, 1996: p. 75.

Ceranic B, Prasher DK, Luxon LM. Micromechanical cochlear changes in tinnitus following noise exposure. Book of abstracts, 2nd European Conference on Protection against noise, London, 1997.

Ceranic B, Prasher DK, Luxon LM. Contribution of otoacoustic emissions in assessment of patients with auditory complaints, but with normal hearing. Book of abstracts, 9th IAPA Symposium, Aalborg, Denmark, 1997: p. 39.

Ceranic B. Susceptibility to noise: Physiological protective mechanisms. Book of abstracts, 3rd European Conference on Audiology, Pre-conference Workshop: The European Collaboration of Concerted Actions on Hearing, Prague, Czech Republic, June 1997: p. 10.

Raglan E, Prasher DK, Ceranic B. Abnormalities of efferent control of cochlear mechanics in patients with minor head injury. Book of abstract, 3rd European Conference on Audiology, Prague, Czech Republic, 1997: p. 184.

PRESENTATIONS (oral)

“Changes in cochlear mechanics due to impulse noise” presented at:

- The monthly meeting of the Cochlear Emissions Research Group, the Institute of Laryngology and Otology, February 1995.
- The European Conference on Audiology, Noordwijkerhout, Netherlands, March 1995.
- The Annual Research Presentations of the Royal National Throat, Nose and Ear Hospital and Institute of Laryngology and Otology, June 1995.

“Does increased variability of spontaneous otoacoustic emissions provide objective evidence of tinnitus?” presented at:

- The XIX Midwinter Meeting of the Association for Research in Otolaryngology, St. Petersburg Beach, Florida, USA, February 1996.

“Endolymphatic hydrops alters cochlear mechanics: evidence from otoacoustic emissions” presented at:

- The postgraduate seminar, Institute of Laryngology and Otology, December 1995.
- The XXIII International Congress of Audiology, Bari, Italy, June 1996.

“Micromechanical cochlear changes in tinnitus following noise exposure”.

- 2nd European Conference on Protection against noise, London, April 1997.

“Contribution of otoacoustic emissions in assessment of patients with auditory complaints, but with normal hearing”

- 9th IAPA Symposium, Aalborg, Denmark, May 1997.

“Tinnitus and efferent dysfunction in head injury”

- BSA Short Papers' Meeting, London, March 1998

INVITED SPEAKER:

“ Tinnitus and noise exposure: a review ”

- 1st European Conference on Protection Against Noise, Bari, Italy, June 1996.

“ Micromechanical cochlear changes in tinnitus following noise exposure”

- 2nd European Conference on Protection Against Noise, London, April 1997.

“ Susceptibility to noise: physiological protective mechanisms “

- 3rd European Conference on Audiology; Pre-conference Workshop: The European Collaboration of Concerted Actions on Hearing, Prague, Czech Republic, June 1997.

ACKNOWLEDGMENTS

I am profoundly grateful to Professor Linda Luxon, for helping me to fulfill my ambition to work in the field of Audiological Medicine and Neuro-otology, for encouraging me to do this research, for supervision, help in funding these studies and trips to meetings throughout this research, and valuable comments on this manuscript.

I am indebted to Dr Deepak Prasher, who supervised and supported this work, for friendly and inspiring discussions, for help in preparation of this manuscript and for encouragement to present the research work at national and international meetings.

To Professor Anthony Wright for providing technical support, including the computer, and a friendly working environment at the Institute of Laryngology & Otology. I am very grateful to the Locally Organised Research Schemes of the Royal National Throat, Nose & Ear Hospital and the Iron Trades Insurance Group for providing financial support.

I am also grateful to Professor David Kemp for helpful discussion on spontaneous otoacoustic emissions measurements.

I sincerely thank to all my colleagues and friends for their support, particularly Dr Li Lin who helped me with scanning of the illustrations and Dr Ade Pye for her ever readiness to discuss any problem and to give valuable advice.

To Dr Ewa Raglan for her enthusiastic support and help in the recruitment of patients for the study.

To all the patients and friends for their participation in the study.

Finally, but not least, I am deeply grateful to my husband Ovrang for his understanding, patience and love, and to my parents who have equipped me with the energy and perseverance to carry out this work.

LIST OF COMMON ABBREVIATIONS

CNS	Central nervous system
dB	decibel
DPOAE	Distortion products otoacoustic emissions
HL	Hearing level
Hz	Hertz
kHz	kilohertz
IHC	Inner hair cells
MOC	Medial olivocochlear (system)
NIHL	Noise induced hearing loss
OAE	Otoacoustic emissions
OHC	Outer hair cells
PTA	Pure tone audiometry
SNHL	Sensorineural hearing loss
SOAE	Spontaneous otoacoustic emissions
SPL	Sound pressure level
TEOAE	Transient evoked otoacoustic emissions

Chapter 1: GENERAL INTRODUCTION

This chapter provides the theoretical background necessary for understanding the multifaceted phenomenon of tinnitus. Section 1.1 presents some general information on tinnitus and the evolution of the understanding of tinnitus from ancient times to the present day, while section 1.2 highlights the complexity of the anatomical and physiological milieu, as a background for the generation of tinnitus. The cochlea is the primary structure considered in this thesis.

This section also provides a basis for the understanding of otoacoustic emissions, which have been the main tool used in the evaluation of tinnitus in this research. The general characteristics of otoacoustic emissions are described in the section 1.3.

1.1 TINNITUS

1.1.1 Definition and epidemiology

Definition

The term ‘tinnitus’ stems from the Latin *tinnire*, to ring, and was introduced by Pliny the Elder (23-79 AD) (Feldmann, 1991). It was adopted into English language by the Oxford English Dictionary in 1693 (Stephens, 1987). However, a reference to tinnitus, as “ringing in the ears”, dates back to the 17th century in Francis Bacon’s *Sylva Sylvarum* (1627).

Tinnitus may be defined variously, as “a sound perceived for more than five minutes at a time, in the absence of any external acoustical or electrical stimulation of the ear and not occurring immediately after exposure to loud noise” (Hazell, 1995), as “phantom auditory perception” (Jastreboff, 1990), or “head noise” (Fowler, 1939). “The term ‘tinnitus’ embraces an infinite variety of auditory sensations that are not caused by externally applied stimulation” (Kemp, 1981).

Tinnitus is sometimes described as either “subjective”, audible only to the patient, or “objective”, audible to the examiner as well, and in the latter case usually caused by arterio-venous malformations, glomus tumours, palatal or tympanic myoclonus, spontaneous otoacoustic emissions, etc. The attribute “objective” seems inappropriate, as tinnitus refers to the sensation perceived by the subject, not the activity giving rise to the sensation, it is, therefore, always “subjective”.

Tinnitus usually differs markedly from auditory hallucinations by the absence of the organisation of its content. In the form of repetitive voices or musical themes, auditory hallucinations are usually reported by the elderly, psychiatric patients, or by subjects suffering from chronic alcoholism. However, the authentication of tinnitus, and clear distinction from auditory hallucination, in clinical practice may on occasions be difficult. Like tinnitus, an hallucination may be masked by external noise, and may comprise simple, rather than more elaborate, auditory sensations.

Epidemiology

Review of the literature shows that there is a large variability in prevalence statistics for tinnitus, reflecting differences in patient selection and symptom criteria. If all forms of tinnitus are taken into consideration, then the prevalence of the symptom would probably be 100% (Heller and Bergmann, 1953).

Comprehensive epidemiological data have been provided from the multicentre National Study of Hearing (Coles, 1984), based on a postal questionnaire, and eliciting information on hearing problems, including self-reported tinnitus. According to this study, about 15 % of the adult population have *prolonged “spontaneous” tinnitus*, i.e. without any obvious temporary cause, such as noise or drugs, of over 5 minutes’ duration: in at least 8% tinnitus interferes with sleep or causes moderate or severe annoyance, and in 0.5 % tinnitus severely affects the ability to lead a normal life. Similar estimates of the prevalence of “*often*” or “*always*” tinnitus has been reported in Sweden by Axelsson and Ringdahl, 1987 (14.2 %) and “spontaneous” (as defined above) tinnitus, in Italy by Quaranta et al., 1996 (14.5%). According to the National Center for Health Statistics (1968), 32 % of all adults in the United States have had

tinnitus at some time, and approximately 6.4 % characterised the tinnitus as debilitating or severe, and results from the Health and Nutrition Examination Survey of 1971-75 in the United States (Cooper, 1994), showed that 13-17 % of the general population have “*bothersome*” tinnitus.

However, the prevalence of “*clinical tinnitus*”, i.e. those subjects who are bothered by tinnitus to the extent that they would seek medical advice, has been estimated to be about 7.2 % (Smith and Coles, 1987), and related to an urban population with good accessibility to medical service.

Who complains about tinnitus?

Although tinnitus is a relatively common experience, the great majority of people do not complain about it. It is generally accepted that the intrusiveness of tinnitus depends on psychological state and emotional response. A study on the complaint behaviour in tinnitus patients (Attias et al., 1993a) has emphasised the importance of psychological factors, as the results suggested that psychogenic symptomatology was more severe, with poorer effective coping abilities, in help-seeking than in non-help seeking tinnitus patients. Attentional mechanisms may also play an important role in patients’ perception of tinnitus (Newman et al., 1997)

Therefore, this dichotomy, tinnitus as a (primary) complaint and tinnitus reported as a non-intrusive perception of sound only, significantly influences the prevalence of tinnitus.

Association with otologic and other medical conditions

If it is not the primary symptom, tinnitus may not be reported, and consequently, the prevalence of subjects having tinnitus, is likely to be underestimated. In patients with medical condition(s) and multiple symptomatology, tinnitus may not be volunteered as a major complaint, and, unless the patient is directly questioned, its existence may remain unknown.

From an historical perspective, among patients who consulted an otologist for any reason, Fowler (1912) questioned 2000 consecutive patients and 85% acknowledged having tinnitus. In 1000 cases with otosclerosis, tinnitus was present in 87%, but it was troublesome in only 10% of cases (Cawthorne, 1955). Analysis of 500 patients, who underwent vestibulocochlear schwannoma section, 83% had tinnitus prior to the surgery and in 11% cases it was the initial symptom (Ramsden, 1987). Tinnitus has also been reported in less than 3% of patients with multiple sclerosis (Daugherty et al., 1983).

Demographic features:

Tinnitus prevalence is a positive function of age (38% <40 and 62% >40 years old, Coles, 1984). Population statistics suggest that females are more affected than males (46.9% males and 53.1% females, Coles, 1984; 42.5% in males and 57.5% in females, Cooper, 1994), and this relative difference appears to be greater in those reporting severe tinnitus (Coles, 1984).

Relation to hearing impairment:

In about 50% of the population with self-reported tinnitus, hearing has been judged (by patients) as normal (MRC Institute of Hearing Research, 1981). Tinnitus prevalence rises with increasing hearing loss (Coles et al, 1990), with 74% of patients complaining of hearing loss (of unspecified type) having tinnitus (Collet et al., 1990a).

Relation to melanin pigmentation:

A negative correlation between tinnitus and the melanin content in the iris/inner ear has been reported (Tota and Bocci, 1967; Coles et al., 1981). However, according to the Health and Nutrition Examination survey in USA (Cooper, 1994), a significantly higher rate of tinnitus complaint was found in blacks than whites.

Laterality of tinnitus:

In general, a greater prevalence of patients with tinnitus, affecting the left ear more than the right, has been reported (Meilke and Walsh, 1984; Hazell et al., 1985), although in some studies, no significant difference between the two ears has been found (Alberti, 1987). Considerable variations exist in tinnitus laterality with age and gender (Coles, 1984).

Socio-economic status:

An overwhelming preponderance of patients in a tinnitus clinic come from the higher socio-economic groups (Shulman, 1988). However, an increasing prevalence of tinnitus in unskilled, in comparison with the professional classes, has been noted (Coles, 1984; Shulman, 1988).

1.1.2 Historical overview - first records and views until XIX century

Tinnitus is, possibly, a phenomenon as old as mankind. One of the oldest written documents on tinnitus, referring to it as the ‘bewitched ear’, is in the Ebers papyrus (based on the tradition of the XVIII dynasty and Old Kingdom, 2-3 millennium BC), as quoted in Kamal’s *Dictionary of Pharaonic Medicine* (Stephens, 1984). In a later papyrus from Crocodilopolis, believed to date from the 6th century BC, tinnitus is more explicitly mentioned, as “humming in the ears”. Throughout history, there have been many interpretations of tinnitus, as a natural phenomenon, as well as the consequence of supernatural power.

According to Assyrian medical documentation written on clay tablets, as early as the 7th century BC, the origin of tinnitus was described as “if the hand of a ghost seizes on a man and his ears sing.....” and three different types of tinnitus were cited, ‘singing’, ‘whispering’ and ‘speaking’ (Stephens, 1984). Tinnitus also played a role in magical rites and superstitions, for instance, tinnitus was used in the practice of divination, and ringing in the ears was considered a criterion for a good medium for the ritual (Demotic Magical Papyri, from Theben, Egypt, III century BC - Feldmann, 1987).

Equally interesting, “primitive” tribal medical views on tinnitus were documented by Politzer (1907) on the basis of Bartel’s work *The medicine of primitive tribes*, from 1893. The view of the Annamites of Eastern India was that the ear is inhabited by a small animal, whose function was to protect the ear. Tinnitus was merely the manifestation of a fight with a similar animal, an “intruder”, or of a disturbance of the “protecting” animal by a foreign body. There is also a reference to tinnitus in the Bible, to quote Jeremiah “Thus saith the Lord of hosts, the God of Israel: Behold, I will bring evil upon this place, the which whosoever heareth, his ears shall tingle” (Feldmann, 1987).

Understandably, throughout history, a number of physicians, scientists and philosophers were intrigued by tinnitus, and there were many attempts to explain tinnitus, by adopting a more natural and pragmatic approach, devoid of mystic frameworks, and based mainly on empirical observations.

During ancient Greaco-Roman time, in agreement with Empedocles' (504-433 BC) humoral theory on the pathogenesis of various symptoms, tinnitus was thought to be a perception of pulsation in the cranial blood vessels (Poltizer, 1907). Hippocrates (460-377), to whom was attributed the first statement on masking tinnitus, was quoted as asking the questions “ Why is it buzzing in the ears ceases if one makes a sound? Is it because a greater sound drives out less?” (Vernon, 1981). Aristotle (384-322 BC), the teacher of Alexander the Great, believed that tinnitus was the consequence of implanted air within the ear, a view later supported ardently by Galen (129-199 AD), and this idea recurred throughout the mediaeval and later times. The statement that tinnitus is “caused by excitement of the senses” by Ibn’i Sina (a Persian, known to the western world as Avicenna) (980-1038), the most outstanding physician and philosopher at the height of Arabic civilisation, was quite remarkable, and is in accord with the modern neurophysiological concept of tinnitus. Furthermore, his observation that tinnitus can be relieved by environmental noise “ to crye and to excite him with crying voice is profitable” (Ogden, 1971), anticipates the present day application of masking techniques. He also referred to tinnitus, caused by specific remedies “leading to retention of humours and winds in certain parts of the brain”, as well as an ototoxic effect of mercury inhalations (Stephens, 1987).

During the Renaissance, Paracelsus (1491-1541) made one of the first statements on the association of tinnitus with loud noises. A century later, Francis Bacon (1560-1626), one of the most celebrated Elisabethan scholars, in his famous *Sylva Sylvarum*, described temporary tinnitus as a consequence of exposure to loud noises.

In another remarkable publication, *Traité de l'organ de l'ouie*, a landmark in otology, by Du Verney (1648-1730), whose approach was based on the natural sciences, particularly anatomy and physics, tinnitus is ascribed to the rushing “internal air” due to disease of the ear, and hyperexcitability within the nerves, secondary to brain disease (a review, Stephens, 1987), and therefore, in some way, this view is the precursor of the division of the causes of tinnitus into peripheral and central.

In the XIX century, Jean Marie Gaspard Itard (1775-1838), in his famous *Traité des maladies de l'oreille et de l'audition*, known for its systematic approach to tinnitus, classified tinnitus into three groups: true, with an acoustical basis e.g. the pulsation of arteries; false tinnitus, due to damage of the cochlear nerve, and fantastic tinnitus,

considered to be a symptom of a psychological disorder (Stephens, 1987). The more common false tinnitus was further subdivided into idiopathic, caused by loud noise, and symptomatic, one of variety of psychosomatic symptoms, which occurred particularly in office workers, hypochondriacs and hysterical women. He advocated the treatment of tinnitus by masking, following the observation that interaction between tinnitus and external noise could alleviate tinnitus. Among his case histories, he described the successful treatment of a lady, living for several months in a water mill (Stephens, 1987). The prominent psychologist Johannes Müller (1801-1858) suggested that tinnitus was due to overstimulation of the auditory nerve associated with cerebral diseases, neural weakness or disease of the auditory nerve, while MacNaughton Jones thought that tinnitus was a consequence of irritation at different levels of the auditory system (1891), and could be treated with a galvanic current (Stephens, 1987)

A number of outstanding figures including artists, scientist and philosophers, have been afflicted by tinnitus, with a profound influence on their lives and work. For Sappho (born 612 BC on the isle of Lesbos), tinnitus was a symptom of high emotions, passionate love or jealousy, depicted in her odes. Tormenting tinnitus was reflected through grotesque visions of Goya's graphic art, and Beethoven was haunted by an inescapable tinnitus and deafness from the age 28 until the end of his life. Bedrich Smetana endured similar fate and was driven to despair by his tinnitus and deafness, with fatalistic reflection in his music (Feldmann, 1987). However, one of the most tragic figures suffering from tinnitus was probably Joseph Toynbee (1815-1866), a father of otology in England. To test a method for treatment of tinnitus, he subjected himself to Valsalva inflation of the vapours of chloroform and prussic acid, that proved fatal, and this tragic accident made him the first known martyr of tinnitus research (Stephens, 1987).

1.1.3 Aetiology of tinnitus

Tinnitus is not a single well defined disease, but a symptom of many pathologies. Sometimes in one patient, several pathological mechanisms may coexist.

Clinical sources of 411 consecutive patients with tinnitus (Axelsson, 1992), based on the data from a questionnaire, history and examination, have related tinnitus to:

- *Ear disease* in 67.6% of the patients: in 7% to conductive loss (unknown aetiology, chronic serous otitis media, otosclerosis, tensor tympani syndrome, traumatic ear drum perforation, or wax), and in the remaining 60.6% to sensorineural hearing loss (SNHL). Among those with SNHL, it is most striking that tinnitus is related to noise-induced hearing loss (NIHL) in 28% of patients (information on the age correction is not available), thus making NIHL the most common single diagnosis associated with tinnitus. In other cases with SNHL, in 4.6% cases tinnitus is attributed to acoustic trauma, in 8.2% to Menière's disease, in 4.1% to sudden deafness, in 4.3% presbycusis, in 4.7% to hereditary-congenital causes, 1.7% to surgery.

- *Unknown aetiology* in 7.5%

- *Neurologic disorders* in 5.8%

- *Bone-joint diseases* in 3.9% (cervical spine degenerative changes, spine trauma etc.)

- *Disorders of teeth and temporomandibular joint* in 1.5%

- *Cardiovascular disorders* in 1%

- *Endocrine-metabolic disorders* in 2.2%

- *Mental disorders* in 2.2%

- *Ototoxic effects* in 0.72%

Clearly, these data highlight the prime importance of ear pathology in the aetiology of tinnitus. This finding is supported by other authors (Tonndorf, 1980; McFadden, 1982; Lenarz et al., 1993; Coles, 1996). Spoendlin (1987) expressed the same view and estimated the frequency of occurrence of tinnitus in the main entities of pathological conditions of the inner ear: sudden deafness 50%, acoustic neurinomas 70%, presbycusis 70%, intoxication 30-90%, chronic noise trauma 50-90%, acute acoustic trauma 100%, Menière's attack 100% and in normal hearing 15-35%.

However, on the basis of his clinical data, Hazell (1995) reported that tinnitus is related to otological events in only 25%, while psychological or stress phenomena are related to tinnitus onset or exacerbation in more than 50%, i.e. significantly more than otological factors. This is supported further by the fact that only 27% of profoundly deaf people (from the group awaiting cochlear implantation in the UK) have tinnitus.

1.1.4 Tinnitus mechanisms

Well founded information on the mechanisms underlying this elusive, subjective phenomenon is difficult to identify. Various explanations of the underlying causes and pathological mechanisms, still highly hypothetical, have been proposed, some of which will be described.

On the basis of empirical data, it would be logical to assume, although difficult to substantiate, that tinnitus may result from a lesion or dysfunction at any level of the auditory system. From aetiological data, it seems quite obvious that tinnitus is a symptom of many diseases, and, therefore, different mechanisms may be involved.

1.1.4.1 "Cochlear" mechanisms

Mechanical tinnitus based on spontaneous cochlear oscillations

The role of cochlear mechanics in the generation of tinnitus was anticipated by Gold (1948). He speculated that "ringing" in the ear originates in the spontaneous mechanical oscillation of the physiologically active feedback mechanisms situated in the cochlea. This hypothesis has been supported with the introduction of otoacoustic emission techniques (Kemp, 1978), which have allowed the examination of cochlear micromechanics.

It has been suggested (e.g. Wilson, 1980 and Kemp, 1981) that spontaneous cochlear vibration (spontaneous otoacoustic emissions) may be a source of tinnitus in some cases, and according to Penner (1990) occurs in about 4% of the tinnitus population.

Mechanical tinnitus following acute noise exposure

Mechanical tinnitus, beside arising spontaneously, may also be evoked by external sound, in which case sound acts as a source of energy to set the cochlea into a state of mechanical instability and sustained oscillations. In his experiments with noise overexposure, Kemp (1982) demonstrated the biphasic effect of noise exposure. First,

the reduction of the cochlear echo was observed, followed by the enhancement of micromechanical cochlear activity (enhanced echo), coinciding with post-noise exposure tinnitus.

Cochlear synaptic tinnitus

It has been proposed (Ehrenberger and Brix, 1983; Pujol et al., 1993; Brix et al., 1996), that tinnitus could be generated in cochlear synapses between the inner hair cells and afferent neurons, as a result of glutamergic neurotoxicity (NB. glutamate is the main afferent cochlear neurotransmitter, see the section 1.2.7). The subsequent disturbed synchronisation of the peripheral stimulus-related evoked activity, could be a basis for tinnitus.

1.1.4.2 Central auditory mechanisms

Feedback interaction between the cochlea and central auditory structures

i.) Descending effect - the efferent system

The high density of the efferent olivocochlear innervation of outer hair cells (OHC) (Rasmussen, 1946) is an expression of the potential influence of the efferent system on cochlear mechanics. This effect is far from fully understood, but it is considered to be predominantly suppressive (Wiederhold, 1986). The higher structures in the auditory system can modulate the excitability of olivocochlear neurons, e.g. inferior colliculi, (Warr and Guinan, 1979; Rajan, 1990), or cortical and subcortical pathways (Attias et al, 1993b), and subsequently may also alter cochlear mechanics. This function raises the possibility of efferent activity having an important role in tinnitus generation.

It has been speculated that a partial cochlear lesion, e.g. due to noise exposure, may trigger *heterogeneous activation* of the efferent system (Spoendlin, 1987; Hazell, 1995). Of particular importance is thought to be a partial OHC lesion, in the presence of intact inner hair cells (IHC), so called *discordant damage* or *functional dissociation of OHC*

and IHC (Spoendlin, 1987; Jastreboff 1990; Jastreboff and Hazell, 1993). A partial OHC lesion leads to reduced afferent input, which in turn leads to “overactivity” of the intact OHC near the lesion, as a result of the feedback response of the efferent system to increased afferent input from the damaged region. This in turn brings about an “overspill” effect into the intact neighbouring OHC. This hypothesis finds support in the common observation that tinnitus pitch corresponds to the slope of hearing loss (Penner, 1980).

Anatomical and functional aspects of the cochlea and the efferent system will be discussed in more detail in section 2.

ii.) Ascending effect of the cochlear lesion

Different morphologic and neurophysiological changes in the central auditory system, following cochlear lesion, e.g. due to noise exposure, have been observed (Salvi et al., 1992). These changes, which may be of relevance in the generation of tinnitus, do not simply mirror peripheral damage. Cochlear lesions alter the activity in the *auditory nerve* and increase excitability of the *cochlear nucleus, inferior colliculus (IC)* (Willot and Lu, 1982; Salvi and Ahroon 1983) and *medial geniculate body* (Gerken, 1979). Since the IC is the obligatory relay for the ascending auditory pathway (Huffman and Henson, 1990), this may cause an imbalance between excitatory and inhibitory mechanisms, mediated by the neurotransmitters of auditory pathways, such as glutamate, glycine, acetylcholine or *γ-amino-butyric acid (GABA)*.

Studies of the auditory *cortical neurons* have indicated changes in their frequency selectivity. Reduced afferent input, due to cochlear lesions, initiates a sequence of changes in the relative levels of excitatory and inhibitory inputs to the primary auditory cortical neurons. This leads to expansion of the receptive field (located in the cochlea, adjacent to the damaged region) of the cortical neurons (Rajan et al., 1992), which in turn raises the threshold sensitivity and broadens frequency selectivity. Restricted damage to the cochlea also produces a tonotopic reorganisation of the *receptor surface in the primary auditory cortex*. The area in the auditory cortex deprived of its characteristic frequency peripheral input acquires a new characteristic frequency, of that at the edge of the region of cochlear damage (Robertson and Irvine, 1989; Schwaber et al, 1993). In other words, the damage to the cochlea leads to an expansion of the cortical representation of a restricted frequency band adjacent to the region of the cochlear loss.

Such plasticity of frequency selectivity and auditory maps may alter perceptual function, and, therefore, may contribute to the emergence of tinnitus.

The edge effect mechanism (in a review, Jastreboff, 1990)

According to this mechanism, tinnitus is based on the abrupt change in auditory neural activity due to a demarcated cochlear lesion (Kiang et al., 1970; Penner, 1980; Salvi and Ahroon, 1983), and is attributed to the phenomenon of lateral inhibition, leading to the enhancement of the neural activity at the transition point. This phenomenon has been observed in the visual system, as the enhancement of contrast in the transition between patterns of different density (Shepherd, 1983), and an analogy between the visual and auditory system has been made.

The gate-control hypothesis (Tonndorf, 1987)

This mechanism draws on the analogy between tinnitus and pain, and is based on an imbalance in the afferent input between IHC and OHC due to the predominant damage of OHC, that “opens the gate” to the tinnitus signal .

1.1.4.3 Neurophysiological concept

The neurophysiological concept of tinnitus generation assumes *active* involvement of the central auditory and other central nervous systems mechanisms. A mechanism proposed by Jastreboff and Hazell (Jastreboff, 1990; Jastreboff and Hazell, 1993), implicates a pathological “signal” in the auditory system triggering a sequence of events, resulting in increased neuronal activity at different levels of the auditory pathway, which may be perceived as tinnitus. However, other systems, particularly the *limbic and autonomic nervous systems*, are thought to be essential for the emergence and preservation of the “phantom” sound, tinnitus.

Several other neurophysiological concepts have been put forward. One of them, by Lenarz et al. (1993), suggests that the induction of tinnitus, which usually takes place in the periphery of the auditory system, results in an alteration in the spectrum of spontaneous activity of central auditory pathways, named by the authors as the *ensemble spontaneous activity*, specifically in the increased neural activity at 200 Hz (see “Recording of the spontaneous spectrum of the auditory nerve “ in section 1.5). Another hypothesis, proposed by Møller and coworkers (1984,1992), suggests that tinnitus results from pathological synchronised (phase-locked) neural activity in the auditory nerve, e.g. due to abnormal communication, “*cross-talk*” or *ephaptic transmission*, between neighbouring auditory nerve fibres following the damage to the myelin sheath (e.g. in acoustic neurinoma or vascular compression).

1.1.4.4 The interaction between auditory and other systems

Beside pathology within the auditory system, tinnitus may also result from neural interaction between the auditory and other sensory/motor system, e.g. visual, such as that occurring in a gaze-evoked tinnitus, due to synaptogenesis and cortical re-organisation, following unilateral deafferentation of the auditory periphery (Whittaker 1982, 1983; Wall et al., 1987; Cacace et al., 1994 a, b). In some forms of tinnitus, an interaction between auditory and extralemniscal multisensory pathways may occur, such as in tinnitus induced by electrical stimulation of somatosensory system, e.g. median nerve (Møller et al., 1992). This model of tinnitus is conceivable in view of the anatomical and physiological connections of auditory and other parts of the central nervous system (see sections 1.2.6 /1.2.7)

1.1.4.5 Concluding remarks

It is assumed that *every* sensation, including sound, is a consequence of a particular pattern of neural activity, which results from the stimulation of the sensory system, and differs from the baseline activity, characteristic for the non-stimulus state. For the perception of tinnitus, therefore, there must be a source. The source of “tinnitogenic”

activity may be any location in the auditory system, from the cochlea to the uppermost levels of the auditory system.

Despite the diversity in possible underlying mechanisms and tinnitogenic sources, it has been assumed that the common neurophysiological correlate to the sensation of tinnitus is altered spontaneous neural activity (altered rate, temporal pattern, and/or temporal correlation between the discharge patterns of different nerve fibres). This view has resulted in a new trend in research on tinnitus - recording of tinnitus-related neural activity: direct recording of spontaneous electrical activity in the auditory nerve, recording of auditory evoked magnetic fields, functional magnetic resonance imaging, positron emission tomography (see "Evaluation of tinnitus"), with the aim of finding an objective pathophysiological correlate(s) of tinnitus.

1.1.5 Evaluation of tinnitus

A crucial goal in developing successful treatment for tinnitus is the ability to identify and quantify tinnitus objectively.

The foundation of the evaluation of tinnitus was laid by Fowler, one of the great forerunners of modern audiology, in his *Tinnitus aurium in the light of recent research* (1941), a milestone in research on tinnitus. Following the introduction of satisfactory audiometric equipment in 1922, Fowler performed systematic experiments on tinnitus, including frequency and loudness match and tinnitus masking. Current attempts to evaluate tinnitus still consist of medical and neuro-otological evaluation, and authentication of the presence of tinnitus and its severity.

1.1.5.1 General medical and neuro-otological evaluation of tinnitus

The first task of the examiner is to exclude significant pathology underlying the complaint of tinnitus and to determine the functional state of the auditory system.

Medical evaluation is aimed at exclusion of medical conditions which have been found to influence tinnitus, including cardiovascular, renal, metabolic and autoimmune disease, and the effect of medications or drug usage.

Neuro-otologic evaluation of tinnitus has the purpose of establishing the integrity of the peripheral and central auditory system and identifying the presence and site of a lesion which may be related to the generation of tinnitus.

The routine test-battery usually includes:

Otoscopy

Pure-tone audiometry

Immittance measurement (tympanometry and stapedial reflexes)

Tinnitus matching and masking

Brainstem evoked auditory responses

Caloric testing

MRI/CT imaging

1.1.5.2 Authentication of the presence of tinnitus

Many attempts have been made to measure tinnitus objectively:

Psychoacoustical measurements of tinnitus

Psychoacoustical measurement of tinnitus is the only method for “authentication” of the presence of tinnitus currently used in routine clinical practice, based on comparison of tinnitus with external sounds. This has little bearing on the proposed treatment or prediction of treatment outcome, but may provide a general characterisation of tinnitus, although such measurements may often lead to spurious results, particularly in complex tinnitus. An attempt was made to develop an integral approach to the analysis of tinnitus composition by the introduction of music synthesisers (Hazell, 1981). However, due to difficulty in calibration, this time-consuming method proved to be impractical. Psychoacoustical measurements of tinnitus include assessment of the pitch, bandwidth, loudness, maskability of tinnitus and residual inhibition.

i) Pitch

Pitch is the perceptual correlate of the frequency; tinnitus pitch match is the procedure of matching the frequency of an acoustic tone or narrow-band noise to the predominant

pitch of tinnitus. Its importance has been emphasised with respect to the aetiology: high frequency (>3kHz) for NIHL-related tinnitus, and low-frequency loss for Menière's disease.

There is a small within-session, but extremely large between session, variability (by 5 kHz) of tinnitus measurements relative to the same measures for objective stimuli (Penner, 1983). The high variability may be due to "octave confusion" (the pure-tone stimulus matched to a harmonic of tinnitus), but is more likely due to a complex, broadband composition of tinnitus. It should also be considered that tinnitus often has a high pitch and that appreciation of the frequency in this region is poor (to judge what is a "high frequency", the highest tone used in musical instruments is C⁵, of 4096 Hz), particularly in those patients with a high-frequency hearing loss, which may further aggravate frequency discrimination. However, fluctuation of tinnitus itself, as an explanation of variability, cannot be ruled out.

ii) Loudness

Loudness of tinnitus refers to the psychological magnitude of sound intensity of tinnitus, coded by the rate of neural activity and by the number of nerve fibres involved. Tinnitus loudness match is the procedure of adjustment of the intensity of a pure tone or narrow-band noise to the same loudness as tinnitus, usually at the pitch-matched frequency. The loudness of tinnitus is measured in the range of 5-10 dB SL, a low level by all standards. Loudness must be, therefore, clearly distinguished from severity/annoyance of tinnitus.

iii) Masking

Masking refers to the reduction of the audibility of a sound by another sound - in tinnitus subjects, a tinnitus sound by a test (masker) sound. Usually, it refers to simultaneous masking.

In the large majority of subjects with tinnitus, the frequency of the masker has no distinct influence on the masking tinnitus frequency, and masking can be achieved effectively by applying the masker either, ipsi or contralaterally (Feldmann, 1971; Tyler and Conrad-Armes, 1983). There is also a paradoxical effect of masking broad-band spectrum tinnitus, by a single pure tone of any frequency (Tyler and Conrad-Armes, 1983). Consequently, iso-masking curves (a graphic presentation of minimum masking levels as a function of the frequencies of the maskers) in tinnitus are usually flat, unlike frequency dependent masking of an external sound, resulting in frequency specific curves (Tyler

and Conrad-Arnes, 1984). This is an indication that tinnitus and external sound are processed in a different way. However, in some tinnitus cases (e.g. spontaneous otoacoustic emissions-related tinnitus), tinnitus masking curves are frequency specific (Penner, 1988), raising speculation that tinnitus in these cases could be coded as an external signal. Subsequently, it has been suggested that frequency-dependent masking is more consistent with a “peripheral” locus of tinnitus, while broad-band, frequency non-specific masking occurs in tinnitus of “central” origin (Penner, 1987; Zwicker, 1987a), which is thought to result from interaction in the cochlear nucleus (Zwislocki, 1971). Therefore, the variety in masking responses “affirms that tinnitus originates in many places” (Tyler, 1992).

iv) Residual inhibition

Residual inhibition is defined as the suppression or complete elimination of tinnitus for a temporary period following masking, and, therefore, it refers to forward (central) masking. There is a high diversity in postmasking recovery that supports the hypothesis of different mechanisms involved in tinnitus generation (Tyler, 1992).

Recording of tinnitus-related neural activity

Recording of tinnitus related neural activity has resulted from a neurophysiological approach to tinnitus, assuming an alteration of spontaneous neural activity leading to perception of tinnitus. The following methods, still in the experimental stage, have been proposed to provide objective evidence of the presence of tinnitus:

i) Spontaneous spectrum of neural activity within the auditory nerve:

Recordings directly from the promontory, or directly from the auditory nerve during acoustic neurinoma surgery, have allowed the identification, in some patients with tinnitus, of an increase in auditory nerve activity at 200 Hz. This peak disappeared or decreased following application of a known tinnitus-suppressor, Lidocaine (Feldmeier and Lenarz, 1996). This 200Hz peak in the auditory nerve spontaneous spectrum has been considered to be an electrophysiological correlate of tinnitus.

ii) Auditory event related potentials (ERP):

Include N100, P200 (>150 ms), and long latency, P300 (>300 ms) components, which reflect neural activity associated with specific perceptual (auditory) processes. A study involving chronic tinnitus patients (n=12) with a history of mainly impulse noise exposure, showed significantly lower amplitudes of the waves N100, P200 and P300 of ERP, than controls with similar degrees of NIHL and type of noise exposure, but without tinnitus (Attias et al., 1993b).

iii) Auditory evoked cortical magnetic fields (AEF)

Measurements of AEF, in particular M200 (which correspond to the electrical wave P200) and M100 (which correspond to the electrical wave N100) components, which have a higher spatial resolution than ERP, have been proposed to provide a means for the detection of neuronal activity associated with the perception of tinnitus.

In the first study using AEF recording in tinnitus patients (Hoke et al, 1989), it was reported that AEF responses in tinnitus patients differ from those in normal subjects, and the amplitude ratio P2/N1 was proposed as an objective parameter of tinnitus.

Several subsequent studies have failed to identify any differences in AEF between tinnitus and non-tinnitus subjects. However, in one of the most recent studies which compared AEF of tinnitus and no-tinnitus state (remission induced by Lidocaine) in the same patients, “sharpening” of N100 peak of AEF was detected, and its late component was almost completely lost, or markedly attenuated, after Lidocaine application (Shiomi et al, 1997b). “Sharpening” of the N100 tip was suggested to be of use as an AEF parameter for objective evaluation of tinnitus.

iv) Functional magnetic resonance imaging (fMRI)

This technique is assumed to be an indirect measure of neural activity, which is increased during sensory, motor or cognitive activation, and accompanied by an increase in local oxygen saturation and, consequently, by an increase in local blood flow. Thus, different images between activated and non-activated conditions, may serve to localise activation sites in the CNS. T₂ - weighted MRI was performed in a unique subset of tinnitus patients, who were able to control their tinnitus perception either by eye gaze or cutaneous stimulation (Cacace et al., 1996). Tinnitus-related activity was found in subjects with tinnitus, but none in controls.

v) Positron emission tomography (PET) of cerebral blood flow:

This technique was used (^{15}O -water) to identify sites mediating tinnitus in patients with hearing loss at frequencies >2 kHz. An increase in cerebral blood flow in the central auditory system, with spillover into regions not usually associated with primary auditory perception was found (Lockwood et al., 1996). This spillover indicates that plastic reorganisation has occurred. The most prominent changes were found in the middle temporal gyrus, hippocampal and fusiform gyri and in the region, including the medial geniculate bodies.

1.1.5.3 Authentication of the severity level of tinnitus

The complaint level of tinnitus is unrelated to psychoacoustic or any objective measurements. Fowler (1941) referred to tinnitus annoyance/severity as an “illusion of great intensity”, as many patients with “unbearable” tinnitus demonstrate, according to the loudness test, very faint tinnitus.

Several subjective questionnaire have been used for assessment of the severity of tinnitus (a review by Erlandsson, 1992). Assessment of the severity of tinnitus is based on subjective (self-rated) tinnitus scaling (tinnitus handicap questionnaires), e.g. Vernon’s (1987) tinnitus grading system, in which patients assign values from 1 to 5 to each of the subjective complaints of loudness, annoyance, and interference with life activities. However, no international consensus has been reached.

Psychological profiling of patients with tinnitus has an important place in assessing the severity of tinnitus, in view of well recognised relationship between tinnitus and psychological or stress phenomena (Hinchcliffe and King, 1992).

A strong correlation between the pre-existing psychopathology and the severity of tinnitus is very likely to exist. The distressed tinnitus patients frequently have a history of depressive episodes prior to the onset of tinnitus (Harrop-Griffiths et al., 1987) and depression (as a syndrome) is considered to be the principal distinguishing feature of the tinnitus complainers (Hinchcliffe and King, 1992). The possible involvement of personality traits, such as social adjustment problems, excessive personal sensitivity, or coping problems, on the severity of the tinnitus perception, has been suggested (Reich

and Johnson, 1983; Attias et al., 1993a), particularly in normally-hearing tinnitus patients (McKee and Stephens, 1992).

In a study by Stephens and Hallam (1985), applying Crown-Crisp experiential index, it was found that tinnitus patients showed an increased psychopathology. In a more recent study, using the Dutch translation of the STSS (Subjective tinnitus severity scale), four psychological variables of the scale, emotional distress, intrusiveness, annoyance and cognitive distress, were found to be significantly correlated with anxiety and depression (van Veen et al., 1998).

1.1.5.4 The role of otoacoustic emissions in the evaluation of tinnitus

Currently, the role of otoacoustic emissions (OAEs) in the evaluation of tinnitus, as a part of neuro-otologic assessment, is primarily to establish cochlear integrity and to detect early cochlear (OHCs) lesions, using transient click-evoked otoacoustic emissions (TEOAEs). This method is gaining an increasing importance in clinical practice. Less frequently applied, and limited to a few centres, is the method of assessment of olivocochlear suppression by recording of TEOAEs under contralateral acoustic stimulation (Veuille et al., 1992; Chéry-Croze et al., 1994a,b; Graham and Hazell, 1994; Attias et al., 1996a), to identify efferently mediated mechanisms underlying tinnitus. This method is still not accepted as a routine test, as its significance is not fully understood, and it lacks sufficient normative data.

There have also been attempts to employ OAEs in the authentication of the presence of tinnitus, which have resulted in observation of the differences between tinnitus and non-tinnitus patients. These are probably consequences of the differences in the degree of outer hair cells lesion (McKee and Stephens, 1992; Mitchell et al., 1996; Janssen et al. 1996).

1.2 AUDITORY SYSTEM

1.2.1 Functional anatomy

1.2.1.1 Outer and middle ear

The auricle funnels sound waves into the external auditory meatus. From the meatus, the external auditory canal passes inward to the tympanic membrane. The outer ear assists in localising a sound source and serves to reinforce the resonance of the tympanic membrane (range 2-7 kHz).

The middle ear (Figure 1.1) is an air-filled cavity in the temporal bone that opens via eustachian tube into the nasopharynx and through the nasopharynx to the exterior. The three inter-articulated auditory ossicles, the malleus, incus and stapes, are located in the middle ear. By attachment of the malleus to the tympanic membrane and the stapes to the oval window, they form an elastic spring, the stiffness of which is controlled by the two muscles of the middle ear, the stapedius and the tensor tympani. The stapedius is attached to the stapes and the tensor tympani to the malleus. In humans, on acoustic stimulation, the stapedius contracts alone, and the tensor tympani contracts if a startle reflex is elicited and it has much smaller effect on acoustic transmission than the stapedius. The neural network of the stapedial reflex is integrated in the lower brainstem and consists of both, ipsilateral and contralateral routes, with its descending pathway including the facial nerve, which innervates the stapedius. Therefore, when either ear is stimulated by an appropriately loud sound (the average threshold for white noise is 65-70 dB above the hearing threshold), both, ipsilateral and contralateral stapedius muscles contract. The main effect of contraction is a reduction in the middle ear transmission of up to 15 dB in the low-frequency range, typically below 1 kHz. Beside contraction to acoustic stimuli, other reflex activities include continuous ongoing changes in muscle tone and contraction associated with other motor events (e.g. vocalisation, chewing, etc.).

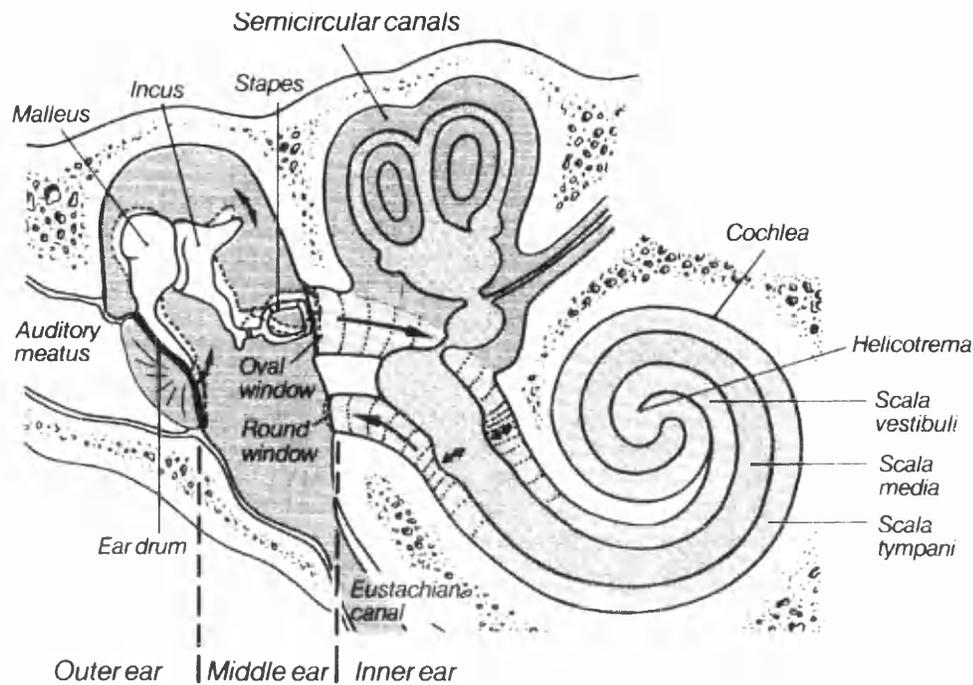


Figure 1.1: A cross-section of the middle and inner ear. Dotted lines in the middle ear (together with arrows) indicate vibratory movements of the ossicular chain, and in the inner ear of the perilymph, driven by sound pressure waves; in the inner ear, longitudinal arrows show the direction of the travelling wave propagation and transversal arrows the site of maximal displacement and vibrations of the scala media. (Adapted from Despopoulos A, Silbernagl S. Color Atlas of Physiology. New York: Thieme Medical Publishers Inc, 1991: p. 319.)

The main function of the middle ear is to transmit sound from a medium with a low impedance for sound waves (air) to one with a high impedance (fluid), with as little loss of sound energy as possible. This impedance matching is achieved largely due to the fact that the sound pressure exerted on a larger area (tympanic membrane 50 mm^2) is transmitted to a small area (oval window, 3 mm^2), and by interpolation by the ossicles, which exert a leverage which increases the force about 1.3-fold. Optimal transmission is for sounds at frequencies in the range 1-2 kHz.

1.2.1.2 The inner ear - cochlea

The inner ear (Figure 1.1) is made up of the bony labyrinth, a series of channels in the petrous portion of the temporal bone. Inside these channels and surrounded by a fluid, perilymph, is the membranous labyrinth, which is filled with a fluid, endolymph. There is no communication between spaces filled with perilymph and those filled with endolymph.

The inner ear consists of the organs of equilibrium and the cochlea. The cochlear portion of the labyrinth is a spiral tube, which is about 35 mm long and makes $2^{3/4}$ turns. Throughout its length, the basilar membrane and Reissner's membrane divide it into three chambers or *scalae*. The upper, *scala vestibuli*, ends at the base of the cochlea, at the oval window, which is closed by the footplate of the stapes and the lower, *scala tympani*, ends at the round window, a foramen on the medial wall of the middle ear cavity that is closed by a flexible membrane. The *scala vestibuli* and *tympani* contain perilymph and communicate with each other at the apex of the cochlea through a small opening, the *helicotrema*. Via *aqueductus Silvii*, the perilymphatic system communicates with the subarachnoid space of the posterior cranial fossa. The middle cochlear chamber, the *scala media*, is continuous with vestibular membranous labyrinth which contains endolymph, and does not communicate with the other two *scalae*. The endolymphatic system of the membranous labyrinth is connected to the *sacculus endolymphaticus* via the endolymphatic canal (passing through the *aquaeduct Silvii*), and thus forms a closed system. The endolymphatic sac is situated on the posteromedial aspect of the temporal bone.

The organ of Corti

The organ of Corti (Figure 1.2), the sensory receptor of the cochlea, is formed by sensory hair cells, supporting epithelial cells and neural elements. It is located on the basilar membrane in the *scala media*, extending from the base to the apex of the cochlea, and consequently has a spiral shape. The structure contains about 20,000 outer hair cells (OHCs), arranged in three to five rows, lateral to the tunnel of Corti, formed by pillar cells, and about 3,500 inner hair cells (IHC), arranged in a single row, medial to the

tunnel. The processes of the hair cells, stereocilia, pierce the tough, membrane-like reticular lamina, supported by pillar cells. Each of the hair cells have roughly 100 stereocilia, whose tips, apart from those of the IHCs, are in close contact with the viscous and elastic tectorial membrane. Stereocilia are composed of packed actin filaments and linked together by fine extracellular filaments and these links play an important role in the mechanical transduction system of the hair cells (Pickles et al., 1984; Hackney and Furness, 1995). Between the apical parts of hair cells and the adjacent phalangeal cells there are tight junctions which prevent endolymph from reaching the bases of the cells. However, the basilar membrane is relatively permeable to perilymph in the scala tympani, and consequently the tunnel of the organ of Corti and the bases of the hair cells are bathed in perilymph. The OHCs are characterised by the presence of contractile elements, actin-myosin complex, in their infrastructure, in the cytoskeleton of the OHC body and its apical part, the cuticular plate, which enables them to perform tonic contractions, as well as fast oscillating contractions (Zenner, 1986).

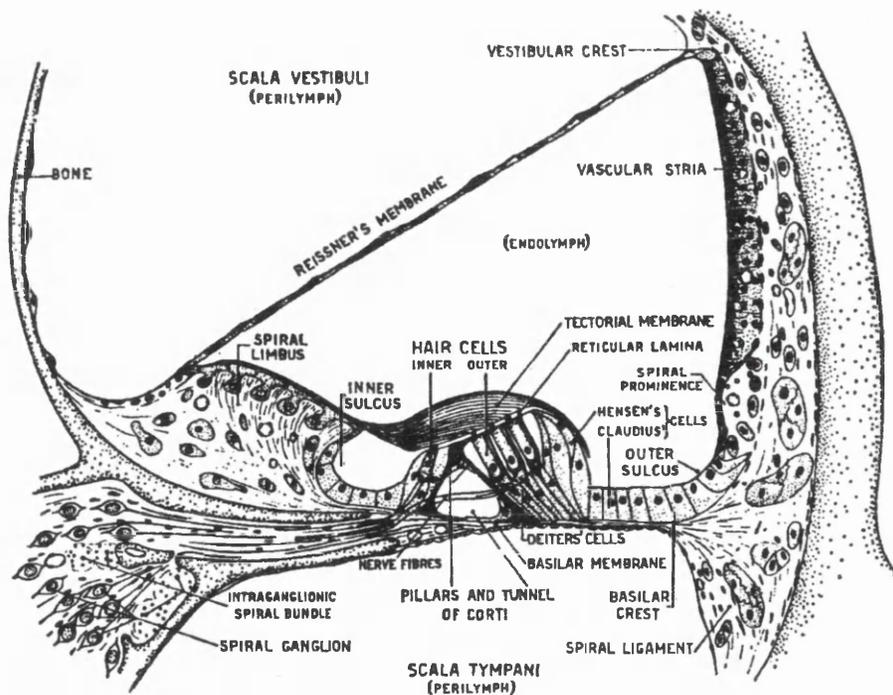


Figure 1.2: A cross-section of the organ of Corti (Iurato S. Submicroscopic structure of the inner ear. Oxford: Pergamon Press, 1967)

1.2.2 Mechanical responses in the cochlea

The vibrations of the stapes footplate in the oval window, driven by sound pressure waves, cause a dynamic displacement of the cochlear partition in the shape of a travelling wave. Since the walls of the endolymphatic duct (scala media) are flexible, the travelling waves are transmitted to the scala tympani, and the wavelike distortion of the endolymphatic duct causes Reissner's membrane and the basilar membrane to swing from one side to the other, i.e. towards the scala tympani and the scala vestibuli, alternatively. The amplitude of the travelling wave has a clearly defined maximum. The site at which maximal displacement of the endolymphatic duct occurs is the "characteristic" for the frequency of sound: high frequencies have their maximum reception near the stapes, while low frequencies are situated towards the apex. The velocity of the travelling waves and their wavelength gradually decrease with increasing distance from the oval window. Among the reasons for this attenuation, beside the dumping properties of the liquid-filled scalae, is that towards the apex, the basilar membrane gradually becomes wider (increased mass) and less rigid (reduced stiffness). This hydrodynamic mechanism, initially thought to be a passive response to the propagating sound, was extensively investigated and described by von Békésy (1960).

The scientific knowledge accumulated over the past two decades has provided the evidence that the cochlea is not just a passive mechanical signal analyser, but it plays an active role in the mechanical processing of sound. The source of active behaviour of the cochlea are OHCs, with their motor capacity for slow and fast contraction. The *slow*, tonic contractions of OHCs (Zenner, 1986) can alter the stiffness of the cochlear partition in a sharply restricted area, thus modifying the envelope of the travelling wave. These slow contraction result from the activity of the efferent system, known as electromechanical transduction (electromotility), and have an important role in setting the position of the basilar membrane. The *fast* contractions (Brownell et al., 1985) are phase-locked to the stimulating sound and follow sound-driven passive vibrations of the cochlear partition. They stimulate the actinomyosin network of OHCs, acting to oppose viscous damping in the cochlea and to enhance the oscillations of the cochlear partition and, thus, they enhance the mechanical stimulation of the OHCs in a sharply tuned way.

These active oscillations of the OHCs are responsible for the generation of otoacoustic emissions (described in the section 1.3).

The oscillations in the endolymphatic duct cause displacement of the tectorial membrane, in which stereocilia are embedded, and the reticular lamina, which holds the tops of the OHCs, in the same direction. However, as they are hinged on different axes, the relative movement of the two membranes with respect to one another leads to shearing of the stereocilia, which provides an adequate stimulus for the transduction of mechanical to electrical energy within the hair cells. The deflection opens ion channels of the stereocilia and ions, driven by the potential gradient, cause voltage fluctuation. This process of transforming the mechanical energy to electrical impulses, known as mechano-electrical transduction, is one of the most fundamental properties of the cochlea. It is described in more detail in the next section.

1.2.3 Bioelectrical potentials of the cochlea

The mechanical events in the cochlea are transduced into alterations of electrical potentials and ultimately into neural activity.

The endolymphatic space has a *standing (resting) potential* of about +80 mV with respect to the perilymphatic space, which is related to the unequal distribution of Na^+ and K^+ between the endolymph and perilymph (about 140 mmol/l K^+ and 3mmol/l Na^+ in endolymph and 4 mmol/l K^+ and 140 mmol/l Na^+ in the perilymph), and is maintained by active transport processes in the stria vascularis. Since at rest, the IHC and OHC have a *cell potential (membrane potential)* of -70 mV and -40 mV, respectively, there is a potential difference of 150 mV and 120 mV, respectively, across ciliated cell membrane (cell interior negative). Additionally, the K^+ concentration of about 140 mmol/l in the endolymph is roughly the same as in the hair cells, so that the K^+ equilibrium potential (NB. corresponds to equilibrium concentration - when electrochemical gradient of K^+ is zero) amounts to 0 mV. Thus, the entire 150 mV and 120 mV, respectively, are available as driving forces for a K^+ influx.

When sound-driven propagating travelling waves induce ciliar shearing that opens mechanosensitive K^+ channels, then there is an influx of Ca^{++} and K^+ and the cell is depolarised, providing a *receptor potential* which causes the release of neurotransmitter (see below in the section 1.2.7). The displacement of stereocilia in the opposite direction, reduces K^+ influx, the cells become hyperpolarised and less transmitter is released. The receptor potential subsequently initiates the *action potential* in the corresponding afferent fibres of the auditory nerve.

In the OHCs, the passive vibrations and sound-induced ionic gating leading to depolarisation, is accompanied by the additional induction of active mechanical movement in the OHC cytoskeleton. Thus, sound-driven mechanical movements induce depolarisation of the electrical potential and a raised intracellular Ca^{++} induces fast a.c. contractions, shortening, of OHCs. The subsequent hyperpolarisation leads to slow d.c. movements, lengthening of OHC (Zenner, 1986), thus creating highly nonlinear and saturating positive feedback system. The OHC a.c. motility, which enhances the basilar membrane motion (near hearing threshold amplification by ≈ 40 dB), is linearly correlated to the intensity of sound stimuli (LePage, 1987). However, with an increase in sound pressure level, the cochlea is capable of correcting undesirable (high) shifts of the basilar membrane by the OHC d.c. movements, leading to reduction of the passive displacement, and nonlinear compression of cochlear dynamics (attenuation). Thus, OHC act as controlled mechano-amplifiers within the cochlea and feed amplified mechanical oscillations to the IHCs, which are directly involved in the transformation of mechanical energy into neural activity.

There are three groups of gross stimulus-evoked potentials that can be recorded when electrodes are placed near the cochlea .

i.) *Microphone potential or cochlear microphonic* is an a.c. phenomenon. It reflects, like a microphone, the temporal course of the sound stimulus as fluctuation in voltage, thought to derive from OHC activity.

ii.) *Summation potential*, is a d.c. shift in the baseline potential, resulting from the activity both, of IHCs and OHCs.

iii.) *Compound action potential* is the massed, synchronised activity of the auditory fibres (action potentials) in response to stimulus onset.

1.2.4 Innervation of the cochlea

The organ of Corti has afferent and efferent innervation (Figure 1.3). Afferent fibres that arborize around the bases of the hair cells are dendrites from bipolar cells whose bodies are located in the spiral ganglion within the modiolus, the bony core around which the cochlea is wound. Efferent fibres are axonal endings of neurons located in the brain stem. About 90-95% (Spoendlin,1979) of 30,000 type I afferents (thin, unmyelinated) originate from the IHC (about 10-20 unbranched fibres are attached to each IHC), while approximately 5-10% of the type II afferents (large, myelinated) originate from the OHCs (one fibre serves about 10 OHCs). This means that, although the OHCs by far outnumber the IHCs, the information transferred from the cochlea almost exclusively comes from the IHCs.

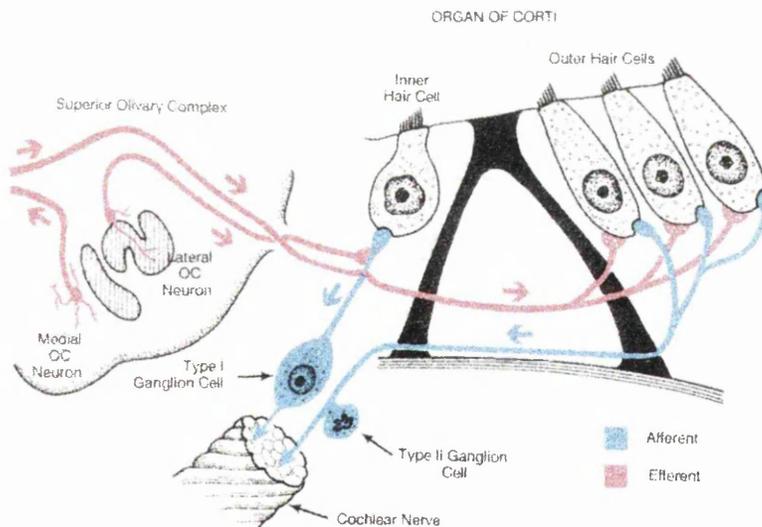


Figure 1.3: The afferent and efferent innervation of the cochlea (Schuknecht HF. Pathology of the ear. Philadelphia: Lea & Febiger, 1993: p. 67)

In contrast, about 95% of all 1800 efferent fibres have direct and wide synaptic contact with the OHC bodies, whilst an almost negligible number of the efferent neurons have indirect postsynaptic contact with IHCs, via the dendrites of the afferent neurons innervating IHCs. The afferent fibres, forming the cochlear nerve, and efferent fibres, forming the olivo-cochlear bundle and travelling along the vestibular nerve, leave the cochlea, pass together through the internal auditory meatus and enter the brainstem at the upper part of medulla oblongata, at the level of the prepontine fossa.

This distinctly different innervation pattern implies specific physiological roles of the dual sensory system (IHCs and OHC)s in the cochlea: IHCs as the primary sensory cells that generate action potentials in the auditory nerve and OHCs as the active mechanoreceptors.

The cochlea also receives sympathetic, adrenergic innervation through the fibres ending on blood vessels in the spiral lamina and fibres terminating near afferent fibres (Spendlin and Lichtensteiger, 1966; Brechtelsbauer et al., 1990), as well as perivascular fibres in the stria vascularis (Liu et al., 1996). The presence of adrenergic innervation in the cochlea implies its role in controlling vasomotor tone and the influence on cochlear hemodynamics.

1.2.5 Central auditory pathways

1.2.5.1 Afferent system

Branches of the auditory nerve fibres (Figure 1.4) run from the organ of Corti to the anteroventral, posteroventral and dorsal *cochlear nuclei*. The afferents are arranged in the three nuclei according to the frequency (tonotopic organisation) and in varying complexity. In these nuclei, lateral inhibition enhances contrast (i.e. suppression of noise). In the *superior olive* and in the *accessory nucleus*, which also receive contralateral impulses, intensity and travelling time of sound are compared (direction).

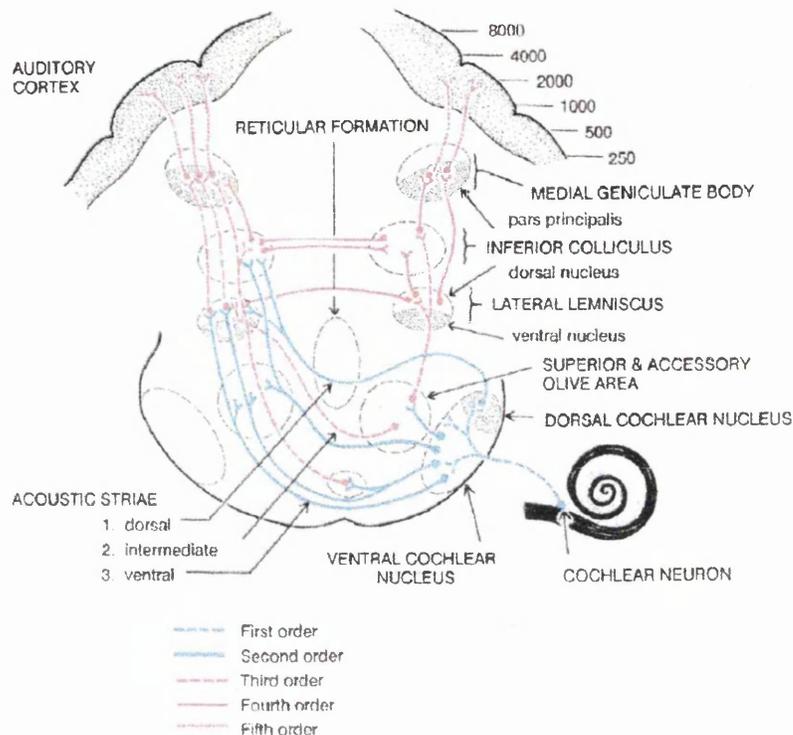


Figure 1.4: The afferent auditory pathways (Schuknecht HF. Pathology of the ear. Philadelphia: Lea & Febiger, 1993: p. 68)

The next relay stations are in the *lateral lemniscus* and, after a predominant crossing of the fibres to the opposite side, in the *inferior colliculus* (IC). The inferior colliculus is a site for integration and relay of information along ascending auditory pathways. In addition to relaying reflexes (e.g. middle ear muscles), the sensory analysis of the cochlear nuclei is compared within the inferior colliculus with the spatial analysis of the superior olive. Via the thalamus (*medial geniculate nucleus*) the afferents finally reach the *primary auditory cortex* (Brodmann's area 41), which is surrounded by the secondary, association areas for hearing. These centres are responsible for a variety of complex auditory processing, including the analysis of complex sounds; short-term memory for comparison of tones; inhibition of unwanted motor responses and for intent listening (attention).

1.2.5.2 Efferent system

The efferent system is much less well defined than the afferent auditory system. Its best known part is the olivo-cochlear (OC) system (Figure 1.5), first described by Rasmussen in 1946. The fibres of OC system originate from the superior olivary complex (SOC) (in medulla oblongata), which consist of the medial and lateral nuclei.

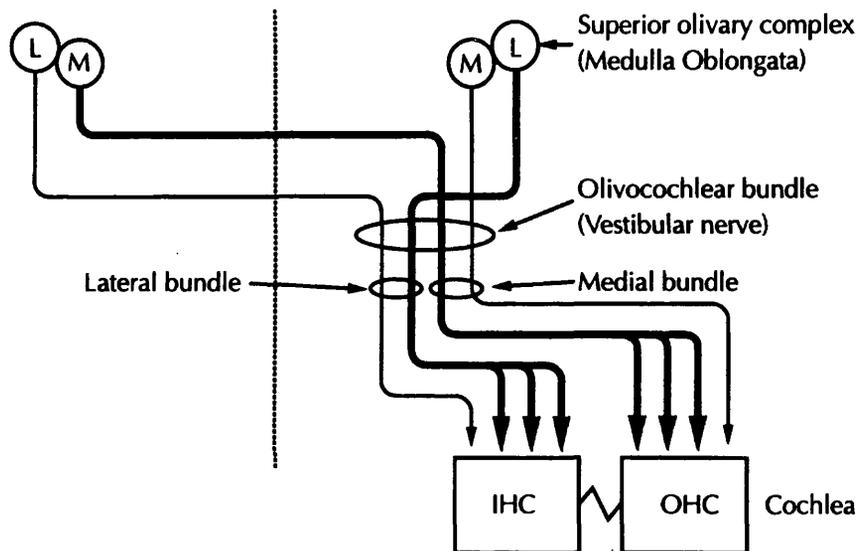


Figure 1.5: Schematic diagram of the olivo-cochlear efferent system

The fibres from lateral nucleus are arranged in the predominantly uncrossed, lateral olivo-cochlear bundle (LOCB) which projects to afferent fibres of IHC (see above). The fibres from the medial nucleus are arranged in the mainly crossed, medial olivo-cochlear bundle (MOCB) and project directly onto the OHC. The medial efferent olivo-cochlear (MOC) system is considered to be inhibitory (Wiederhold, 1986) and responsible for the control of OHC motility (cochlear micromechanics). With the introduction of otoacoustic emissions (Kemp, 1978), the MOC system has been extensively investigated (see the section 1.3.5). However, very little is known about the lateral olivo-cochlear (LOC) system. It is believed that it plays an important role in the firing of auditory neurons and, therefore, may have a protective role against excessive noise and/or excitotoxicity (Pujol, 1994).

The olivo-cochlear system has multisynaptic connections with the upper parts of the auditory system. Of special interest is the connection with the *inferior colliculus* (IC), emphasising its important role in the descending auditory pathway. It projects to the superior olivary complex, and in particular, to the source of the OC neurons, allowing direct collicular influence on cochlear mechanics. Anatomical and physiological studies of the ICs connections with SOC strongly suggest that IC plays a role in the activity of the OC system. This is supported by studies, e.g. by Dolan and Nuttall (1988), which have demonstrated that stimulating the IC produces changes in the auditory nerve responses and micromechanical properties of the cochlea (evident from otoacoustic emissions and cochlear microphonic potentials), similar to changes seen with stimulation of the MOC system.

The connections of the IC with acoustic cortex rostrally, and with OC system caudally, imply a descending trisynaptic pathway from the cortex to the cochlea and, thus, the possibility for an efficient feedback mechanism (Huffman and Henson, 1990).

1.2.6 Extra-auditory neural connections

The auditory pathway has connections with other parts of central nervous system, the significance of which still remains largely unknown.

Via the IC, the auditory pathway has input from the *hypothalamus* (Adams, 1980) - the principle organ of integration of the endocrine system and the control centre of all autonomic functions (including mechanisms of adaptation - response to stress and emotions: enhancement of sympathetic activity elicited by catecholamines), thus regulating the “internal milieu” and maintaining homeostasis. Projections from hypothalamic α -melanocyte-stimulating hormone-ergic cells to IC (Shiosaka et al., 1985) may be of relevance to the function of the cochlear melanocytes, which are thought to be of importance for hearing sensitivity. The hypothalamus is intimately connected with the limbic system, the reticular formation and, via the thalamus, with the cerebral cortex.

The reticular formation, although anatomically a diffuse entity, has great physiological significance, being responsible for the behavioural states of arousal and sleep. In addition, it plays a part in the control of many functions, including motor activity, sensory function (by modulating sensory input to the thalamus), autonomic activity, circadian rhythms and endocrine secretion (via the hypothalamus).

The limbic system, which is the site of instinctive behaviour and emotions, has cortical (hippocampus, parahippocampal gyrus, cingulate gyrus) and subcortical divisions (amygdaloid body, septal area, anterior thalamic nucleus), and reciprocal connections with the hypothalamus and with the temporal and frontal cortices. The latter serve for integration of perception and evaluation of signals from the “outer world” and memory content. The limbic system receives projections from the medial geniculate body, which is hypothesised to serve as a primary link for attaching emotional significance to acoustic stimuli (LeDoux et al., 1983).

The auditory system has connections with the *somatosensory system*. The IC, with its multisensory connections suggesting a role in multisensory integration, and the medial division of the *medial geniculate body* (MGB) (a multisensory thalamic area) probably play the most important role in the phylogenetically “old” connection between the auditory and somatosensory system. Connections with the somatosensory system are also possible via the *extralemniscal system*, which branches off from the classical ascending lemniscal auditory system at the level of the IC and projects to the associative cortices (prefrontal area, limbic portions, temporal, parietal and occipital areas) rather than to the primary auditory cortex (Graybiel, 1972). Neurons of the extralemniscal system respond much less specifically to sound stimulation than neurons in the lemniscal system. Some neurons in the extralemniscal system receive input, not only from the auditory, but also from the somatosensory system, and, therefore, respond to somatosensory stimulation leading to the perception of sound (e.g. electrical stimulation of the median nerve) in addition to auditory stimulation (Møller et al., 1992).

Another important relay in the polysensory system is the *superior colliculus*, which includes maps of visual and tactile receptive fields, aligned with the auditory map, and which, in part, therefore, coordinates auditory, visual and somatic information (Huffman and Henson, 1990).

1.2.7 Cochlear homeostasis: neuro-humoral modulation

Homeostasis of the cochlear system and adaptation in cochlear performance, are exquisitely balanced by complex feedback system(s), involving, as a general rule, the nervous and endocrine systems. The first, which is specialised for the rapid transmission of signals by means of neurotransmitters (substances released in the synapses of neural endings following their stimulation), regulates/modulates OHC permeability and contractility. The second, the endocrine system, acts in close co-operation with the autonomic system in the brain, providing slow, chronic transmission of signals, by means of hormones, within the circulatory system: the perilymphatic fluid, which communicate with cerebrospinal fluid and cochlear blood circulation, including the stria vascularis. The stria vascularis has an important role in maintaining osmotic balance and electrical potentials in the cochlea.

The main neurotransmitter of the centrifugal, afferent system, originating predominantly from IHCs, which transduce the mechanical displacement into neural activity, is *glutamate*. Beside its potent excitatory effect, glutamate also displays a highly neurotoxic effect, observed in various pathological conditions, e.g. acoustic trauma (Puel, 1995).

The centrifugal efferent medial olivocochlear (MOC) innervation to the OHCs, can be considered to be a part of the parasympathetic autonomic nervous system. It provides efferent control of the OHCs via predominantly cholinergic fibres, which are mainly confined to the basal OHCs (high-frequency region of the cochlea) and *γ-aminobutyric acid* (GABA)-ergic fibres with a predominantly apical (low-frequency) distribution (Altschuler and Fex, 1986; Plinkert et al., 1993). Another important neurosubstance localised in the medial efferents, which may play some role in neuromodulation of OHCs activity, is neuropeptide calcitonin gene related peptide (CGRP) (Pujol, 1994).

Stimulated cholinergic fibres release *acetylcholine* which induces depolarisation of OHCs by opening Ca^{++} - dependent K^{+} channels (Housley and Ashmore, 1991), leading to contraction (shortening) of the OHC body. Synaptically released GABA activates $GABA_A$ receptors (N.B. GABA acts on two different types of receptors, A and B, of which A-type is present in the cochlea, Plinkert et al., 1993) leading to the opening of

chloride-permeable ion channels and resulting in hyperpolarisation, causing the elongation of the OHCs, making them less responsive to excitatory input (Gitter and Zenner, 1992).

The MOC system is considered to be mainly inhibitory (Wiederhold, 1986). This effect is consistent with the results of a number of studies, in which stimulation of the efferents in silent condition has been employed (see section 1.3). However, when efferents are activated in noisy background, they exhibit an enhancement of the transient stimulus (Dolan and Nuttall, 1988; Kawase et al., 1993).

There is now evidence that GABA-ergic system can act not only as an inhibitory, but also as an excitatory system. This has been demonstrated by diurnal variation of, during day excitatory, and at night inhibitory, GABA-ergic effect on the suprachiasmatic nucleus of the hypothalamus, which mediates in the process responsible for the generation of circadian rhythms (Wagner et al., 1997) through the variation of melatonin, a hormone of the pituitary gland. Whether this switch from excitation to inhibition, thought to be driven by daily variation in intracellular chloride, exists in the cochlea, is open to question.

As melatonin is found in the bloodstream and cerebrospinal fluid, its presence in the perilymph, which is in continuity with the cerebrospinal fluid, is possible. Thus the diurnal effect of melatonin may influence cochlear mechanics, in addition to neural activity. The possible effect of the circadian rhythm on the cochlea is supported by experimental findings of systematic diurnal changes of otoacoustic emissions (see 1.3.4.1).

It has been recognised that female *reproductive hormones* (regulated through pituitary-gonadal axis) stimulate the secretion of GABA (Perez et al., 1986; Brechtelsbauer et al., 1990), and alter GABA-mediated responses in the brain (Wilson, 1992). Therefore, cochlear micromechanics could be modulated by variations in reproductive hormones.

It is also possible that, via the reticular formation, the monoaminergic pathway systems, noradrenergic, dopaminergic and serotonergic neurons may exert an effect on auditory

function: adrenergic for positive reinforcement (arousal or interest), while serotonergic for “disinterest”.

Such enormous variety in the neurochemistry of the efferent pathways and modulating humoral factors create infinite possibilities for chemical inhibition or stimulation of the OHCs. The ultimate aim is the control of cochlear homeostasis, of which one of the most important variables is the mean position of the basilar membrane (optimal operating point of the OHCs despite changes in the frequency and sound levels), or the resultant force controlling its position. This is achieved by preserving the contractile capacity of the OHCs, their tonus and osmolarity, which is necessary to maintain sensitivity for mechano-electrical transduction and neurotransmission.

1.3 OTOACOUSTIC EMISSIONS

1.3.1 Introduction

Otoacoustic emissions (OAEs) are weak acoustic signals that can be recorded in the ear canal and considered to reflect OHC activity. They, therefore provide a direct means of communication with the sensory cells. In 1978, OAEs were demonstrated and recorded, for the first time, by David Kemp. Over time, recording of OAEs has progressed from an experimental procedure, limited to a few laboratories, to a widely used, routine clinical techniques worldwide. This revolutionary discovery has made a profound impact on hearing research (e.g. in understanding OHC activity and the medial olivocochlear system) and clinical audiology.

1.3.1.1 History

The basic understanding that sound is collected by pinna, transmitted by the middle ear to the cochlea, and that the cochlea converts sound waves into nerve impulses which are transmitted into the brain, existed 200 years ago. The progress in understanding how the cochlea processes sound developed in parallel with the increasing interest in the theory of music and of musical instruments. As a result, the “*passive resonance*” theory was born. However, this theory could not explain how sound overcomes the dumping properties of the fluid, the presence of which in the living cochlea was proved by Cotugno in 1760 (Feldmann, 1991). Similarly, this could not be explained by the “*place resonance*” theory, assuming that the cochlea consists of the resonant elements for the analysis of different frequencies, proposed by von Helmholtz (Feldmann, 1991), nor by the “*telephone theory*”, which suggested that the ear worked as a non-resonant electromechanical transducer, implying that pitch information is presented in the periodicity of neural discharge. This view, that hearing is based on a direct electric analogue of sound, was dismissed in 1940s, by a series of experiments on cadavers, conducted by an eminent telephone engineer, von Békésy. He observed slow (in contrast to the rapidly fluctuating telephone signal) mechanical displacement of the basilar membrane in response to sound, and described his classical *travelling wave*.

Although undoubtedly significant, his experiments also failed to demonstrate a mechanism against dumping of the travelling wave end energy loss. In 1948, a biophysicist Thomas Gold, applying the same logic to the cochlea as to the enhancement of the selectivity of radio receivers, anticipated an *active involvement* of the cochlea in a *positive feedback*, self-inforced system, which compensates the energy loss of sound propagation through the viscous, highly dumping inner ear fluids. Nevertheless, at that time, his views were not seriously considered. Only with discovery of the existence s by Kemp in 1978, his vision became reality - OAEs have implied the existence of active mechanical amplification of sound in the cochlea, and a small “leakage” of sound energy from that process can be recorded in the ear canal.

1.3.2 Generation of otoacoustic emissions

Kemp has proposed that OAEs are emitted from the cochlea as a by-product of an active nonlinear biomechanical, feedback process from the OHCs to the basilar membrane. This process improves low-level sensitivity and sharpness of tuning, by enhancing the vibration of a narrow region of the cochlear partition.

The concept of sound emission from the cochlea implies a transmission mechanism to propagate the sound out of the cochlea, what was contrary to the previous belief of only anterograde (from the base to the apex of the cochlea) propagation of a travelling wave. According to Kemp (1986), this retrograde energy transmission in the cochlea could be due to some form of “localised perturbation”, possibly discontinuities in OHC arrangements, and modified propagation of forward travelling wave.

Substantial evidence exists that OAE generation is related to active, fast and slow, physiologically vulnerable, motility of OHCs (Brownell et al., 1985; Zenner, 1986), through the contraction of the actinomyosin complex in the cytoskeleton of the OHC, and therefore, the capacity of OHCs to act, as peripheral effector cells. This has been demonstrated by efferently-induced, OHC motility following electrical (Brownell et al., 1985 ; Nuttall and Ren, 1995) or chemical (GABA) stimulation (Plinkert et al., 1993). As described the section 1.2, complex neuro-chemical feedback loops control/modulate this activity, and in similar way they may affect OAEs.

1.3.3 General properties of otoacoustic emissions

The properties of OAEs can be summarised:

1. OAEs are acoustic energy of physiological nature and a consequence of active sound processing in the cochlea. However, OAEs are not only the driving force of the cochlea, but also reflect the transmission of the middle ear and resonant characteristics of the sealed ear canal.

2. OAEs exhibit periodicity in their microstructure. The phenomenon of local periodicity, the presence of the “peaks” and valleys”, has been observed in the frequency spectra of SOAEs (Kemp, 1979, 1981; Schloth, 1983; von Dallmayr, 1985), stimulus-frequency and transient evoked otoacoustic emissions (Zwicker, 1986; Zweig and Shera, 1995), as well as in the fine structure of acoustic distortion products (He and Schmiedt, 1993). The distance between the “peaks” in the microstructure, and inter-peak spacing of SOAEs, is about 1/10 of the octave. A possible source of the periodicity is in the “cochlear resonances”, the places where OAEs peaks are most likely to occur (Kemp, 1981).

3. OAEs are highly reproducible, with temporal and spectral properties unique for each individual, being commonly described as “fingerprints” of the inner ear.

1.3.4 Classes of otoacoustic emissions

Otoacoustic emissions can be recorded in the ear canal either in the absence of acoustic stimulation, as spontaneous otoacoustic emissions (SOAEs), or can be evoked by acoustic stimuli: transient evoked (TEOAEs), distortion product (DPOAEs) and stimulus frequency (SFOAE) otoacoustic emissions. In this section, SOAEs and TEOAEs are described in particular detail, as they are of importance in this study.

1.3.4.1 Spontaneous otoacoustic emissions

General properties

Spontaneous otoacoustic emissions (SOAEs) are a unique class of OAEs since they can be recorded by a sensitive microphone placed into the ear canal in the absence of any acoustic stimulation (Kemp, 1979). They result from the process of enhancing the vibration of a narrow region of the cochlear partition, due to OHC electromotility, feeding energy back into the mechanical system. The excess of acoustic energy from that feedback process is radiated out of the cochlea and a small amount of that energy is recorded in the ear canal.

In the normal population, SOAEs show intra-session, as well as inter-session, short-term (few hours) and long-term (four months) frequency stability with physiological variations (see in the next section), being typically less than 1%, but rarely exceeding 2% (Strickland et al., 1984; Wit, 1985; Whitehead, 1991; Bell, 1992; Haggerty et al., 1993; Penner, 1995). The amplitude of SOAE, however, may vary over a much wider range (more than 10 dB SPL) (Wit, 1985; van Dijk and Wit, 1990).

Recording of SOAEs

Two methods for recording of SOAEs have been used. In one, the sound pressure level in the ear canal is recorded by a sensitive microphone (e.g. Etymotic research, ER 10A) with no stimulus applied and the signal is averaged in frequency domain. In the other (used in the ILO88 system), SOAEs are synchronised by acoustic stimuli (click), using averaging in the time domain. This method allows the detection of sustained oscillations following stimulus (click)-evoked otoacoustic emissions (see 3.3.3.3).

Studies using different methods have shown, generally, good correspondence of SOAEs obtained by the two methods (Gobsch and Tietze, 1993; Smurzynski and Probst, 1996). Using the synchronising method, SOAEs exhibit lower levels (≈ 10 dB) and additional peaks (? better sensitivity in recording of SOAEs) than those obtained by direct recording, the reasons for which are yet to be clarified.

Prevalence of SOAEs

SOAEs can be recorded in 30-50% (~30% males and ~50% females) of normal ears, and the prevalence of SOAEs in individuals above the age 50, is markedly reduced (review by Probst et al., 1991). It has been recognised that the detection of SOAEs depends on the sensitivity of the recording system, and that technological advance may increase the number of subjects with recordable SOAEs. A recent study by Penner and Zhang (1997) demonstrated that the detection of SOAEs (62% for males and 83% for females) can be increased by suitably tailored spectral analyses.

Beside the difference in the prevalence of recordable SOAEs in females in comparison with males, there have also been reported racial differences, SOAEs being more common in black than white populations (Whitehead et al., 1993), as well as a laterality effect, with SOAEs being more commonly recorded in right ears (Bilger et al., 1990; McFadden, 1993; Penner et al., 1993). The latter authors reported that right ears are 13% more likely to have SOAEs than left ears and that the occurrence of multiple SOAE is much more prevalent in females than males. A genetic contribution to the expression of SOAEs is thought to be significant (review by McFadden and Loehlin, 1995).

Clinical relevance of SOAEs

SOAEs have been extensively investigated in the normal population, but their clinical significance still remains unclear. They could be an expression of the cochlear integrity, as their presence is associated with functionally intact OHCs and exquisite hearing sensitivity, with audiometric thresholds, according to the most authors better than 15 dB HL, but less than 20 dB HL at homologous frequencies (Probst et al., 1987; Bonfils, 1989). Furthermore, it has been demonstrated that individuals with recordable SOAEs have lower psychophysical thresholds than those without (McFadden and Mishra, 1993). It is widely accepted that SOAEs are sensitive (vulnerable) to alterations in the cochlear status: for example, physiological degeneration, i.e. aging, leads to their loss (Moulin et al., 1993a). Furthermore, SOAEs are subject to alterations during physiological, e.g. circadian (Wit, 1985; Bell, 1992), or menstrual (Bell, 1992; Haggerty et al., 1993; Penner, 1995) cycles, in the form of systematic frequency shifting, which is thought to be governed by daily variation in the secretion of melatonin by the pineal gland, and, in

females, by monthly variations linked to the pituitary-gonadal axis (the effect of melatonin on the secretion of oestrogen and progesterone). These observations indicate that SOAEs are not only an expression of the cochlear status, but can be influenced by the higher levels of the auditory and/or other central nervous system structures, and this effect may be exerted through efferently induced mechanisms of electro-mechanical transduction (Zenner, 1986), which may alter the gain in the feedback loop of a cochlear amplifier, and further, the SOAE frequency spectrum.

Kemp (1981) suggested that SOAEs may result from some areas of localised damage in the cochlea which could interfere with normal active feedback mechanisms. Furthermore, Ruggero et al. (1983) have demonstrated that SOAEs could be generated from the segment of the organ of Corti where there is a sharp transition between relatively normal OHC and adjacent damaged area. SOAEs were also reported at the frequencies which correspond to the abnormalities on the audiogram (Wilson and Sutton, 1981). In experiments with chinchillas, SOAEs have been induced by traumatic noise exposure (Zurek and Clark, 1981; Powers et al., 1995), and there is evidence they may interfere with auditory function: it has been observed that the presence of strong SOAEs degrades a neuron's ability to respond to sound (Powers et al., 1995). There is no sufficient data to explain the significance of these "pathological" SOAEs and their clinical relevance remains unclear.

The possible clinical applications of SOAEs can be summarised as follows:

In normal population,

- SOAE presence is indicative of structural integrity of the cochlea (OHCs) and exquisite hearing sensitivity
- SOAEs could be used for intra-subjects monitoring of the cochlear status as the most vulnerable by-product of the active process in the cochlea (Kemp, 1997)
- SOAE presence is indicative of the "overactivity" of the cochlea, with an "excess" of acoustic energy from the positive feedback loop, and therefore reflects functional status of the cochlea, as well as of the higher levels in the auditory system.

In cochlear pathology,

- SOAEs may result from altered feedback control mechanisms, but their clinical application as indicators of the pathology is yet to be investigated.

Nevertheless, to date, SOAEs have been used very little in clinical practice.

1.3.4.2 Transient evoked otoacoustic emissions

General properties

Transient evoked otoacoustic emissions (TEOAEs) are recorded in response to transient stimuli and show a delay (latency) with respect to the onset of the acoustic stimulus. The click is the most commonly used stimulus, as in the ILO88 system, because it has energy over a broad range of frequency. Similar to the travelling wave, click-evoked OAEs also demonstrate frequency dispersion, with the shortest latency being for the high, and longest for the low frequencies (4ms for 5kHz; 20ms for 0.5kHz).

TEOAEs exhibit “compressive” nonlinearity, i.e. “compressive” growth of the TEOAE amplitude as a function of the stimulus intensity. The source of such active and nonlinear behaviour are OHCs, with their active motor capacity for slow and fast contraction, resulting in “amplification” of sound of lower, and “attenuation” of sound of higher intensity. The maximal gain occurs at lower hearing levels (around hearing threshold up to 20-30 dB HL) and gradually reduces with an increase in sound intensity, before reaching saturation level, after which further increase in sound intensity does not lead to an increase in TEOAE amplitude (Kemp, 1978).

TEOAE responses, across the frequency range, have been shown to have excellent test-retest, within-ear stability and a measurement error with variability of amplitude of less than 1 dB (Harris et al., 1990; Franklin et al., 1992; Engdahl et al., 1993). Therefore, TEOAEs were often regarded as a physiologically based “cochlear fingerprints”. However, TEOAE have demonstrated considerable between-ear variability (Kemp, 1978; Robinette, 1992).

However, a major limitation of TEOAEs is that the emitted response of the OHC activity are small amplitude signals, with a limited dynamic range before response saturation, (as in the other tests of physiological activity in the auditory system, e.g. recordings of the early-, middle- and late-evoked potentials), and are further compromised before measurements by the necessary reverse transmission through the middle ear.

Prevalence and clinical relevance

Since TEOAEs are invariably associated with functioning OHCs, they can be, practically, recorded in all subjects with normal hearing (Probst et al., 1991): OAEs are present in 96-100% of normal-hearing ears and absent if hearing loss is greater than 25-35 dB HL). Therefore, the presence of TEOAEs responses is a reliable indicator of cochlear (OHCs) structural integrity from 0.5 to 5 kHz, and the best responses are recorded in the 1-2 kHz range, where reverse-transfer function of the middle ear, is most effective (Kemp, 1980). Their absence suggests at least a 25 dB loss due to either middle ear or cochlear lesion. In general, TEOAEs cannot be elicited if the hearing loss is greater than 35 dB HL (Bonfils, 1989; Harris and Probst, 1992).

In the impaired cochlea, as judged by sensorineural hearing loss, the incidence and amplitude of TEOAE decrease and the detection threshold increases (Bonfils and Uziel, 1989). In subjects with a history of noise exposure, TEOAEs exhibit a reduction/absence of the response amplitude in the regions where the audiometric thresholds are unaffected (Prasher et al., 1994b; Hotz et al., 1993). Therefore, by recording OAEs, a subclinical cochlear lesion may be detected, and this is in agreement with the finding that up to 30% of OHC population may be damaged prior to audiometric evidence in the quarter-octave audiometry from 0.125 to 16 kHz (Bohne and Clark, 1982).

It has been demonstrated that in addition to the lower amplitudes and “worse” non-linearity thresholds, the spectra of TOAEs in ears with noise-induced hearing loss were narrow in comparison with those with normal hearing (Reshef et al., 1993). This confirms that, although TEOAE frequency spectrum is not a direct measure of hearing sensitivity, frequency bands parameters can indicate whether hearing sensitivity at a homologous audiometric frequency is normal or abnormal (< or >20 dB HL) (Kemp et

al., 1990; Hurley and Musiek, 1994) and therefore can be useful in detection of frequency specific subclinical cochlear (OHCs) lesions.

The aetiology of the cochlear impairment may also be of relevance: TEOAEs can vary in amplitude and spectral composition in cases with a similar configuration of hearing loss of different aetiology. This has been demonstrated for noise-induced hearing loss (Probst et al., 1987), where the incidence and spectral peaks of TEOAEs showed significant reduction in comparison with ears with similar audiometric patterns caused by other factors, and in patients with Menière's disease (Harris and Probst, 1992), the amplitudes of TEOAEs were significantly lower and contained fewer spectral peaks in comparison with results obtained from a database. These results illustrate that changes in the parameters of TEOAEs may represent an expression of the degree and variety of the pathological processes in the cochlea.

TEOAEs are in clinical use since the commercial availability of the hardware and software developed by Bray (1989). Their extensive use is contributed by the non-invasiveness of the method and the speed at which can be recorded (≤ 60 sec per ear).

In summary, the main clinical applications of TEOAEs are:

- A method for evaluating cochlear (OHCs) integrity in general
- In view of their frequency specificity, the examination of the spectra may help to identify localised OHCs lesion
- Since they exhibit high stability, TEOAEs can be used in clinical intra-subjects monitoring (e.g. the influence of noise exposure, ototoxicity, anaesthesia, cochlear function during acoustic neurinoma surgery) (Hotz et al, 1993; Probst and Harris, 1993).

At present, the most important application of TEOAEs, and OAEs in general, is in neonatal hearing screening (e.g. Kemp and Ryan, 1993; White et al., 1994).

1.3.4.3 Distortion product otoacoustic emissions

Distortion product otoacoustic emissions (DPOAEs) are a subclass of evoked OAEs, defined as acoustic energy from nonlinear interaction of two simultaneously applied pure tones, known as the primaries f_1 and f_2 , at closely-spaced frequencies. The stimulation of two tones result in partial overlapping of the vibration fields in the cochlea.

DPOAEs were known in the past as “combination tones”, but clinical interest has been significantly raised by the development of the emission measurement technique. Similarly to TEOAEs, DPOAEs are generated by nonlinear active process in the cochlea, and can be recorded, essentially, in all normal-hearing subjects.

The advantages of DPOAEs over TEOAEs are:

- DPOAEs are more frequency specific (Avan and Bonfils, 1993)
- DPOAEs have better responses at high frequencies (up to 6-8kHz) than in TEOAEs, where due to time-gating and cut-off in the first 2.5-3ms response (see in 3.3.3.2) responses are recorded up to 5 kHz.

These two characteristics enables DPOAEs to be used as a sensitive method for site-of-lesion testing to track the pattern of OHCs lesion (Lonsbury-Martin et al., 1993).

- DPOAEs are less sensitive to hearing loss and can be recorded in ears with hearing loss up to 45 dB HL (Probst and Harris, 1993), because continuous stimulus level provides a more intense stimulus than the mean level used in standard TEOAE recording.

However, of DPOAEs have significant practical disadvantages:

- Lower frequency responses are easily contaminated by noise because the DPOAE response is frequency shifted downwards from the test frequencies by 2/3 octave. Additionally, the noise rejection system cannot be applied in DPOAE recording
- Longer duration of the test.

1.3.5 The role of OAE in assessment of the efferent system

Animal studies have shown that the medial olivocochlear (MOC) system influences the activity of the OHCs, e.g. the electrical stimulation of MOC bundle increases cochlear microphonics (Fex, 1959). However, the discovery of the existence of OAEs and the fact that most of the OHCs are innervated by the medial olivocochlear (MOC) system, have allowed selective stimulation of the MOC system by contralateral noise and examination of the function of the MOC system in humans, *in vivo*.

It has been demonstrated that in normal subjects contralateral acoustic stimulation can alter the *frequency* and reduce the level of SOAE (Mott et al., 1989; Harrison and Burns, 1993), and reduce the *amplitude* and shift the phase of TEOAE (Collet et al., 1990b; Ryan et al., 1991). This implies an inhibitory function of the MOC system. There is a suggestion that MOC may exhibit a laterality effect, with a greater effect in left ears (McFadden, 1993; Khalfa et al., 1997).

The magnitude of suppressive effect on OAE responses during efferent MOC stimulation, depends on the intensity of both, contra- and ipsilateral stimuli. The MOC can be activated by low-level contralateral acoustic stimulation (e.g. 30-40 dB SPL,) and the suppressive effect increases with more intense contralateral stimulation (Collet et al., 1990b; Ryan et al., 1991). However, suppressibility of OAE response evoked by the lower levels of ipsilateral stimulation, e.g. 50-60 dB SPL, is greater than those responses evoked by higher intensity stimuli (Moulin et al., 1993a; Veuille et al., 1996). This property is consistent with physiological role in the amplification of low-intensity sounds. At high ipsilateral stimulus level, a loss of contralateral effect has been observed. This “compressive” growth function can be attributed to the MOC system, implying a role in defining the dynamic range of cochlear activity. With the ability to modulate the activity of the OHCs, the MOC system appears to be responsible for automatic gain control, adaptation and homeostasis of the cochlea.

Clinical application

The alteration (reduction, enhancement) of MOC effect has been observed in patients with tinnitus (Chapter 2), hyperacusis (enhancement, in single case, Collet et al., 1992), vestibular (olivo-cochlear bundle) section (Williams et al., 1993), and central nervous system pathology (Ryan et al., 1991; Prasher et al., 1994). This implies that this test may help in the identification of pathological states in which abnormal activity of the MOC system leads to the alteration of cochlear mechanics.

Confounding effects of the stapedius acoustic reflex and “cross-talk”

The stapedius reflex (SR) also attenuates acoustic stimuli, with the major difference being in the effect - at the level of the middle ear. Its effect is bilateral, unlike the effect of the MOC system, which has a predominantly contralateral effect. Therefore, the SR may have a synergistic effect with the MOC system. This is supported by the findings of particularly strong suppressive effect of the MOC system in patients with no SR (Moulin et al., 1993a), or a fall in SR thresholds after surgical section of OCB in rabbits (Borg, 1971).

The interaction between the MOC system and SR could be the result of a direct anatomical link at the brainstem level, by overlapping in the distribution of OC neurons with those of the stapedius motor neurons (in cats, Joseph et al., 1985), or through the indirect connections at higher levels in the central nervous system. However, the contribution of the SR to the MOC suppressive effect is diminished by the application of contralateral acoustic stimulation at the level necessary to produce this effect, which is considerably lower than the intensity of sound, which triggers the SR (section 1.2.1.1).

Acoustic “cross-talk” is another factor with a potential confounding effect on the MOC reflex. However, experimental evidence, based on testing MOC activity in unilaterally deaf subjects (absent suppression), is against any significant effect of “cross-talk” on the suppressive effect produced by low level, contralateral acoustic stimulation (Collet et al, 1990b).

Chapter 2. TINNITUS AND OTOACOUSTIC EMISSIONS: A REVIEW, STUDY AIMS AND HYPOTHESIS

Following the discovery of OAEs existence by Kemp in 1978, a number of studies have been conducted which were aimed to determine the role of OAEs in assessment of patients with tinnitus. Although all main classes of OAEs have been studied, most of the work has been focused on SOAEs.

2.1 A REVIEW OF PREVIOUS WORK

2.1.1 Spontaneous otoacoustic emissions

The question of the relationship between tinnitus and internal (aural) sounds was raised more than half a century ago. In his classical paper on tinnitus, Wegel (1931) reported that a test tone sounded “pure and smooth”, except when the frequency of the test tone interacted with tinnitus, in which case two sounds would “beat” with each other. Was Wegel’s tinnitus an audible and annoying spontaneous otoacoustic emission?

The discovery of the existence of spontaneous otoacoustic emissions (SOAEs) (Kemp, 1979), led to the expectation that that they might be an objective correlate of tinnitus, and the relationship between tinnitus and SOAEs has, therefore, been studied extensively. Two recent reviews (Norton et al., 1990; Penner, 1992) provide details of individual work. Table 2.1 summarises the data currently available and highlights patients in whom tinnitus was considered to be related to SOAEs.

A number of different experimental criteria have been applied to link tinnitus with SOAEs, the most common being the correspondence of tinnitus pitch and the frequency components of SOAEs. Other criteria include the simple coexistence of tinnitus and SOAE; recording of emissions and, on subsequent playback, identification of SOAE frequency as the pitch of tinnitus; the effect of the interaction of SOAEs and

Table 2.1. Studies examining the relationship between tinnitus and SOAEs

Authors	Numbers of subjects (s) or ears (e) with tinnitus		
	Hearing Normal / < 30dB	Hearing > 30dB	Correlated to SOAE
Wilson, 1980.	10e		7
Wilson and Sutton, 1981.	4s	5s	4 0
Zurek, 1981.	4s	2s	0 0
Tyler and Conrad-Armes, 1982.		25s	0
Hazell, 1984.	18s	53s	2 0
Probst et al., 1987.		22e	0
Zwicker, 1987		30s	0
Penner and Burns, 1987a.	6s	23s	0 0
Penner, 1988.	1s		1
Penner, 1989.		1s	1
Bonfils, 1989.		82e	0
Norton et al., 1990.	6s		0
Plinkert et al., 1990.	1s		1
Penner, 1990.	96s		4
Penner and Coles, 1992 .	1s		1
Baskill and Coles, 1992.	120e		9
Burns and Keefe, 1992.	1e		1
Baskill and Coles, 1996a.	423e		27

mechanical/acoustic stimuli on the audibility of tinnitus. The selection of the test criterion in any individual patient was often determined by the particular finding in that patient

and, thus, it is difficult to compare the information in different reports. Consequently, a set of criteria for establishing a relationship between tinnitus and SOAEs, has been proposed by Penner and Burns, 1987:

- (1) Correlation of tinnitus pitch with SOAE frequency
- (2) Suppression of SOAE making tinnitus inaudible
- (3) Masking of tinnitus abolishing SOAE
- (4) Frequency specific isomasking contours of tinnitus.

All these criteria should be met if tinnitus is to be directly related to the presence of SOAEs. Due to diversity of the experimental criteria, it is difficult to assess the relationship between tinnitus and SOAEs on the basis of the published studies. According to Penner (1990), the 95% confidence limits for the prevalence of tinnitus among members of a self-help group were 1% and 9.5%.

Although, in general, attempts to attribute tinnitus to SOAEs have been disappointing, there are some patients with convincing evidence of a close correspondence between tinnitus and SOAEs (Penner 1988; Penner, 1989; Penner, 1990; Plinkert et al., 1990; Penner and Coles, 1992; Baskill and Coles, 1992; Burns and Keefe, 1992; Baskill and Coles, 1996a,b). This conviction is based on the fulfillment of the test criteria proposed above, which makes the relationship more than circumstantial. However, as set out above, these criteria were not applied in other cases, and so the true prevalence of SOAE-related tinnitus remains unknown. Moreover, the subjects examined in the reviewed studies, most of them as case studies, constitute a heterogeneous group with respect to age, aetiology and audiometric patterns, and therefore, the existence of the SOAE-related tinnitus and its prevalence in any single aetiological group of patient with tinnitus remains undetermined.

Frequency of spontaneous emissions and tinnitus

Correlation between the frequency of SOAE and tinnitus pitch in patients with tinnitus has been observed for frequencies less than 3kHz. As it is more difficult to record SOAE components at higher frequencies, one possible explanation for the better correlation at

low frequency may be restricted reverse-transfer function of the middle ear that is most effective in the 1-2 kHz frequency range (Kemp, 1980). From this, it follows that the correlation of SOAEs and tinnitus of higher frequencies may be underestimated in considerable number of patients with high-frequency hearing loss (e.g. noise-induced hearing loss), as it is established that tinnitus pitch usually correlates with the slope of the audiogram (Hazell, 1984).

Audiometric pattern and spontaneous emissions

Spontaneous emissions are more likely to be related to tonal tinnitus if the subject has normal/near normal hearing, or at least an island of normal hearing (Norton et al., 1990; Kemp, 1981), as emissions recordability decreases to zero as the hearing loss approaches 30 dB (Probst et al., 1987; Bonfils and Uziel, 1989). The results in the previous studies demonstrated correlation of tinnitus and SOAEs in just such patients.

However, to date, there has been no systematic and standardised study of SOAEs in patients with tinnitus, either with normal audiometric thresholds, or localised cochlear lesion.

Process of adaptation and spontaneous emissions

As indicated earlier (1.3.4.1), SOAEs generally show remarkable frequency stability in normal subjects. However, there have been reported cases of patient with tinnitus who had fluctuation of SOAE frequency and amplitude, which may have made them audible (Penner, 1988; Burns and Keefe, 1992). It has been hypothesised that continuous emissions do not produce an auditory perception because of adaptation and that perception occurs only in non-adaptive situations (Penner et al., 1981; Schloth and Zwicker, 1983; Penner, 1988; Burns and Keefe, 1992). The non-adaptive situation can be simulated in experimental conditions, e.g. by changing the impedance of the middle ear, which may cause change in the frequency spectrum of SOAEs, making them audible to the subject (Wilson and Sutton, 1981; Kemp, 1981; Schloth and Zwicker, 1983).

External factors influencing spontaneous emissions and tinnitus simultaneously

Beside mechanical factors, which may change the impedance of the middle ear, as discussed above, other external factors can produce a change in frequency and amplitude of SOAE, and consequently influence the perception of tinnitus. While suppression of SOAE by acoustic stimuli makes tinnitus inaudible (Wilson and Sutton, 1981; Schloth and Zwicker, 1983), synchronisation of external acoustic stimuli with the phase of SOAE can result in audible “beats”(Wilson, 1980; Wilson and Sutton, 1981). Low-frequency acoustic overstimulation can cause mechanical instability of the cochlea, with a brief period of residual inhibition, during which emissions decrease and tinnitus becomes inaudible, followed by a period of enhancement, with increased emissions and tinnitus perception (Kemp, 1981; Kemp, 1982).

Another external factor which may influence tinnitus and SOAE is aspirin, which in some patients can abolish SOAE and make tinnitus inaudible (McFadden and Plattsmier, 1984; Penner and Coles, 1992; Baskill and Coles, 1996b).

2.1.2 Transient evoked emissions

Currently available data show that the expression of altered micromechanisms in the cochlea of patients with tinnitus, as judged by TEOAEs, is not uniform. In some patients, there is an increased response amplitude in the frequency region, which corresponds to the frequencies of steeply sloping sensorineural hearing loss, as well as to the tinnitus pitch (Norton et al., 1990). This supports the hypothesis of enhanced active cochlear micromechanisms at the junction of a normal and pathological region (Wilson and Sutton, 1981; Zurek and Clark, 1981; Ruggero et al., 1983). In other cases, subtle changes may also interfere with cochlear mechanics in the region which audiometrically appears to be normal. This is in agreement with the finding that diffuse damage of OHCs of up to 30%, with intact IHC, can occur prior to the detectable hearing loss (Bohne and Clark, 1982). This may explain reduced, “worse” (McKee and Stephens, 1992; Chéry-Croze et al., 1994b), or even absent (Garrubba et al., 1990) TEOAE in normally hearing patients with tinnitus, compared with patients without tinnitus. Beside the general finding of reduced amplitude of SOAE in the ears with tinnitus, there is the dependency of

TEOAE amplitude on the spectral characteristics of tinnitus, being lower if tinnitus includes a greater number of frequencies (Chéry-Croze et al., 1994b). Finally, Norton et al., (1990) have demonstrated that active cochlear mechanics can be altered to produce prolonged, oscillating and modulating TEOAEs. The authors have found this type of emissions in five out of six subjects with tinnitus, in two of whom it was attributed to the synchronising effect of SOAEs. In contrast, two subjects without tinnitus did not show oscillating or modulating emissions. The authors hypothesised that oscillating evoked emissions and tinnitus were related to a common underlying pathological mechanism.

2.1.3 Distortion product emissions

A number of studies of the amplitudes and growth function of DPOAEs in normal subjects and patients with sensorineural hearing loss, have produced results which indicate that the pattern of DPOAE provide frequency specific information on cochlear integrity, and suggest that they are a specific and sensitive tool for objective screening, at least for frequencies between 1 and 8 kHz.

DPOAE-grams (a graphic presentation of DPOAE amplitudes as a function of frequency f_2) in normal-hearing tinnitus patients shows significantly reduced amplitudes compared with normal subjects (Shiomi et al., 1997a), which could be explained by subclinical lesions of OHC. In a study by Mitchell et al., (1996), DPOAE input/output functions in tinnitus patients were suggestive of selective damage of OHCs, with intact IHCs. Similarly, Janssen et al. (1996), demonstrated more linear, steeper input/output curves in the majority of tinnitus patients, as a result of OHCs damage and consequent loss of non-linearity, in comparison with normal subjects. Furthermore, a paradoxical increase in DPOAE amplitudes around the tinnitus pitch, in spite of the associated hearing loss, has been observed. This could be a result of heterogeneous efferent activation (1.1.4.2).

2.1.4 Cochlear emissions and contralateral stimulation in tinnitus

Recording of cochlear emissions under contralateral acoustic stimulation is a recognised method for investigating the function of the medial olivocochlear (MOC) system (1.3.5), and has also been used in the assessment of patients with tinnitus.

Preliminary studies on recording TEOAE under contralateral acoustic stimulation by broadband low intensity noise, in patients with unilateral tinnitus (comparing findings in the ears with and without tinnitus in the same subject), have reported that the MOC system was less effective in ears with tinnitus (VeUILlet et al., 1992; Chéry-Croze et al., 1993). By recording TEOAE a reduced global MOC suppressive effect was demonstrated, while DPOAE provided more frequency specific information, indicating that, in the majority of cases, medial efferent activity was not effective around tinnitus frequencies.

However, subsequent studies (Chéry-Croze et al., 1994a,b) have shown a significant inter-subject variability and have suggested that, in some cases, the suppressive effect could be low even in the ears without tinnitus. In another study with patients with unilateral tinnitus, there was a tendency for a lower suppressive effect in tinnitus than in non-tinnitus ears, but statistical significance could not be reached (Lind, 1995). In this study, the suppressive effect of contralateral noise on TEOAE was examined for responses up to the 2 kHz only, as the majority of patients had high frequency hearing loss.

Beside inter-subject variability, considerable inter-session (intra-subject) variability has been found, being significant for the patients with tinnitus in comparison with normal subjects (Graham and Hazell, 1994). This latter observation has led to speculation that the fluctuation in efferent activity had resulted from a change in neurophysiological activity.

In another study (Attias et al., 1996a), MOC function was compared in subjects with noise-induced hearing loss (with and without tinnitus) and with normal hearing (with and without tinnitus). OAE responses up to 1.5 kHz only, due to the absent responses in higher frequency bands in noise-induced hearing loss, were considered. A significant difference, (an *enhancement* of TEOAE in the presence of contralateral stimulation) was found in tinnitus, in comparison with non-tinnitus groups, and attributed to a global

efferent dysfunction. In contrast, a study comparing the efferent effect between the normal hearing (PTA, 125 - 8000 Hz) patients with tinnitus and normal control subjects (Duchamp et al., 1996), suggested "a likely impaired functioning of MOC", with less pronounced MOC effect in patients with tinnitus.

Clearly, from these studies, no consensus view emerges. The diversity in the findings, some of them conflicting, is probably a result of different methods of evaluation applied and heterogeneity of the tinnitus groups studied (e.g. aetiological, audiometrical, or/and age-related).

2.1.5 Conclusions

Early studies, aimed at understanding the cochlear mechanisms involved in the generation of tinnitus, almost exclusively concentrated on SOAEs, as it was thought they might cause tinnitus or share the same underlying pathological mechanisms. However, tinnitus has been found to be caused by SOAEs in only about 4% of patients. As outlined above, most of the studies describe single cases which, all together, constitute a heterogeneous group with respect to age, aetiology and audiometric patterns, and therefore, the significance of SOAEs in generation of tinnitus in particular aetiological background remains unknown. It appears that tinnitus and SOAEs may be related, but no definite conclusion can be drawn in the absence of any large study with universally agreed diagnostic criteria and clearly defined groups of subjects.

Similarly, insufficient data are available to come to any firm conclusion regarding the utility of TEOAEs in the evaluation of subjects with tinnitus. The results of several studies in which different responses (enhanced, reduced or absent) in tinnitus patients have been demonstrated, may reflect different underlying mechanisms, but may, merely, reflect different techniques of evaluation.

Studies using DPOAEs have demonstrated the importance of this method in defining cochlear mechanics in frequency specific manner, e.g. around the tinnitus pitch or audiometric slope .

Finally, the method of recording OAEs under contralateral acoustic stimulation has been used for assessment of the function of the MOC system in patients with tinnitus. However, its relevance to the generation of tinnitus is unclear, although available data indicate that the efferent activity in tinnitus patients may be altered (in general, reduced). Therefore, the question of the role of MOC system in patients with tinnitus still remains unanswered.

2.2 STUDY AIM AND HYPOTHESIS

Aim

The aim of this study is to identify changes in micromechanics of the cochlea, which may be associated with the perception of tinnitus. This may enable better understanding of mechanisms of tinnitus generation and help in the objective assessment of tinnitus.

Tinnitus is a symptom of different pathophysiological states of the ear and the central nervous system (CNS)(1.1.3); the variety in tinnitus masking patterns (section 1.1.5.2), or variable efficacy in treating tinnitus (e.g. drugs or electrostimulation) has led to the conclusion that tinnitus originates at different levels of the auditory system and that it may result from different underlying mechanisms. Therefore, it seems important to study cochlear mechanics in patients with tinnitus in *groups homogeneous with respect to the aetiology and audiometric thresholds*. It is expected that this approach would not only reduce variability in results, but also identify group characteristics.

Why use otoacoustic emissions?

Otoacoustic emissions (OAE) reflect the activity of OHC, which is modulated, from one side by acoustic signals from the external environment, and from the other, by the CNS input through a complex neuro-humoral feedback system (as described in the sections 1.2.5 - 1.2.7). In other words, the cochlea is the site of interaction of local activity, input from the CNS and external noise, and, therefore, from a functional point of view, cannot be considered simply as the “periphery” of the auditory system. Thus, the information obtained from OAE would not be of a purely local (cochlear) character.

Bi-directional interaction between the cochlea and CNS

The notion of a bi-directional interaction between the cochlea and CNS is supported by a number of experimental findings:

A. Centripetal:

- Powers et al. (1995) in experiments with chinchillas, following the application of intense impact noise which generated SOAEs, observed vigorously activated auditory nerve fibres and raised spontaneous auditory activity. The high “spontaneous rate” created a “line busy” signal, that led to an increase in neural thresholds and hearing loss, without detectable hair cell damage.
- Kemp (1982) observed a biphasic effect of noise overexposure on OAEs: first suppression, then enhancement; the enhancement of OAE coincided with the perception of tinnitus. This demonstrated that external noise alters cochlear mechanics, with the consequence of the perception of tinnitus.

To summarise, external noise can alter cochlear mechanics and the ascending structures with consequent changes in auditory perception (in the above examples, elevated hearing thresholds or tinnitus).

B. Centrifugal:

Cochlear mechanics are controlled and modulated by inputs from higher levels of the auditory and other parts of the central nervous systems (Kemp, 1986; McFadden, 1993). This is demonstrated in a number of studies, such as efferently mediated amplitude suppression and frequency shifting of TEOAE (Collet et al., 1990b; Ryan et al., 1991; Rossi et al., 1993; and of SOAE by contralateral sound (Mott et al., 1989; Harrison and Burns, 1993), the effect of visual (Puel et al., 1989; Fröhlich et al., 1990) and auditory selective attention (or arousal) and sleep (Fröhlich et al., 1993; Meric and Collet, 1993). There are also suggestions of alteration of cochlear mechanics during physiological, e.g. circadian (Wit, 1985; Bell, 1992), and menstrual (Bell, 1992; Haggerty et al., 1993; Penner, 1995) cycles (as described in the section 1.3.4.1).

To conclude, these findings suggest that OAEs are not only an expression of the cochlear status, but can be influenced by the factors external to the cochlea.

Hypothesis

The proposed hypothesis is that OAEs provide the evidence for cochlear micromechanical changes relevant to the presence of tinnitus, regardless of the site of the “tinnitogenic” source, either at the periphery of the auditory system or in the central nervous system (CNS).

This is based on the evidence for a bi-directional interaction between the cochlea and the central pathways, as discussed above, and raises the expectation that altered central activity in patients with tinnitus could in some way be reflected within the cochlea.

This hypothesis is summarised in Figure 2.2.

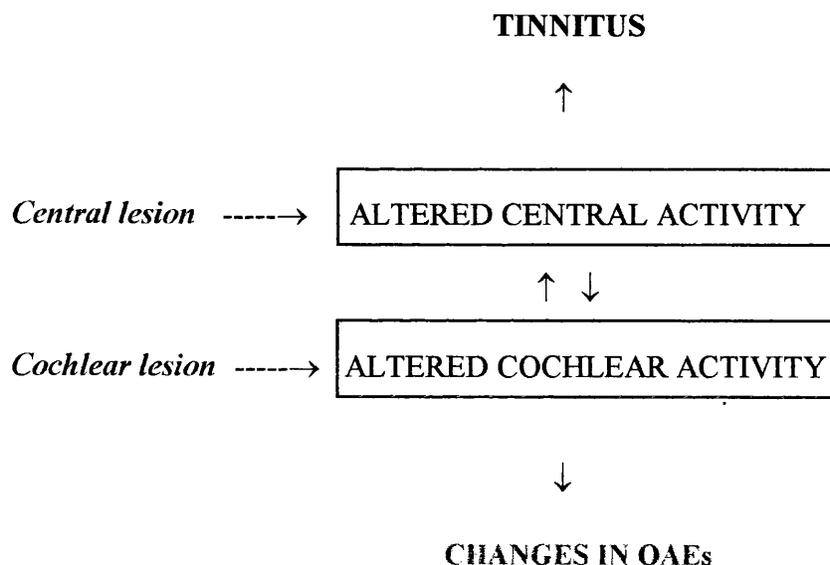


Figure 2.2: Schematic view of the generation of tinnitus, interaction between central auditory and cochlear activity, and consequent changes in otoacoustic emissions (OAEs): a lesion at either peripheral or central level may lead to bi-directional functional changes in the cochlea and CNS.

Chapter 3: MATERIAL AND METHODS

3.1 SUBJECTS

The entire study includes 60 normal subjects and 180 patients.

More specific details regarding the subjects are to found in Chapter 4.

3.1.1 Normal subjects

This group was formed by volunteers, matched for gender and age with tinnitus groups, recruited from amongst friends and hospital staff, by direct approach.

Inclusion criteria:

1. Negative history of ear diseases, ototoxicity, significant head injury or excessive noise exposure; negative family history of hearing loss.
2. Normal otological examination
3. Normal hearing, defined as hearing thresholds equal to, or better than 20 dB HL at octave-step frequencies from 0.25 to 8 kHz.
4. Normal middle ear function, defined as the ear drum compliance from 0.3-1.7 cm³ and the peak middle ear pressure \pm 50 daPa. This criterion was essential in view of the known influence of the middle ear transmission properties on OAE (Kemp, 1981; Schloth, 1983; Hauser et al, 1993).
5. Stapedial reflex thresholds consistent with HL values at analogous frequencies

3.1.2 Subjects with tinnitus

All subjects in this group were consecutive patients, selected to form homogeneous groups, with respect to aetiology and audiometric thresholds, who attended the Neuro-

otology clinics at the Royal National Throat Nose & Ear Hospital and the National Hospital for Neurology & Neurosurgery.

Definition of tinnitus

Subjects included in this group had continuous or intermittent tinnitus (>50% of the time), for at least six months, and the tinnitus was present at the time of testing.

Inclusion criteria

As in the normal group, subjects with tinnitus had normal otological examination and normal middle ear function (above, 2. and 4.). With regard to the audiometric thresholds, they had normal hearing (criterion 3), or an “island” of normal hearing, defined as normal threshold level at one or more test frequencies.

Groups

For the reasons explained earlier (section 2.2, *Aims*), five groups of subjects with tinnitus have been considered. The choice of groups to be included in the project was based on having the opportunity of studying tinnitus with different underlying mechanisms, including both, “central” and “peripheral”, origin. These groups were homogenous with respect to the audiometric thresholds and aetiology:

- Tinnitus and normal hearing, with no identified pathology
- Tinnitus and abnormal hearing, with no identified pathology
- Tinnitus following head injury, with normal hearing
- Tinnitus related to noise exposure
- Tinnitus and Menière’s disease

Each of the groups will be defined in the appropriate study in Chapter 4.

3.2.1 Study design

Five separate studies form the integral part of the thesis.

STUDY I: Frequency stability of SOAEs in tinnitus
(included different aetiological groups)

STUDY II: Tinnitus following head injury
(tinnitus with central nervous system pathology)

STUDY III: Tinnitus and normal hearing
(with no identified pathology)

STUDY IV: Tinnitus related to noise exposure

1. Noise-related tinnitus in subjects with normal hearing
2. Tinnitus following noise-induced hearing loss

STUDY V: Tinnitus and Menière's disease

The study I, which explores an unique form of spontaneous (mechanical) activity, includes all five groups of subjects with tinnitus.

The next four studies examine cochlear mechanics in each of the above subjects groups (3.1.2), except subjects with abnormal hearing of unknown origin, as within the "unknown" must exist an unidentified aetiology, which would make this group heterogeneous. In each study, a group of patients with tinnintus was compared with another of matched (for age, gender and audiometric thresholds) normal control subjects, of similar sample size.

3.2.2 General protocol

All subjects underwent a protocol which included:

- An interview to obtain relevant information
- Otoscopy, to exclude visual evidence of ear disease
- Standard pure-tone audiometry
- Impedance audiometry:
 - Tympanometry, necessary to ascertain normal middle ear properties, comparable between the groups
 - Acoustic reflex threshold measurements (AR)

- Recording of otoacoustic emissions:
 - Transient click-evoked otoacoustic emissions (TEOAE)
 - Spontaneous emissions (SOAE)
 - Olivocochlear suppression test

DPOAE were not considered due to disadvantages, as outlined in the section 1.3.4.3, which make their application in a larger number of subjects, and in clinical setting, less practical.

Ethical approval for conducting this work has been obtained from both the Joint Medical Ethics Committees at the Royal National Throat, Nose & Ear Hospital and the National Hospital for Neurology & Neurosurgery (Appendix I).

Consent to participate in the study was obtained from all the subjects, after a full explanation of the nature of the tests involved and the aims of the project (Appendix II).

3.3 PROCEDURES

All tests were performed in a sound treated booth (ISO 8253-1, 1989), with double doors and the walls covered with low reflective, absorbent materials.

3.3.1 Standard pure-tone audiometry

Equipment: GSI 16 Audiometer (Grason-Stadler Inc. Model 16)

Test method

Hearing thresholds for pure-tone stimuli at frequencies from 0.25 Hz to 8 kHz in octave steps (in addition at 6 kHz) were measured by employing a routine clinical, modified method of limits, as recommended by the British Society of Audiology (1981). Tone pulses, to avoid adaptation, with pulse duration in the range 1-2 sec, to avoid influence from temporal integration, have been used in repeated series, with ascending sound levels in steps of 5 dB.

3.3.2 Impedance audiometry

Equipment: GSI 33 Middle Ear Analyser (Grason-Stadler Inc. Model 33)

3.3.2.1 Tympanometry

Test method

Single frequency tympanometry has been performed with a probe signal, an 85 dB SPL continuous tone at 226 Hz, as recommended by the British Society of Audiology (1992).

3.3.2.2 Acoustic reflex measurements

Test method

The acoustic reflex thresholds have been measured in response to ipsi- and contra-lateral tones of 0.5, 1, 2 and 4 kHz at levels ranging from 70 to 100 dB HL in 5 dB steps. A

consistent change in compliance of ≥ 0.03 ml following stimulation, was a criterion for the presence of the acoustic reflex.

3.3.3 Otoacoustic emissions tests

3.3.3.1 Introduction

As outlined in the section 3.2.2, three OAE test procedures were included in this study:

- i) Transient evoked emissions test
- ii) Spontaneous otoacoustic emissions recording
- iii) Medial olivocochlear suppression test

It is anticipated that tests i) and ii) provide (frequency specific) information on the structural and functional state of the cochlea (OHC) (described in more details in sections 1.3.4.1/1.3.4.2). The technical advantages, such as short duration of testing, ≈ 1 min each, and noise-protected responses (sections 1.3.4.2/1.3.4.3/ 3.3.3.2), of importance for testing in clinical settings, have contributed to their inclusion in the protocol.

Test iii) was used to assess the function of the medial olivocochlear system in the control of cochlear mechanics (as described in 1.2.5.2/ 1.3.5).

All three tests were, conveniently, performed using the same recording system:

Equipment: ILO88/92 Otodynamic Analyser hardware and software, version 4.2

(Otodynamics Ltd. Hatfield, England), connected to the IBM compatible computer.

B-type probe consisting of a miniature microphone (Knowles BP 1843) and transducer (Knowles BP 1712).

3.3.3.2 Transient evoked emissions test

Test method

The stimulus presentation, data recording, averaging and spectrum analysis have been carried out as described by Kemp et al., (1990).

The stimuli are unfiltered rectangular clicks (bandwidth \approx 5 kHz), duration of 80 μ s, presented at a repetition rate 50/s, with peak reception level 80 dB \pm 3 dB SPL. They were presented in the non-linear differential mode: 4 clicks, with 3 clicks at the same level and polarity and fourth click three times greater in level and reverse polarity, and 10 dB increase in amplitude. This paradigm cancels the linear portion of the stimulus and response, including meatal and middle ear echo, so that nonlinear cochlear emissions can be extracted.

The stimuli were delivered via a probe B, inserted securely in the ear canal using disposable foam eartip.

A checkfit procedure is automatically performed by ILO88/92, ensuring that the probe is properly coupled to the ear canal. A good probe fit was indicated by setting up the rejection threshold above the noise in the ear canal; the meatal response waveform with a large positive and negative deflection within the first microsecond and minimum after ringing and the reference stimulus spectrum, being relatively flat from 0.5 - 4 kHz.

The number of sweeps, during the period of collection, was 260 and they were recorded and averaged alternately in two separate, A and B, buffers, using a synchronous time-domain averaging technique. The post-stimulus analysis time was 2.5 - 20ms (this time-gating was designed to remove the primary stimulus artifact and to transmit cochlear TEOAE signals, with a latency of around 4ms for 5 kHz to 20 ms for 0.5 Hz) and the passband 0.5 - 6 kHz.

In addition to manipulating subaverages using linear cancellation, the noise contamination of the cochlear response is controlled using the artifact rejection threshold, which is based on eliminating responses that exceeded a preselected noise level. The random noise contamination, the main sources of which are low-frequency biological noise from the subject and ambient noise, is controlled by setting the rejection threshold as low as possible, and thus allowing less noise to get into the “response”.

The (three point smoothed) Fast Fourier Transformation (FFT) spectrum analysis of averaged waveforms (to give frequency-dependent energy power spectra), with the frequency resolution of 12.2 Hz is automatically performed and plotted against the averaged random noise in the ear canal. From this frequency spectrum display, the presence or absence of TEOAE at specific frequency was determined.

A typical screen of a normal adult was displayed in Figure 3.1.

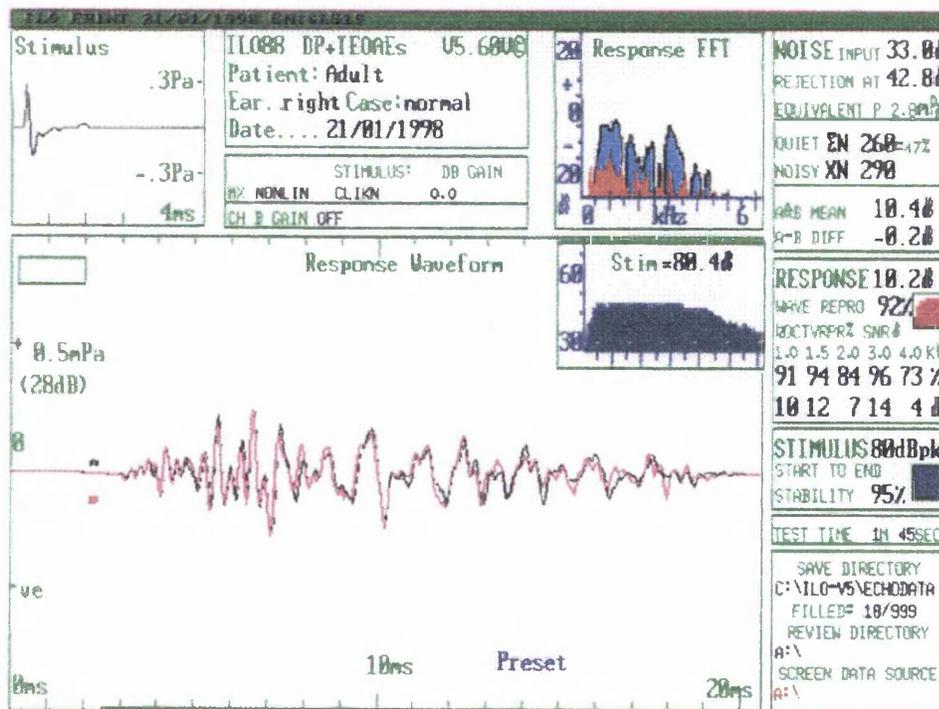


Figure 3.1: Transient evoked otoacoustic emissions recorded with non-linear click stimuli of 80.4 dB SPL from a normal subject, showing in the response window two alternate (A and B) recorded time waveforms and the FFT with the frequency spectrum of the response.

Data considered

The following data, supplied by the ILO92 software, have been considered:

- TEOAE response level (dB SPL): the overall click-evoked response level, corresponding to the sum of echo powers in the whole frequency range of the power spectrum, the mean level of A and B waveforms (results from a rms measure of the averaged raw echo waveform, converted to dB SPL and represents an estimate of echo size plus ear canal noise)
- Noise level (dB SPL): represents the arithmetic difference between the two waveforms, A - B, and is a good expression of the random noise
- Reproducibility (%): is expressed as the cross-correlation of two averaged waveforms (A and B), which conventionally, if > 50% indicates the presence of OAE, and if <50% indicates the absence of OAE (providing a low noise contamination, indicated by the value A-B)
- TEOAE spectral analyses:

Signal-to-noise ratio (S/N) in the bands (≈ 1 kHz width) centered at 1, 2, 3, 4 and 5 kHz, as the simplest form of TEOAE spectral analysis, and can be directly read from the main standard TEOAE screen.

1/3 octave band analysis - TEOAE energy in the specific frequency-centered 1/3 octave band and at least 3 dB above the noise level

- Noise of the corresponding band

This information can be obtained from the main screen by Alt-H, Alt-3 key manipulations.

3.3.3.3 Spontaneous otoacoustic emissions recording

Test method

Click-synchronised SOAEs were recorded using the Otodynamics ILO88 in "SOAE search" mode. In this mode, a small trigger stimulus, a single 80 μ s click, was presented every 80 ms at a peak level of approximately 75 dB SPL through a probe fitted in the external ear canal. As most of the subsequent response lasts less than 20 ms, the microphone signal, averaged over a 20-80 msec post-stimulus, silent period, represents mostly spontaneous cochlear activity. Typically, 260 responses were averaged and FFT analysis performed in the spectral band from 0 to 6250 Hz, with a resolution of 12.2 Hz. The characteristics of the synchronised SOAEs were determined after examining two spectra, i.e. signal spectrum and noise spectrum, that were calculated and displayed by the ILO88 system. The frequency and amplitude of SOAE corresponding to the maximum level of the narrow-band signal, in the targeted frequency range, or in the entire available SOAE spectrum, from 0 to 6250Hz, was determined using a cursor.

Figure 3.2 shows a standard default screen with SOAEs

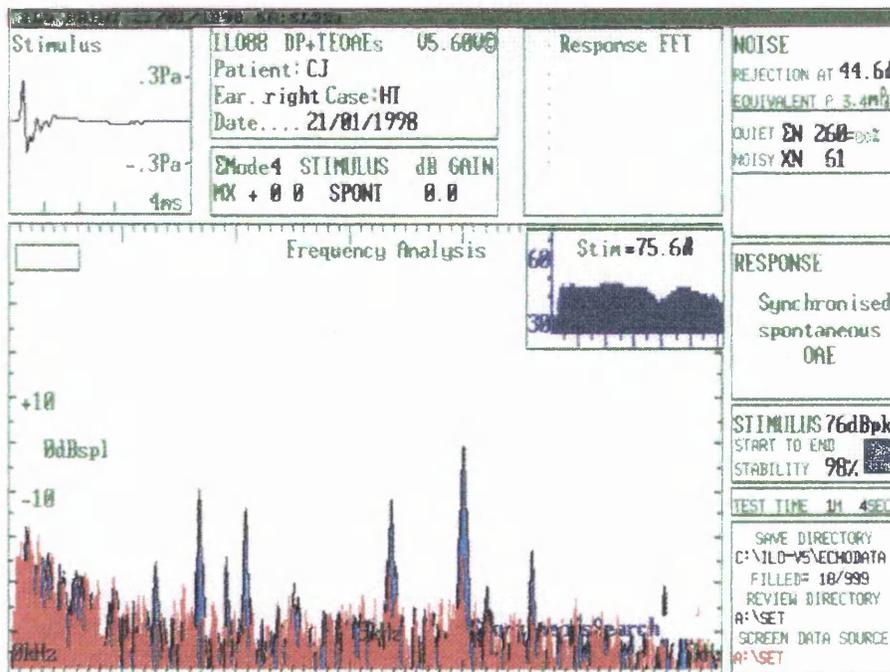


Figure 3.2: Spontaneous otoacoustic emissions in a normal subject with multiple frequency component spectrum

The presence of SOAEs was observed as spectral peaks of amplitude of -30 dB SPL or greater, and at least 5 dB above the noise floor, repeatable in two consecutive scans. SOAEs at frequencies < 500 Hz were not considered due to the higher susceptibility to noise contamination in this frequency region.

3.3.3.4 Medial olivocochlear suppression test

This test consists of recording of TEOAEs with and without contralateral stimulation and the difference in responses is considered, at least in part, to be the MOC effect.

A dual channel OAE analyser was used, one channel (A) for ipsi- and the other (B) for contralateral acoustic stimulation. Both, ipsi- and contralateral, stimuli were delivered through the identical B-type ILO88 probes (section 3.3.3, *Equipment*). For ipsilateral stimulation a click in linear mode (4 clicks of identical intensity and polarity) was used. An intrameatal peak stimulus level of 60 ± 3 dB SPL was used, being sufficiently low to be within “compressive” range of the cochlear activity (described in the section 1.3.5) and to reduce artifacts - middle ear ringing (as linear click is not noise-protected), and sufficiently high to elicit TEOAE response in all subjects. For contralateral stimulation a 5ms burst of white noise (0.5 - 6 kHz) was used, as this was known to be the most effective for suppressing OAE (Collet et al., 1990b) at 40 dB SL. This level was low enough not to trigger the acoustic reflex and avoid “cross-talk” (sections 1.2.1.1 and 1.3.5), but sufficiently high to elicit contralateral effect, through the activation the medial olivocochlear reflex. An alternating technique, a “Difference B on/off” mode, from the ILO92 software was used. This mode allows alternating recording of TEOAE responses with and without contralateral stimulation. A total of 600 sweeps were recorded, in 10 groups of 60 sweeps. The average responses were directly computed and the difference obtained by their subtraction, represented the suppression effect.

3.3.3.5 Calibration

Calibration of the ILO88 system was performed using a 1 cm^3 - test cavity supplied by the manufacturer, on average once a week. Synthetic stimuli, three tones at different frequencies,

provided by the ILO88 software, were delivered through the probe tip inserted into the test cavity. Additional, “biological”, calibration was carried out by the author, on average twice a month. The inter-session performance of the probe remained stable (within $\pm 1\text{dB}$) throughout the project execution. Figure 3.3 illustrates the stability of the probe output intensity.

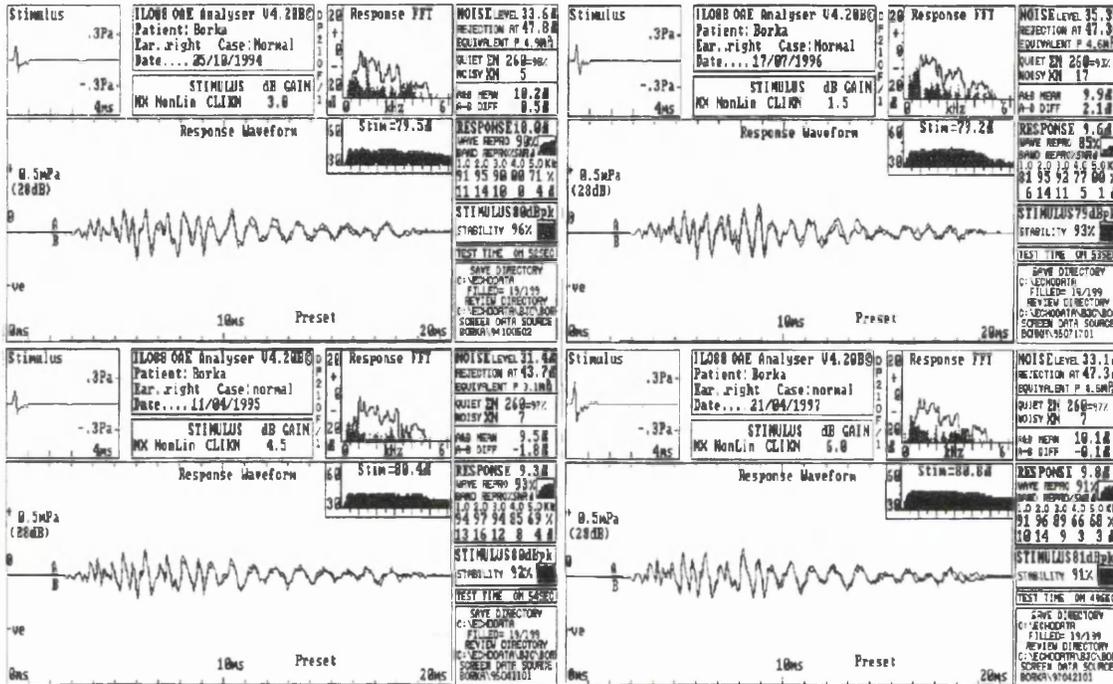


Figure 3.3: TEOAE responses recorded from the right ear of a normal subject (the author) over the period 1994-1997, demonstrating the output stability of the ILO88 system, as well as a high intrasubject reproducibility of the response amplitude ($< \pm 1\text{ dB}$) and power spectra.

3.4 STATISTICAL ANALYSIS

All data were analysed using SPSS (Statistical Package for Social Sciences), including routine statistical procedures, at the significance level $p < 0.05$.

Measures of variability

The spread of variation was expressed by the mean \pm standard deviation and range.

Additionally, for graphic presentation, a 95% confidence interval (CI) was used, deducting a 95% probability that the true mean of the population was within ± 2 standard errors of the sample mean.

Tests for statistical significance

i.) Numerical data

The significance of the data was analysed applying different tests, depending on distribution. The normality of distribution of a variable was estimated by inspection of the normality plots (e.g. histogram distribution), with normal distribution being in the shape of the Gaussian curve.

For the comparison between two groups:

- Independent t-test (Levene's) for parametric data, with normal distribution, was used to compare the means of the two independent groups of subjects, or
- Mann-Whitney U-test, for non-parametric data, when the data were not normally distributed.

For the comparison between three or more groups:

- One-way analysis of variance (ANOVA), for normal distribution

Post hoc Bonferroni multiple comparison test was used to determine which group means are significantly different from others, or

- Kruskal-Wallis test, for the data without normal distribution, was employed.

ii) Nominal data

χ^2 - test was applied to analyse the statistical significance of nominal (frequency) data of subjects assigned to one of two different categories (e.g. gender: male or female). This test analyses the distribution of a categorical variable against the hypothesis that each category has a specified proportion of cases in the population.

Chapter 4. OTOACOUSTIC EMISSIONS STUDIES IN PATIENTS WITH TINNITUS

This chapter includes five studies on the application of otoacoustic emissions in objective assessment of patients with tinnitus, grouped on the basis of particular aetiological background. The rationale for this approach was discussed in the Chapter 2. (2.2, Aims).

In the first study, which examines a unique spontaneous mechanical cochlear activity, patients of all groups were included. The following four studies were presented in the descending order of presumed pathology, of relevance for the generation of tinnitus, from the CNS to the cochlea.

All subjects included in the first study were also included in the subsequent studies, supplemented by further subjects.

4.1 FREQUENCY STABILITY OF SPONTANEOUS EMISSIONS IN TINNITUS

4.1.1 Introduction

SOAEs have already been the subject of great interest in relation to the generation of tinnitus (see Chapter 2.1.1), primarily aimed at establishing a direct cause-effect relationship between tinnitus and spontaneous otoacoustic emissions in individual cases. However, this study has adopted a different approach. SOAEs are considered as a possible *correlate* of a pathophysiological process, rather than as a *cause* of tinnitus, although the latter, in some cases, cannot be ruled out.

As highlighted in the Chapter 1 (1.1.2), a number of hypotheses have been proposed, in an attempt to explain tinnitus generation. Despite the diversity in possible underlying mechanisms and tinnitogenic sources, it has been assumed that the common neurophysiological correlate to the sensation of tinnitus is altered spontaneous neural activity at one or more levels of the auditory system.

This study examines a unique form of spontaneous (mechanical) activity at the cochlear level, by the recording of spontaneous otoacoustic emissions (SOAEs), which in part may reflect changes in neural activity. This assumption has been made on the basis of the experimental data, suggesting that SOAEs, in addition to being an expression of cochlear integrity, may, in some way, reflect the functional state of higher levels of the auditory/central nervous system: it has been reported that SOAEs are subjects of physiological variations (see 1.3.4.1, Clinical relevance of SOAEs; 2.2, Bi-directional interaction between the cochlea and CNS) and can be altered by activation of the medial olivocochlear reflex, during contralateral acoustic stimulation (section 1.3.5).

Spontaneous otoacoustic emissions (SOAEs) have been widely studied in normal subjects and there is evidence of their high frequency stability in repeated recordings (see 1.3.4.1, General properties of SOAEs). Whether this is the case with SOAEs in patients with tinnitus, is the subject of investigation in this study, which examines the prevalence and inter-session frequency stability of SOAEs in patients with tinnitus, in the comparison with normal subjects without tinnitus.

SOAEs have been explored in patients with tinnitus as a group *in toto*, but also in different *subgroups*, homogenous with respect to the aetiology. As outlined in Chapter 2 (2.2), it is anticipated that this approach would enable a better understanding of mechanism(s) of tinnitus generation and reduce variability of results.

4.1.2 Materials and methods

Subjects

The selection criteria for all subjects were the presence of at least one SOAE peak in one ear and normal hearing or an “island” of normal hearing, in order to obtain SOAEs.

1. *The control group* comprised of 20 consecutive subjects, 6 males and 14 females, selected from 38 volunteers: 18 males and 20 females, who were screened for SOAEs, aged from 18 to 44 years (mean: 30 ± 6 years). They all had normal hearing (3.1.1), and no complaint of tinnitus.

2. *The tinnitus group* consisted of 53 subjects with tinnitus, 21 males and 32 females, selected from 100 consecutive patients, 43 males and 47 females, attended the Neurotology department of the Royal National Throat, Nose and Ear Hospital. The subjects, aged from 20 to 70 years (mean 40 ± 11 years), formed five subgroups according to aetiology :

(i) Tinnitus and normal hearing: 20 subjects, 8 males and 12 females, selected from 35 referred, 10 males and 25 females, with normal hearing and no apparent otological pathology, as judged by the general protocol (3.2.2), aged from 21 to 54 years (mean: 40 ± 8 years).

(ii) Tinnitus and abnormal hearing (with an “island” of normal hearing, as defined in the section 3.1.2): 10 subjects, 3 males and 7 females, selected from 21, 6 males and 15 females, with tinnitus and sensorineural hearing loss (SNHL) of unknown aetiology, aged from 32 to 70 years (mean: 50 ± 11 years).

(iii) Tinnitus and head injury: 10 subjects, 3 males and 7 females, selected from 10, with tinnitus following head injury, but normal peripheral hearing, as judged by the pure-tone audiometry, aged from 20 to 46 years (mean: 30 ± 4 years). This group included

patients with minor, moderate or severe head injury, as classified by Symonds (1962) and Berman and Fredrickson (1978) (in more detail in 4.2.2).

(iv) Tinnitus and Menière's disease: 10 subjects, 4 males and 6 females, selected from 16 patients, 6 males and 10 females, with Menière's disease, aged from 27 to 69 years (mean: 48 ± 12 years). Diagnosis of Menière's disease in 13 ears (of 10 subjects) was based on the characteristic clinical history (Committee on Hearing and Equilibrium, AAOO, 1995). A shift in audiometric threshold of more than 10 dB HL at two or more different frequencies was present in all affected ears.

(v) Tinnitus and noise exposure: 3 subjects, selected from 17, all males, with tinnitus and hearing loss secondary to the exposure to noise. Two had been exposed to recreational (shooting) and 1 to industrial activity. Out of 17 screened patients, 13 had been exposed to industrial and 4 to recreational (shooting) noise. They were aged 52, 60 and 62 years. The mean age of 14 other screened patients who did not have SOAE was 40 ± 6 years.

Protocol

The protocol consisted of two sessions separated by a time period of 1 to 16 weeks, with a mean for the tinnitus group of 3.9 ± 4.4 weeks, and for the control group of 4.8 ± 3.0 weeks. The decision to use only two test sessions, to provide information on SOAEs over a period of time, was a compromise to enable the inclusion in the study of a larger number of subjects ($n=73$). The first session included: an interview with the subject to obtain information about hearing and tinnitus; otoscopy to exclude visual evidence of ear disease; pure-tone audiometry and tympanometry; recording of click-evoked transient otoacoustic emissions (TEOAEs) and spontaneous otoacoustic emissions (SOAEs). In the second session, besides recording of otoacoustic emissions, tympanometry was performed, to ensure comparable middle ear pressures in both sessions, (the mean difference was 5.7 ± 4.3 daPa in the tinnitus group and 7.3 ± 3.4 daPa for the control group).

Recording of otoacoustic emissions

SOAEs were recorded in two sessions using the Otodynamics ILO88 Analyser, version 3.4 in its default setting, as described in the section 3.3.3. To achieve comparable noise floors of SOAEs in the two sessions, the probe check-fit procedure and signal-to-noise ratio during TEOAE recording, which always preceded SOAE recording, served as a reference. TEOAE that precede SOAE were not expected to affect the characteristics of the subsequent SOAE (Kulawiec and Orlando, 1995). Additionally, the noise levels were controlled by the noise-rejection threshold system during SOAE recording.

Data analysis: Designation of SOAE peaks.

In subjects with multiple frequency components in the SOAE spectrum, it was necessary to designate "spikes" in the power spectrum as SOAE peaks, and to minimise the presence of "satellite", spurious SOAEs, which might result from e.g. interactions among SOAEs (Burns et al., 1984), noise, or a relatively long averaging period of a fast-shifting SOAE.

In order to define SOAE peaks, the inter-peak distance at which SOAE occurred was employed. The phenomenon of local periodicity has been observed in the frequency spectra of SOAE (Kemp, 1979, 1981; Schloth, 1983; von Dallmayr, 1985), stimulus-frequency and TEOAE (Zwicker, 1986; Zweig and Shera, 1995), as well as in the fine structure of acoustic distortion products (He and Schmiedt, 1993). It has been suggested by Kemp (1979) that the approximate frequency spacing between adjacent SOAE peaks is 80 Hz around 1kHz, and 160 Hz around 3 kHz, which represent the intervals between the "cochlear resonances", the places where SOAEs are most likely to occur. Similarly, Schloth (1983) suggested that SOAE peaks occur at intervals of about 100 Hz, and not at less than 50 Hz, and von Dallmayr (1985) at intervals of 0.1 octave or 0.4 Bark (critical bandwidth). Accordingly, in this study, an SOAE "spike" was designated to be an SOAE peak, if it was the "strongest" peak in approximately 1/10 of octave intervals ($\Delta F/F < 0.1 \pm 0.05$, where ΔF is the distance between two neighbouring frequency components). This criterion could be applied for all frequency ranges, in this study from 500 - 6250 Hz. An additional criterion to minimise the presence of spurious

SOAEs, was the exclusion of within-session non-repeatable frequency components on recording of SOAEs in two consecutive scans.

Data analysis: SOAE stability

For the purpose of examining SOAE stability, all SOAE peaks were classified into three categories:

- (1) "stable", if SOAE frequency in two sessions remained unchanged,
- (2) "shifted", if SOAE peaks were present in both sessions, but shifted in frequency, and
- (3) "on-off" SOAE peaks: "on", present in one session and "off", absent in the other.

To delineate two situations, namely a "shifted" SOAE peak from an "on-off" SOAE, the 0.1- octave criterion was used: the shifting was considered to occur if SOAE frequency peaks in two sessions were within a 0.1 - octave range of the frequency of SOAE peak as a centre frequency ($\Delta f/f < 0.1$), and the "on-off" SOAE when that range was exceeded ($\Delta f/f > 0.1$).

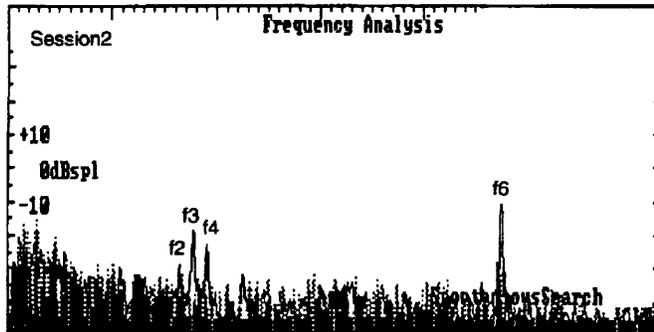
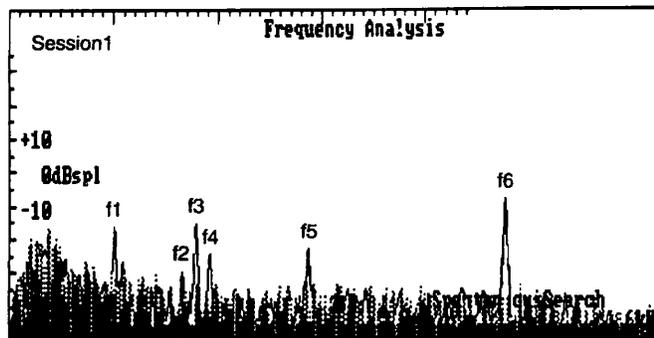
The stability of SOAE was determined by two factors, reproducibility and relative frequency shift:

a. Reproducibility of SOAE was determined by the presence of "stable", "shifted" and "on-off" SOAE peaks: the higher the number of "stable" or "shifted" SOAEs and the lower the number of "on-off" SOAE peaks, the higher was the reproducibility of SOAE.

b. Relative frequency shift (rFs) was an expression of the magnitude in frequency shifting of an SOAE peak, and it was calculated as the percentage of the difference in absolute frequencies of SOAE peak recorded in two sessions ($\Delta f/f$), in relation to the centre frequency of SOAE peak (f):

$$\text{rFs (\%)} = \Delta f/f \times 100.$$

Figure 4.1.1. illustrates all three categories of SOAE peaks in a subjects with tinnitus.



	f1	f2	f3	f4	f5	f6
Session I	1001 Hz	1648 Hz	1782 Hz	1917 Hz	2869 Hz	4773 Hz
Session II	absent	1648 Hz	1770 Hz	1904 Hz	absent	4749 Hz
	"on-off"	"stable"	"shifted" 12 Hz (0.7%)	"shifted" 13 Hz (0.7%)	"on-off"	"shifted" 24 Hz (0.5%)

Figure 4.1.1: SOAE spectra of a subject with tinnitus, recorded in two sessions, exemplifying all three categories of SOAEs

Influence of change in body position on SOAEs

Subsequent to the completion of the protocol, an additional test was performed, to identify one possible source of SOAE variability. Changes in body position may alter conditions in the middle ear and thus, in turn, may influence the stability of SOAE. In 10 subjects (5 with and 5 without tinnitus), SOAEs were recorded in two consecutive scans: first, in the usual upright sitting position, and second, with anteflexion of the upper part of the body, so that the subject's head angulated at 160-180 degrees from the previous position. SOAEs from the two recordings were analysed for their stability in the manner described above.

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4.1.3 Results

Prevalence and number of SOAE peaks

1. *Control group.* Out of 38 screened volunteers, 20 subjects with SOAEs were identified (prevalence 52%), and in these, 127 SOAE peaks were defined. All subjects had normal audiometric thresholds at all test frequencies (Figure 4.1.2).

2. *Tinnitus group.* Out of 100 examined subjects with tinnitus, 53 subjects had SOAEs (prevalence 53%), and 239 SOAE peaks were recorded. The mean audiometric thresholds for each tinnitus subgroup are shown in Figure 4.1.2.

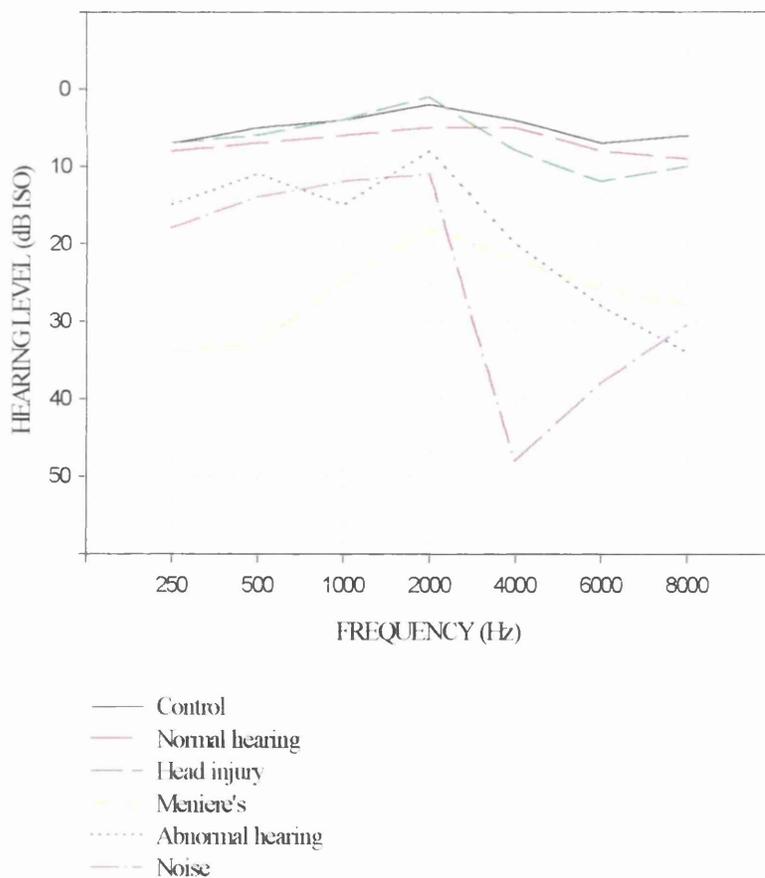


Figure 4.1.2: The mean pure-tone audiometric threshold levels for the control group and tinnitus subgroups.

SOAE prevalence and number of peaks were as follows (Table 4.1.1):

- (i) Tinnitus and normal hearing: in 35 subjects, 20 patients with SOAEs were found (prevalence 57.1%), and in these, 78 SOAE peaks were recorded.
- (ii) Tinnitus and SNHL of unknown origin: in 10 subjects, from 21 patients (prevalence 47.6%), 42 SOAE peaks were recorded.
- (iii) Tinnitus and head injury: in 10 subjects, SOAEs were recorded in both ears of all 10 subjects (prevalence 100%), in total 84 SOAE peaks, with the greatest number, 4.2, of SOAE peaks per ear.
- (iv) Tinnitus and Menière's disease: in 10, from 16 subjects (prevalence 62.5%), 24 SOAE peaks were recorded.
- (v) Tinnitus and noise-induced hearing loss: in only 3 from 17 subjects with SNHL due to noise exposure, SOAEs were recorded (prevalence 17.6%), with a total of 8 peaks.

Table 4.1.1: Number of subjects, ears, SOAE peaks and SOAE prevalence in the control and tinnitus group/subgroups

	Number of		Prevalence (%) of	No. of SOAE peaks:	
	subjects	ears		subjects with SOAEs	total
Controls	20	31	52	127	4.1
Tinnitus	53	76	53	239	3.1
Normal hearing	20	23	57.1	78	3.4
Abnormal hearing	10	15	47.6	42	2.8
Head injury	10	20	100	84	4.2
Menière's	10	13	62.2	24	1.8
Noise	3	5	17.6	11	2.2

SOAE frequency stability

In comparison with the control group, the results showed significantly lower *reproducibility* of SOAE peaks in the tinnitus group: the number of “stable” SOAE peaks in the tinnitus group, 57 of 239 (23.8%) was significantly lower than in the control group, 74 of 127 (58.2%), while the number of “on-off” peaks was significantly higher in the tinnitus group, 113 (47.3%) as compared to the control group, 7 of 127 (5.5%), (t-test, $p < 0.001$). These results are shown in Table 4.1.2, which also displays the data for tinnitus subgroups and the significantly lower SOAE reproducibility in the tinnitus subgroups (one-way ANOVA, $p < 0.05$).

The number of "shifted" SOAE peaks did not differ significantly between the control and tinnitus group/subgroups, but the magnitude of frequency shifting, expressed as *relative frequency shift* (rFs), was significantly higher in the tinnitus group ($0.59 \pm 0.9\%$) than in the control group ($0.25 \pm 0.4\%$), (t-test, $p < 0.001$), and was particularly so in the tinnitus/head injury subgroup ($0.84 \pm 1.3\%$), (one-way ANOVA, $p < 0.05$). The comparison of the rFs means between the controls and tinnitus group/subgroups is illustrated in Table 4.1.3 and Figure 4.1.3.

Table 4.1.2 : SOAE peaks classified according to their reproducibility in two sessions:
"stable", "shifted" and "on-off"

	SOAE peaks:		"Stable" SOAEs:		"Shifted" SOAEs:		"On-off" SOAEs:	
	total	per ear	total	per ear	total	per ear	total	per ear
Control	127	4.1	74 (58.2%)	2.4	46 (36.2%)	1.5	7 (5.5%)	0.2
Tinnitus	239	3.1	57 (23.8%)	0.7 **	69 (28.9%)	0.9	113(47.3%)	1.5 **
Nor.hearing	78	3.4	14 (17.9%)	0.6 *	23 (29.5%)	1.0	41 (52.6%)	1.8 *
Abn.hearing	42	2.8	12 (28.6%)	0.8 *	14 (33.3%)	0.9	16 (38.1%)	1.0
Head injury	84	4.2	24 (28.6%)	1.2	28 (33.3%)	1.4	32 (38.1%)	1.6 *
Menière's	27	1.8	4 (16.7%)	0.3 *	3 (12.5%)	0.2	17 (70.8%)	1.3 *
Noise	11	2.2	3 (27.3%)	0.6	1 (9.1%)	0.2	7 (63.6%)	1.4

statistically significant ** (t-test, $p < 0.001$) , * (ANOVA, $p < 0.05$)

Table 4.1.3: Relative frequency shift (rFs) of SOAE in the controls and tinnitus group/subgroups ("stable" and "shifted" SOAEs are included)

	SOAE number	rFs Mean (%)	rFs SD	rFs Range
Controls	120	0.25	0.4	0 - 2.1
Tinnitus	126	0.59** *	0.9	0 - 5.6
Normal hearing	37	0.47	0.5	0 - 1.8
Abnormal hearing	26	0.38	0.5	0 - 2.4
Head injury	52	0.84 *	1.3	0 - 5.6
Menière's	7	0.20	0.3	0 - 0.8
Noise	4	0.45	0.9	0 - 1.8

Statistically significant ** (t-test, $p < 0.001$), *(ANOVA, $p < 0.05$)

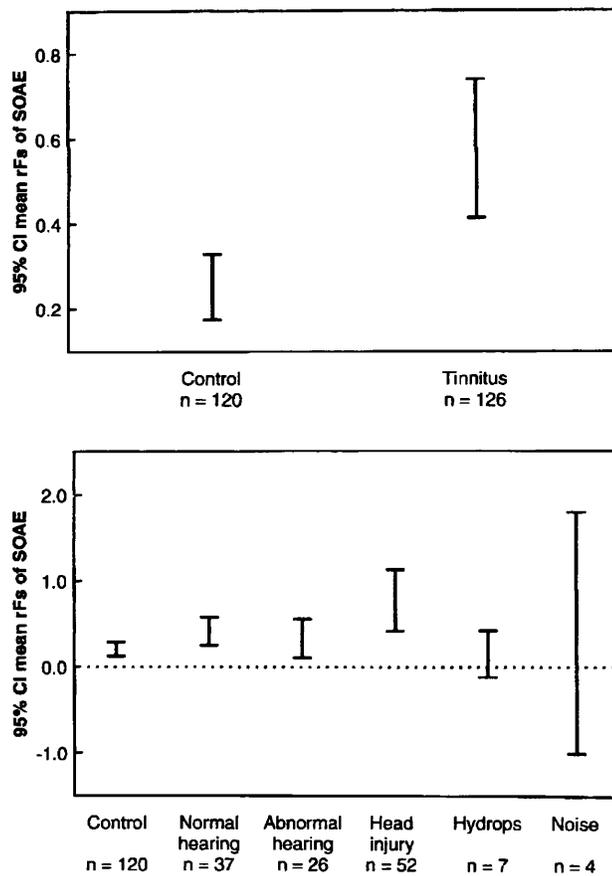


Figure 4.1.3: 95% confidence interval (CI) for the mean of the relative frequency shift (rFs) of SOAE peaks in the control and tinnitus subgroup

Influence of change in body position on SOAE

A total of 48 SOAE peaks were recorded from 16 ears of 10 subjects in both test-positions. These were analysed for frequency stability. All 48 SOAE peaks were reproducible, 40 of them (83%) being “stable” and 8 (17%) “shifted”, with the mean of relative frequency shift $0.1\pm 0.3\%$, demonstrating that SOAE were not subject to the variability secondary to the change in body position. In view of the above data, it seems that casual changes in head/body position cannot be called upon to account for the frequency variability of SOAE in two sessions.

4.1.4 Discussion

The prevalence of SOAEs in the control group was 52%, which was in agreement with that previously reported for a normal population (30 -50%) (Probst et al., 1991), but lower than recently reported results by Penner and Zhang (1997) (62- 83%). This discrepancy between the studies may be explained by the differences in recording equipment and the methodology: in Penner and Zhang’s study SOAEs were directly recorded using Etymotic Research ER-10A microphone and analysed using “suitably tailored spectral responses”, while in this study click-synchronised SOAE were recorded and analysed using an ILO88 Analyser. The prevalence of SOAEs in the tinnitus group *in toto* was 53%, which was similar to that of the control group (52%). However, the consistent presence of SOAEs in the subgroup of subjects with head injury was notable and a 62% prevalence in patients with Menière’s disease was higher than that normally expected, considering the age and elevated audiometric thresholds. In this latter group, the prevalence was higher despite the older age range (in the controls mean: 30 ± 4 years and in Menière’s mean: 48 ± 12 years), which, according to the normal age dependence, should have resulted in a reduction of SOAE prevalence. The low prevalence of SOAE in subjects with SNHL due to noise exposure (17.6%) is in agreement with even lower previously reported results (Probst et al., 1987; Penner, 1990). The SOAE reproducibility, indirectly proportional to the presence of “on-off” SOAE peaks, and directly proportional to “stable” SOAE peaks, was significantly lower in the tinnitus group, particularly in the subgroup tinnitus/normal hearing and tinnitus/head injury. The

relative frequency shift (rFs), representing the magnitude of SOAE frequency shifting in the two sessions, was significantly higher in the tinnitus group ($0.59\pm 0.9\%$) than in the control group ($0.25\pm 0.4\%$). Direct comparison of the data (rFs) in this study, with previously reported physiological shifting of SOAEs was not possible, due to the differences in instrumentation.

These results lead to the conclusion that the variability of SOAEs is, in a significant number of subjects, associated with the complaint of tinnitus.

SOAEs are, in general, thought to arise as a response to random perturbations in cochlear mechanics due to inherent irregularities in OHCs arrangement (Kemp, 1986). In normal subjects, in whom cochlear structural arrangement and functional capacity remain unchanged, and control mechanisms are well balanced, there is no reason for changes in SOAEs, and this is confirmed by the finding of stable SOAEs. These weak narrow-band signals, due to their continuous presence, are subject to perceptual adaptation, and are, therefore, inaudible. Conversely, the instability of SOAEs, as reported previously in some subjects with tinnitus (Penner et al., 1981; Burns and Keefe, 1992), may lead to their audibility. *Stable SOAEs and tinnitus* may be present in subjects in whom the process of adaptation is impaired, with consequent audibility of SOAEs. This may occur in stressful situations, which are well recognised to trigger or exacerbate tinnitus (Hinchcliffe and King, 1992).

Besides being perceived, and therefore being the direct cause of tinnitus [according to Penner, (1990), the 95% confidence limits for the prevalence SOAE-related tinnitus were 1% and 9.5%], SOAEs may be viewed as pathophysiological correlates of tinnitus.

Unstable SOAEs may correspond to the unstable cochlear mechanics due to some local causes, resulting from mutual interaction of multiple peaks, changes in the middle ear transfer properties, and various external (acoustic, mechanical) and internal factors. However, variable SOAEs, as mentioned above, may also reflect instability of the higher central nervous structures. The effect of the central auditory system on cochlear mechanics may be exerted through efferently induced mechanisms of electro-mechanical transduction (Zenner, 1986), which may alter the gain in the feedback loop of a cochlear amplifier, and further, the SOAE frequency spectrum. This may find support in the observation of significantly higher inter-session variability of the medial olivocochlear

suppression in patients with tinnitus in comparison with normal subjects, reported by Graham and Hazell (1994), which would correspond to the finding of unstable SOAEs. It could be speculated that abnormality/dysfunction in the higher auditory and other central structures may alter the control mechanisms of the cochlea, e.g. disinhibition of suppressive efferent function, leading to an increase in cochlear output, and consequently to the occurrence of unstable SOAE.

This "scenario" is supported by the SOAE findings in the tinnitus/head injury subgroup, which demonstrate the highest prevalence of SOAEs, the bilateral presence in all subjects, the largest number of SOAE spectral peaks and the most prominent relative frequency shift. These subjects had normal audiometric threshold levels, thus implying normal peripheral auditory function, so that SOAE findings could be suggestive of "undamped" cochlear activity, subsequent to central efferent disinhibition following head injury. The altered central auditory activity, reflected in cochlear micromechanics, may provide a basis for the generation of tinnitus in this subgroup of patients. In addition to tinnitus, these patients with head injury also complained of hyperacusis, which is commonly described as an increased gain in auditory function, and the SOAE findings would, indeed, support this hypothesis.

The high SOAE prevalence and reduced reproducibility of SOAEs in subjects with Menière's disease may also be an indication of the involvement of the central nervous system mechanisms in the pathogenesis of this condition. It has been suggested (LePage, 1989) that dysfunction of the efferent medial olivocochlear system, through its capacity to modulate the osmotic forces internal to the OHCs, could lead to failure of local homeostasis, and Menière's disease. The presence of SOAE in Menière's disease may be an expression of a prolonged excitatory state of the cochlea, leading to an increase in spontaneous activity of auditory neurones and, subsequently, to tinnitus.

In conclusion, this study has shown that an increased variability of SOAEs is associated with the complaint of tinnitus in a significant number of subjects. This implies that variable SOAEs may be a pathophysiological correlate of tinnitus. SOAE may, therefore, be used as an objective indicator of the presence of tinnitus in a subset of subjects with recordable SOAEs, and the presence of variable SOAEs may increase the probability of a subject having tinnitus. On the basis of this study, a subject with tinnitus may be

considered 7.5 times more likely to have “on-off” SOAEs or 3 times less likely to have “stable” SOAEs, and relative frequency shift greater than 0.3%, than a subject without tinnitus.

Additionally, the difference in the SOAE prevalence between tinnitus subjects observed *in toto* and in the subgroups emphasises the importance of studying tinnitus in aetiologically homogeneous groups, to identify group-characteristics as a consequence of particular underlying mechanisms. The high prevalence of variable SOAEs may be suggestive of the involvement of central mechanisms in the generation of tinnitus, and thus SOAEs may provide an insight into the activity of higher auditory structures.

4.2 TINNITUS FOLLOWING HEAD INJURY

4.2.1 Introduction

A separate study to explore cochlear mechanics in patients with tinnitus subsequent to head injury has been undertaken. An observation of the high prevalence of SOAEs (100%) in these subjects in the previous study (4.1) raised the suspicion that tinnitus in this group may be the result of changes in the central nervous system.

There is a paucity of literature concerning tinnitus induced by head injury (Lackner, 1976; Vernon and Press, 1994) and tinnitus in these cases is probably largely unreported. According to Vernon and Press, 8% of the patients from their Tinnitus Data Registry (n= 1240) constituted the group with head injury.

It is assumed that tinnitus is a consequence of altered neural activity and may result from a lesion or dysfunction at any level of the auditory system, and, therefore, the source of “tinnitogenic” activity could be anywhere in the auditory system (section 1.1.4).

In patients with tinnitus following head injury, in whom an “intact” auditory periphery is found, there is a strong indication that the “tinnitogenic” signal, leading to the perception of tinnitus, results from a lesion within the central nervous system.

In this study, TEOAEs were recorded as they are invariably associated with functioning OHCs, and, therefore, their presence is a reliable indicator of cochlear (OHCs) structural integrity, and their absence may indicate a cochlear lesion (section 1.3.4.2). SOAE, beside being an indicator of OHC integrity at corresponding frequencies, may be an expression of increased gain in cochlear activity, with an excess of energy from the positive feedback process (section 1.3.4.1). TEOAEs under contralateral acoustic stimulation were also recorded to assess the function of the efferent medial olivocochlear system, which controls the activity of the OHC (section 1.3.5).

The medial olivocochlear efferent system is only a part of the regulatory complex, which also includes higher auditory structures, above the superior olivary complex (medulla oblongata), which can modulate the excitability of olivo-cochlear neurons, e.g. inferior

colliculi (Warr and Guinan, 1979; Rajan, 1990), or cortical and subcortical pathways (Attias et al., 1993b) and, indirectly, exert their influence on cochlear mechanics.

The MOC system is classically considered to be *inhibitory* (Wiederhold, 1986), a reduction in the OAE response amplitude, being demonstrated in a number of studies by presenting stimuli against silent background, and simultaneous contralateral acoustic stimulation (section 1.3.5). However, there is evidence to suggest that the MOC system *enhances* transient stimuli if they are presented against a continuous background noise (Kawase et al, 1993). In this study, in view of the test conditions, an inhibitory effect is expected in the presence of a normally functioning MOC system.

4.2.2 Materials and methods

Subjects

All subjects included in the study (Table 4.2.1) have fulfilled the general criteria, as outlined in the Chapter 3 (section 3.1).

Table 4.2.1: Subjects included in the study

	<i>Subjects (n)</i>	<i>Gender (f/m)</i>	<i>Ears (n)</i>	<i>Age (years)</i>
Subjects with head injury and tinnitus	20	12/8	37	36±9 (20-49)
Normal subjects	20	12/8	40	37±7 (24-50)
Subjects with head injury without tinnitus	12	7/5	23	34±8 (21-50)

1. Subjects with tinnitus following head injury

Twenty consecutive patients attended the neuro-otology clinic, with tinnitus lasting at least one year following head injury due to a road traffic accident (13/20, 65%), sport injury (3/20, 15%), blow to the head (2/20, 10%) or a fall (2/20, 10%). According to the classification of head injuries for severity (Symonds, 1962; Berman and Fredrickson, 1978), 6 (30 %) patients sustained minor (post-traumatic amnesia lasted less than 3 hours and no skull fracture), 11 (55%) moderate (a skull fracture was identified, or post-traumatic amnesia lasted between 3 hr to 7 days) and 3 (15%) severe head injury (post-traumatic amnesia lasted more than 7 days) (Table 4.2.2). All patients complained of tinnitus of complex composition, which included different sounds, variable in pitch and volume and aggravated by environmental noise. Other auditory complaints included hyperacusis (in 90%) and difficulty in listening in background noise (in 85%).

Apart from the auditory disorders, other aspects of head injury in these patients have not been taken into consideration in this study.

Table 4.2.2. Subjects according to the severity of head injury

Head injury:	<i>minor</i>	<i>moderate</i>	<i>severe</i>
Subjects with head injury and tinnitus	(6/20) 30%	(11/20) 55%	(3/20) 15%
Subjects with head injury without tinnitus	(2/12) 16.7%	(8/12) 66.6%	(2/12) 16.7%

2. Subjects with head injury, but without auditory complaints

Twelve consecutive patients who sustained head injury due to a road traffic accident (7/12, 58.3%), blow to the head (2/12, 16.7%), sport injury (2/12, 16.7%) and due to a fall (1/12, 8.3%), were included in the study. With respect to the severity, 2 of them (16.7%) had minor, 8 (66.6%) moderate and 2 (16.7%) had severe head injury.

3. Normal subjects without auditory complaints

Twenty consecutive subjects were selected to match the group with tinnitus for age and gender. This control group was introduced at a later stage of the study, following the observation of significantly reduced OAE responses in the group without tinnitus in comparison with the group with tinnitus. The lower level of OAE responses might result from a lower gain of the cochlear amplifier, but might also be a consequence of OHCs damage. As OAEs represent the OHCs population - based response, scattered lesion of OHCs could lead to a reduction in amplitude, without significant change in the microstructure of the response pattern (He and Schmiedt, 1993). Therefore, by examining the spectral bands of the OAE response, this type of OHC lesion would not be identified.

The introduction of the group of normal subjects as another control group is considered to be adequate, as there is no reason to suspect that the group with tinnitus following head injury was not a part of the normal population prior to head injury.

Protocol

All patients underwent the standard general protocol (3.2.2), but, in addition, auditory brainstem responses (ABR) were undertaken, to assess, together with the AR, the integrity of auditory pathways up to the superior olivary complex.

Auditory brainstem responses

Auditory brainstem responses (ABR) were recorded as a part of the routine test battery during neuro-otological assessment. They were recorded (Medelec Sensor) using alternating click stimuli at a maximum intensity of 100 dB HL presented through TDH 39 headphones at a rate of 10 Hz. A total of 1024 sweeps were averaged and latencies of wave I, III and V were analysed for central conduction times, which were considered abnormal if they exceeded two standard deviation from the normal mean, or if the response was unrepeatable or absent.

Otoacoustic emissions

TEOAE recording

TEOAEs are recorded as described in the section 3.3.3.2.

The following data have been considered:

- The overall TEOAE response,
- The noise level, to ensure comparable noise levels between the groups
- The signal-to-noise (S/N) ratio in the bands (approx. 1 kHz-width) centered at 1, 2, 3, 4 and 5kHz, as the simplest form of TEOAE spectral analysis.

This analysis was performed in order to identify subclinical cochlear lesions (absence of the response in a spectral band).

SOAE recording

Synchronised SOAEs were recorded as described in the section 3.3.3.3.

The prevalence of SOAEs and the number of SOAE peaks per ear were determined.

Medial olivocochlear suppression test

This test is performed as explained in the section 3.3.3.4.

4.2.3 Results

Pure-tone audiometry

Results of pure-tone audiometry confirmed normal hearing in all subjects and there were no significant differences in the mean threshold levels between the groups (Figure 4.2.1).

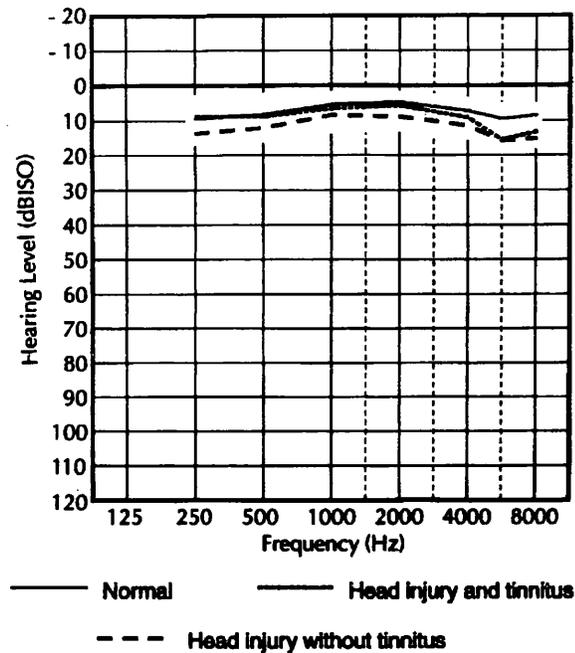


Figure 4.2.1: The mean pure-tone audiometric thresholds for all groups

Tympanometry

Tympanometric measures in all subjects were within normal ranges and the middle ear pressure was comparable between the groups. The results are summarised in Table 4.2.3.

Acoustic reflexes (AR)

In all subjects, acoustic reflexes, ipsi and contralateral, were lower than 100 dB across at least three adjacent frequencies, with the exception of one patient with tinnitus, in whom reflexes were elevated.

Table 4.2.3: Tympanometric measurements in tinnitus and control groups

	<i>Ear drum compliance (ml)</i>	<i>Peak pressure (daPa)</i>	<i>Ear canal volume (cm³)</i>
Subjects with head injury and tinnitus	0.7±0.3	5.6±1	1.2±0.4
Normal subjects	0.8±0.3	-0.7±9	1.4±0.4
Subjects with head injury without tinnitus	0.6±0.2	-0.4±9	1.3±0.4

Auditory brainstem responses (ABR)

In all 12 patients with head injury without tinnitus, and in 16 out of 20 patients with head injury and tinnitus, ABR were normal. In the patient with tinnitus end elevated AR, the ABR was also abnormal, with unilateral delay of wave V. In the remaining 3 patients, ABR could not be performed due to the patient's oversensitivity to the acoustic stimuli.

Otoacoustic emission tests

Transient evoked otoacoustic emissions (TEOAE)

The mean of the overall TEOAE amplitudes in subjects with tinnitus was significantly higher than in normal subjects, as well as in subjects with head injury, but without tinnitus. This difference was demonstrated in the presence of comparable noise level in all three groups (Table 4.2.4), and is illustrated in Figure 4.2.2, showing 95% confidence intervals for the means for all three groups.

Table 4.2.4 : Mean TEOAE and noise levels in subjects with tinnitus and control groups

	<i>TEOAE responses(dB SPL)</i>	<i>Noise (dB SPL)</i>
Subjects with head injury and tinnitus	12.8±4 *	-1.0±1
Normal subjects	8.0±3	-1.5±1
Subjects with head injury without tinnitus	6.2±4	-0.9±1

* significant (ANOVA, $p < 0.05$)

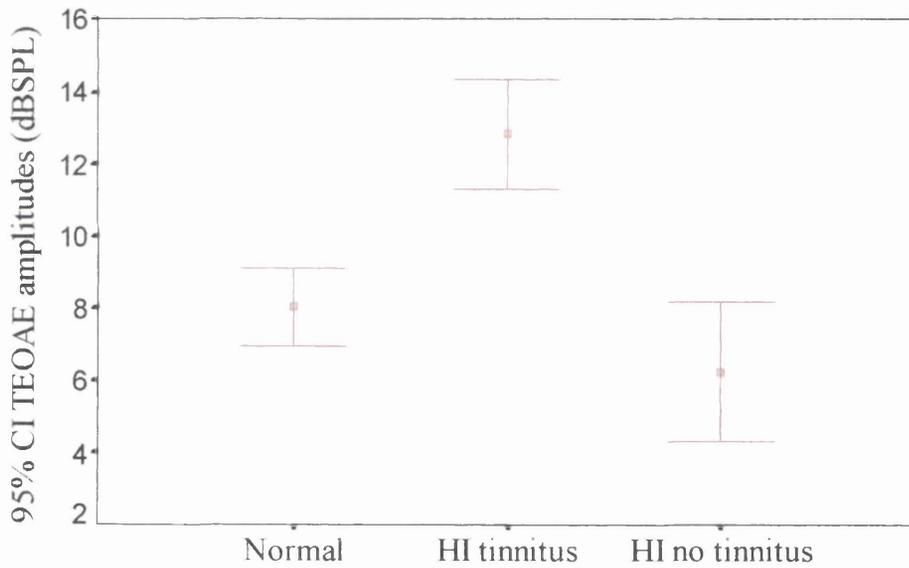


Figure 4.2.2: The overall TEOAE amplitude responses of subjects in normal and head injury (HI) groups: 95% confidence intervals (CI) for means

TEOAE spectral analyses showed a similar distribution of the presence of TEOAE responses in 1, 2, 3, 4 and 5 kHz bands (Figure 4.2.3A). However, in subjects with tinnitus, the mean TEOAE responses in all frequency bands were significantly higher than those in the control groups (Figure 4.2.3B).

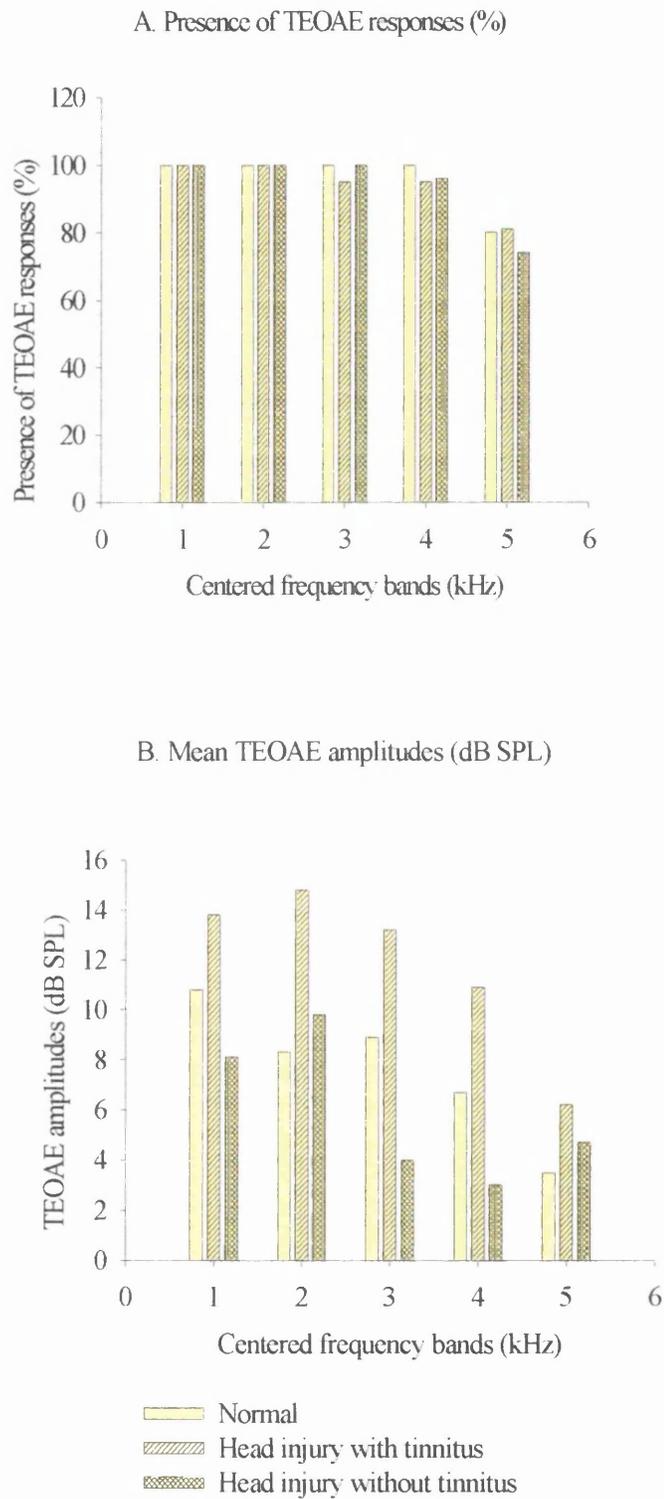


Figure 4.2.3: TEOAE spectral analysis for subjects in normal and head injury groups

Spontaneous otoacoustic emissions (SOAEs)

The analysis of SOAE spectra, showed a 100% prevalence of SOAEs in the group of 20 subjects with tinnitus. This was significantly higher than in the normal subjects (10/20, 50%) and the subjects with head injury without tinnitus (2/12, 17%). Similarly, the number of SOAE peaks were significantly higher in tinnitus (4.4 per ear) than in the normal (1.7) and head injury without tinnitus (0.25) groups. The summarised results of SOAEs, including the prevalence of SOAEs per ear, and per subject, are shown in Table 4.2.5.

Table 4.2.5: Results of SOAEs recorded in subjects with tinnitus and in controls

	<i>Prevalence (%)</i>		<i>Number of peaks</i>
	<i>per ears</i>	<i>per subjects</i>	<i>per ears</i>
Subjects with head injury and tinnitus	92*	100	4.4**
Normal subjects	38	50	1.7
Subjects with head injury without tinnitus	17	17	0.25

significant: * (χ^2 - test, $p = 0.000$) ** (ANOVA, $p < 0.05$)

Medial olivocochlear suppression test

The suppression effect of the medial olivocochlear (MOC) system was obtained by subtraction of the TEOAE responses under contralateral stimulation from those without contralateral stimulation. In all normal subjects, this suppression effect was ≥ 1 dB. Therefore, 1 dB was considered to be a cut-off point, below which the MOC suppression was labelled as reduced (< 1 dB), or absent (0). Accordingly, all subjects in the control groups (20 normal subjects and 12 patients with head injury, but without tinnitus) had normal efferent suppression, while in subjects with tinnitus, normal suppression was found in only 7 out of 20 (35%) subjects, or in the other words, in a significant number

of subjects (65%), MOC suppression was found to be reduced/absent in one or both ears (Table 4.2.6).

Table 4.2.6: Suppression of TEOAEs by contralateral noise

	<i>Suppression ≥ 1dB per ears/subjects (%)</i>	<i>Mean and range (dB)</i>
Subjects with head injury and tinnitus	57*/ 35	1.2±1 (0-3.5)
Normal subjects	100	2.1±1** (1-5.8)
Subjects with head injury without tinnitus	100	1.7±1 (1.1-3.8)

significant: *(χ^2 - test, $p = 0.00546$) ** (ANOVA, $p < 0.05$)

In patients in whom the MOC suppression was ≥ 1 dB, TEOAEs and SOAEs displayed similar characteristics to those with the MOC suppression < 1 dB.

The summarised results of one of the patients with tinnitus are illustrated in Figure 4.2.4.

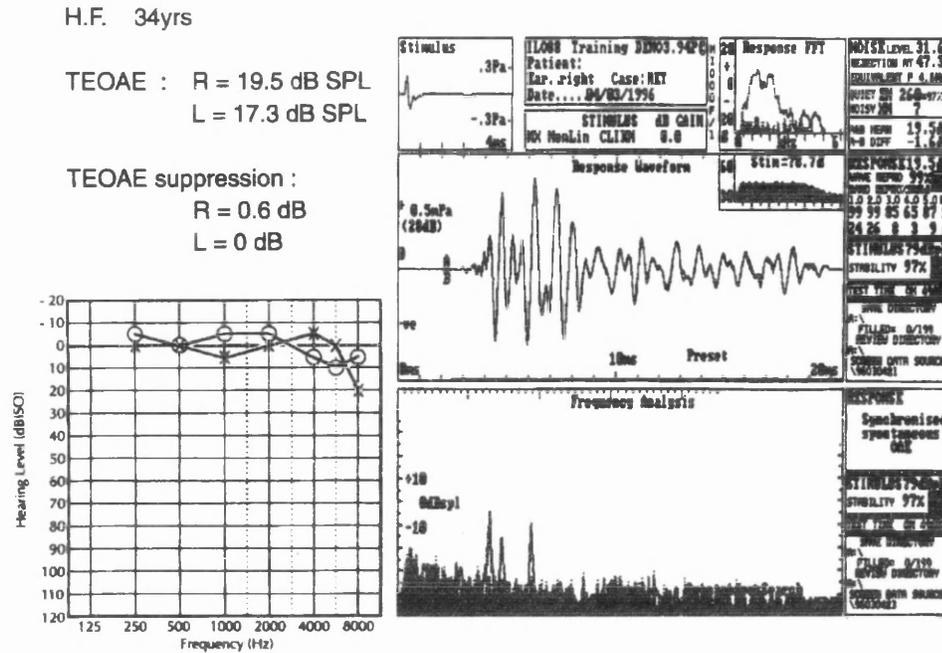


Figure 4.2.4 : Findings in a subjects with tinnitus, hyperacusis and difficulty in listening in background noise, following severe head injury; only OAE traces for the right ear are illustrated

4.2.4 Discussion

Subjects with tinnitus and other auditory complaints, including hyperacusis and difficulty in listening in background noise, following head injury, showed significantly higher TEOAE amplitudes (12 ± 4 dB SPL) than subjects who had no auditory complaints, but who also sustained head injury (6.2 ± 4 dB SPL). They were matched for gender and age, and had similar audiometric patterns. In order to exclude subclinical cochlear lesions, with the subsequent reduction of TEOAE amplitudes, and therefore to avoid potential bias in favour of the group with tinnitus, a simple spectral analysis, signal-to-noise ratio in 1, 2, 3, 4 and 5 kHz - centered bands, was performed. This analysis, which was considered to be, together with audiometric thresholds, an additional clinical criterion for normal hearing, did not show any significant difference in the distribution of the

presence of the TEOAE responses in frequency bands between the tinnitus and non-tinnitus head injury groups.

However, this analysis could not exclude scattered OHCs lesion, with a reduced number of OHCs contributing to TEOAE response, leading to a reduction of amplitude, but without obvious change in the pattern of frequency dispersion. Therefore, TEOAE responses, overall and in frequency bands, in head injury patients with tinnitus were additionally compared with those in normal subjects, who had neither tinnitus, nor head injury. As expected, no subclinical cochlear lesions were detected in normal subjects, but TEOAE amplitude in patients with tinnitus still remained significantly higher than in this control group (8.0 ± 3 dB SPL).

A striking 100% prevalence of recordable SOAEs, as well as the largest number of SOAE spectral peaks per ear (4.4), in subjects with tinnitus was observed, significantly higher than in both control groups: in normal subjects the prevalence of SOAEs was 50%, with 1.7 SOAE peaks per ear and in subjects with head injury without auditory complaints, SOAEs prevalence was 17%, with 0.25 SOAE peaks per ear. The SOAE prevalence in normal subjects was in agreement with previously reported results for normal subjects (Probst et al., 1991).

The magnitude in relative TEOAE reduction under contralateral acoustic stimulation in comparison with TEOAE amplitude without contralateral stimulation, was found to be ≥ 1 dB in all control subjects and these subjects were considered to have normal medial olivocochlear (MOC) suppression (in this study 1 dB TEOAE reduction was taken as the cut-off point to separate subjects with normal and abnormal MOC suppression). In contrast, in a significant number of patients with tinnitus (65%), MOC suppression was reduced (< 1 dB) or absent (0 dB).

The effect of a central nervous lesion (e.g. at the brainstem level) on the MOC function, leading to the absence or reduction of MOC suppression has already been documented (Ryan et al., 1991; Berlin et al., 1993). Whether the lesion affects the afferent or efferent, or both parts of the olivocochlear reflex, is open to question. The integrity of the afferent input and access to the efferent pathways were judged on the basis of normal stapedial reflexes and auditory brainstem responses, in all subjects, with the exception of four

patients with tinnitus, one of whom had abnormal acoustic reflexes (AR) and auditory brainstem responses (ABR), and in three of whom ABR were not recorded, because they could not tolerate the necessary acoustic stimulation. As the acoustic reflex, auditory brainstem responses and the olivocochlear reflex share the same ascending pathways, it is likely that reduced or absent suppression of TEOAEs in these patients results from dysfunction of the descending auditory pathway. However, in the case of abnormal AR and ABR, the dysfunction could be in either the ascending and/or descending pathways.

In this study, there is an indication of auditory efferent dysfunction, involving the MOC system, in 65% patients with tinnitus. In the remaining 35% of the patients, who exhibited similar characteristics with respect to the auditory symptoms and OAE findings, the suppression test showed TEOAE reduction values > 1 dB, implying normal MOC function. Since this test activates the MOC system, the functioning of the rest of the efferent system, above the superior olivary complex (medulla oblongata), remains obscure. In view of the known multisynaptic connections of MOC system, within the inferior colliculi and via the inferior colliculi to the auditory cortex, suggesting a descending trisynaptic pathway from the cortex to the cochlea, it could be speculated that higher auditory pathways may be implicated in a more global efferent dysfunction, with, the above described, consequences.

The presence of significantly higher TEOAE responses, high prevalence of SOAEs with a large number of SOAE spectral peaks and reduced/absent MOC efferent suppression in subjects with tinnitus, was interpreted to be due to an increase in the cochlear amplifier gain secondary to the dysfunction in the efferent control of cochlear mechanics (disinhibition of suppressive effect), subsequent to head injury. There have already been suggestions that the size of emissions is related to the status of the MOC system (Berlin et al., 1993), which may be abnormal structurally, i.e. demonstrable morphological lesion, or functionally, e.g. imbalance of central neurotransmitters. This was illustrated by an experiment by Salonna et al. (1990) in which i.v. administration of atropine (an antagonist of acetyl-choline, the principle neurotransmitter of the MOC system), in ten healthy human subjects, led to a marked increase in emissions, elevated pure-tone audiometric thresholds and reduced frequency selectivity.

In normal conditions, central auditory system exerts its effect on the cochlea through efferently induced mechanisms of electromechanical transduction (OHC electromotility) (Zenner, 1986), thus extending the dynamic range of the cochlea. The resulting cochlear amplification or attenuation is, presumably, a basis for the high sensitivity and frequency selectivity. However, reduced/absent MOC suppression, as has been demonstrated in this study in patients with head injury, may lead to a reduction in the dynamic range of the cochlea, leading further to a reduced ability of fine tuning and to difficulty to extracting transient stimuli in background noise. This could be a possible explanation for the symptom of the difficulty in listening in background noise, reported by 85 % of patients in this group of patients.

At the same time, the loss of damping effect (attenuation) on afferent cochlear activity, normally produced by stimulation of the MOC bundle, and an increase in amplifier gain causes an increase in the cochlear partition displacement as a response to auditory stimuli, could be responsible for abnormal sensitivity to ordinary environmental sounds, i.e. hyperacusis, reported by 90% of patients. This increased auditory gain may also result in abnormal neural excitation, abnormal central sound processing, and, consequently, tinnitus.

It is apparent that tinnitus and other auditory complaints, hyperacusis and difficulty in listening in background noise, attributed to head injury, and associated with normal peripheral auditory function (normal/nearly normal audiometric thresholds) and undamped OAEs, robust TEOAEs and almost invariably recordable SOAEs, are the consequences of an extracochlear phenomenon and constitute a clinical presentation which may be termed "disinhibition syndrome", subsequent to central efferent auditory dysfunction.

Additionally, the assessment of MOC system by recording TOAEs under contralateral acoustic stimulation, in suspected central nervous system lesion, could contribute to the neuro-otological topographic diagnostics.

4.3 TINNITUS IN SUBJECTS WITH NORMAL HEARING

4.3.1 Introduction

This study, examines cochlear mechanics in subjects with tinnitus and normal hearing. However, this study includes only those patients with tinnitus, in whom underlying pathology could be neither identified, nor suspected. Patients with normal hearing and tinnitus, often present with other auditory complaints, such as difficulty in hearing, hyperacusis, sound distortion, or “pressure” in the ears, and they are usually difficult to evaluate clinically.

It is anticipated that otoacoustic emission (OAE) techniques, with their properties described in the Chapter 1 (1.3.2, 1.3.4.1, 1.3.4.2 and 1.3.5), and applied in the previous study, may help in the assessment of these patients too.

Patients with tinnitus and normal hearing may represent a significant proportion of the tinnitus population. According to Hazell (1984) about one third of patients in tinnitus clinic had normal audiometric thresholds on standard pure-tone audiometry, and according to the MRC Institute of Hearing Research (Coles et al., 1981), approximately a half of the people with severe tinnitus did not report having hearing impairment. However, Sanchez and Stephens (1995) reported that only 8% of patients from their tinnitus clinic, had normal hearing (thresholds < 25 dBHL, from 0.25 to 8kHz). Undoubtedly, the prevalence of patients with tinnitus associated with normal hearing depends on the definition of normal hearing.

In this study, patients who, in addition to normal audiometric thresholds, as defined in the Chapter 3 (3.1), had recordable TEOAE responses (signal-to-noise ratio) in the 1, 2, 3, 4 and 5 kHz frequency bands, were regarded as having normal hearing.

4.3.2 Materials and methods

Subjects

This study included 30 consecutive patients with tinnitus and normal hearing, in whom underlying pathology has been excluded by standard procedures used for neuro-otological assessment (section 1.1.5.1). None of them had a history of noise exposure, ototoxicity, head injury or ear disease, and no other cause could be identified. Besides tinnitus, they had (at least one) other auditory complaints, such as hearing difficulty (73%), hyperacusis (66%), sound distortion (26%), or “pressure” in the ears (20 %). They were compared with 30 normal control subjects matched for gender and age (Table 4.3.1).

Table 4.3.1: Subjects included in the study

<i>Subjects</i>	<i>number</i>	<i>age (years)</i>
With tinnitus	30 (16F, 14M)	38 ± 9
Controls	30 (17F, 13M)	39 ±10

All subjects complied with the general inclusion criteria, as outlined in the introduction to this study (for normal hearing) (3.1).

Method

The subjects underwent the protocol as described in the section 3.2.2, which included:

- Pure tone audiometry
- Impedance measurement
- OAE recording :
 - TEOAE
 - Click-synchronised SOAE
 - Olivocochlear suppression test

All tests were performed in the manner described in the Chapter 3 (3.3).

Data considered:

- TEOAEs: - The presence and the amplitude of overall response
 - The level of noise
 - The presence and the amplitudes (S/N ratio) per spectral bands centered at 1, 2, 3, 4 and 5 kHz
- SOAEs: The prevalence of SOAEs per ears/subjects in the groups of subjects
- Medial olivocochlear (MOC) suppression, as a reduction in TEOAE response under contralateral stimulation: the difference in TEOAE amplitudes without and with contralateral noise.

4.3.3 Results

Pure tone audiometry

The mean PTA thresholds of patients with tinnitus and control subjects were within normal range (Figure 4.3.1).

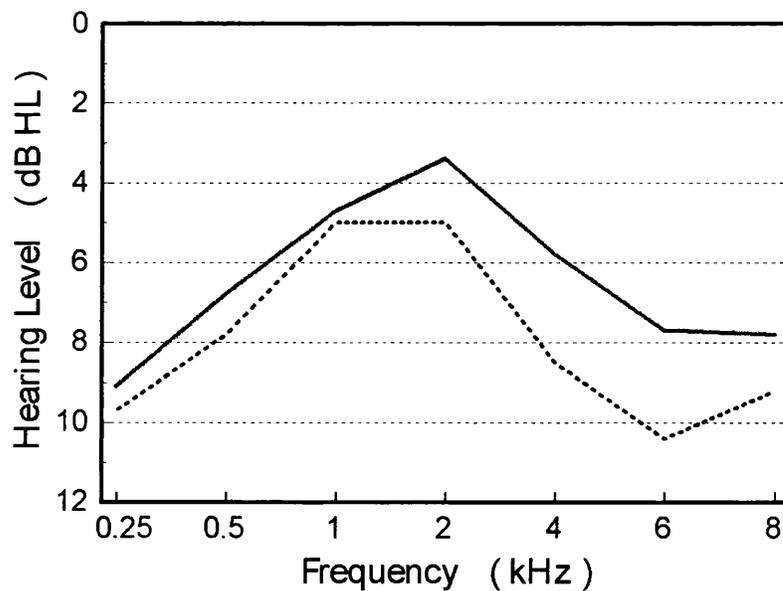


Figure 4.3.1: Mean pure-tone audiometric thresholds for tinnitus (dotted line) and control subjects (green line)

Tympanometry

The immittance measurements showed comparable middle ear pressure and acoustic compliance between patients and subjects, which also fall within normal range (Table 4.3.2).

Table 4.3.2: Tympanometric measurements in patients and control subjects

	<i>Mean middle ear pressure (daPa)</i>	<i>Compliance (ml)</i>	<i>Ear canal volume (cm³)</i>
Subjects with tinnitus	3.5 ± 9	0.6 ± 0.3	1.2 ± 0.5
Control subjects	2.4 ± 9	0.7 ± 0.4	1.3 ± 0.5

Otoacoustic emissions

Transient evoked emissions (TEOAEs)

TEOAE responses were present in all subjects of either group. However, response amplitudes in patients with tinnitus (13.2 ± 4 dB SPL), in comparison with those in the controls (9.5 ± 3 dB SPL), were significantly higher (Mann-Whitney U-test, $p < 0.001$), in the presence of comparable noise levels (Table 4.3.3).

Table 4.3.3: TEOAEs and noise levels in patients and control subjects

	<i>Mean TEOAE (dB SPL)</i>	<i>Noise (dB SPL)</i>	<i>TEOAE prevalence per ears (%)</i>
Subjects with tinnitus	13.1 ± 4	- 1.1 ± 2	100
Control subjects	9.5 ± 3	- 1.1 ± 2	100

Beside the overall TEOAE responses, TEOAEs were also present in all frequency bands centered at 1, 2, 3, 4 and 5 kHz in subjects of both groups, thus implying the absence of subclinical cochlear lesions. The amplitudes of the TEOAE responses per

frequency bands in patient with tinnitus were also higher than in control subjects, as shown in Figure 4.3.2.

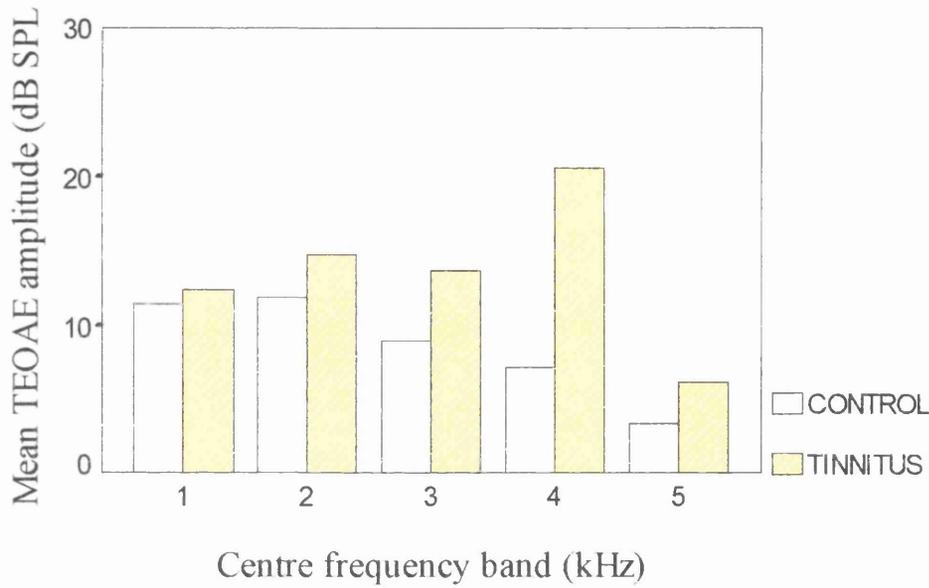


Figure 4.3.2: Mean TEOAE amplitudes (signal-to-noise ratio) in the frequency bands centered at 1, 2, 3, 4 and 5 kHz.

Spontaneous otoacoustic emissions (SOAEs)

The prevalence of SOAEs in patients with tinnitus was also significantly higher than in controls (Table 4.3.4).

Table 4.3.4: SOAE prevalence in patients and control subjects

<i>SOAE prevalence (%)</i>	<i>per ears</i>	<i>per subjects</i>
Subjects with tinnitus	85 *	93.3
Control subjects	48	66.6

* significant (χ^2 - test, $p = 0.0009$)

Medial olivocochlear suppression test

The result of suppression test show that in 63% of ears of patients with tinnitus (50% per subjects), reduction of TEOAE response amplitudes under contralateral acoustic stimulation was ≥ 1 dB, in contrast to those of controls, in all of whom the suppression was greater than 1 dB SPL in both ears (Table 4.3.5).

Table 4.3.5: TEOAE suppression in subjects with tinnitus and controls

<i>Suppression > 1 dB (%)</i>	<i>per ears</i>	<i>per subjects</i>
Subjects with tinnitus	63 *	50
Control subjects	100	100

* significant (χ^2 -test, p=0.0000)

Figure 4.3.3 shows otoacoustic emissions of a subjects with tinnitus, difficulty in hearing in background noise and hyperacusis, in whom very large TEOAE responses and strong SOAE were recorded. In this subject with normal audiometric thresholds and tympanometric measurements, a reduced MOC suppression was obtained (Table 4.3.6).

Table 4.3.6: PTA thresholds, tympanometric measurements and TEOAE suppression values in a subject with tinnitus and normal hearing

<i>PTA thresholds (dB HL)</i>	<i>0.25</i>	<i>0.50</i>	<i>1</i>	<i>2</i>	<i>4</i>	<i>6</i>	<i>8 kHz</i>
Right ear	5	0	-5	-5	0	0	0
Left ear	5	5	-5	-5	0	0	5

<i>Tympanometric measurements:</i>	<i>Canal volume (cm³)</i>	<i>Middle ear pressure (daPa)</i>	<i>Compliance (ml)</i>
Right ear	0.9	5	0.4
Left ear	0.8	0	0.5

Medial olivocochlear suppression (dB): Right ear 0.7
Left ear 0.2

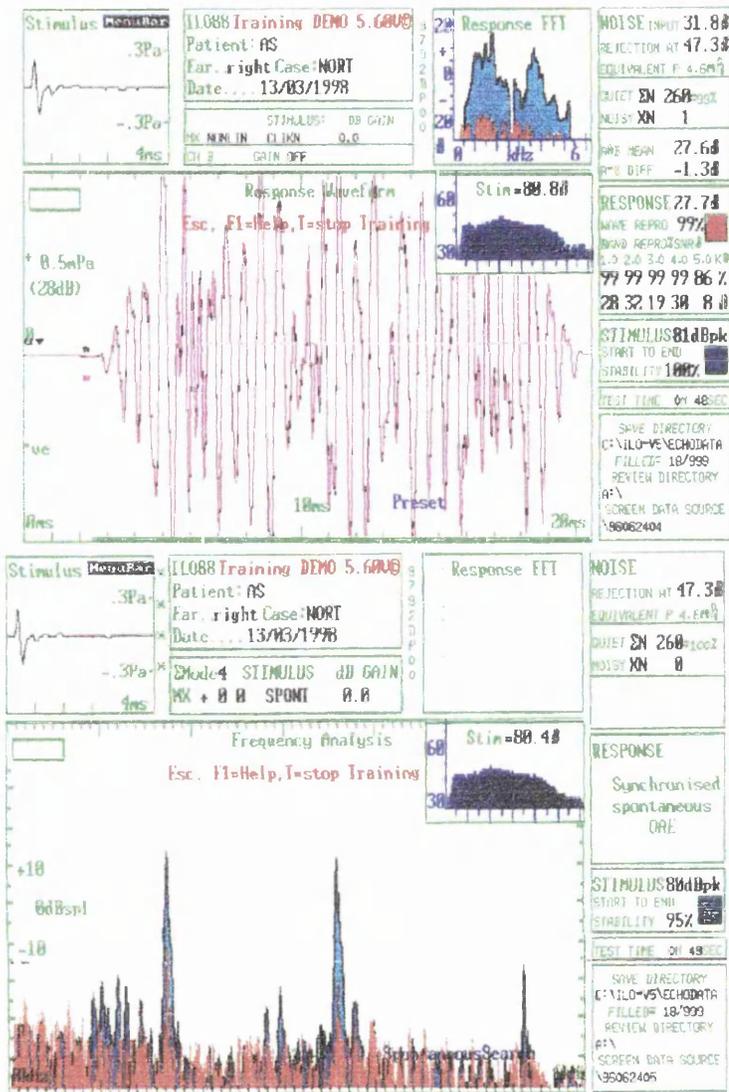


Figure 4.3.3: An example of otoacoustic emissions (right ear only shown) in a subject with normal hearing and tinnitus, without identified underlying pathology

All patients, regardless of the results of the MOC suppression, demonstrated similar characteristics with respect to the size of TEOAE amplitudes and the SOAE prevalence.

4.3.4 Discussion

This study examines a population of tinnitus patients in whom a cochlear lesion could not be identified, and furthermore, there was no hypothetical cause of tinnitus. In that respect, the underlying mechanism(s) of tinnitus generation in these patients appeared to be outside the auditory system, as assessed by standard means, in contrast to the usual

concept of tinnitus generation, which assumes the existence of a lesion in the auditory system as a prerequisite for the generation of this symptom. It is most frequently considered that a lesion, leading to the perception of tinnitus, is located in the cochlea (Tonndorf, 1980; McFadden, 1982; Lenarz, 1993). Even in cases in which conventional method for the evaluation of normal cochlear function, the pure-tone audiometry, fails to demonstrate a cochlear lesion, other techniques, e.g. the audioscan, which tests 64 frequencies within an octave, may help to identify subtle cochlear lesions, which could be a basis for the generation of tinnitus. For instance, Sirimanna et al. (1996) found that 96% of patients with tinnitus (n=26) and normal audiometric thresholds, exhibited notches between 0.25 and 8 kHz on the audioscan. Otoacoustic emissions provide another technique to detect cochlear lesions before they are clinically discernible, and they are, therefore, used in this study to extend the criteria for normal hearing.

In all subjects in this study, hearing was judged to be normal on the basis of normal hearing thresholds on standard pure-tone audiometry (thresholds < 20 dBHL, 0.25 -8 kHz), and the presence of TEOAE responses (signal-to-noise ratio) in all frequency bands (1, 2, 3, 4 and 5 kHz). This implied the absence of cochlear lesion in all subjects included in this study.

The two groups of subjects, with and without tinnitus, who exhibited normal hearing as defined above, were compared with regard to the cochlear dynamics and the medial olivocochlear (MOC) function.

TEOAE responses, overall and in the frequency bands, were found to be *present* in subjects of both, tinnitus and non-tinnitus, groups. However, TEOAE response *amplitudes* were significantly higher in tinnitus patients (13.1 ± 4 dB SPL) than in control subjects (9.5 ± 3 dB SPL). The group with tinnitus also exhibited a significantly higher prevalence of SOAE (93.3%) than the control group (66.6%), of which the latter is in agreement with the values reported by other authors (Probst et al., 1991).

With regard to the MOC function, in all normal subjects MOC suppression effect was equal or greater than 1 dB, and, therefore, 1 dB-value was used as a cut-off point above which the suppression effect was considered normal, and below was considered abnormal (reduced or absent suppressive effect). A reduced or absent MOC suppression was found in a significant number of patients with tinnitus (50%), in comparison with the normal control group.

The findings of the greater TEOAE response amplitudes, higher prevalence of SOAE and reduced/absent MOC suppressive effect in significant number of the patients with tinnitus, in comparison with normal control subjects, may imply a functional difference in the cochlea of the two groups. This difference in cochlear dynamics raises the suspicion of malfunction (disinhibition) in the efferent control of cochlear mechanics in the tinnitus group, with subsequently higher gain in cochlear function. The cause(s) of such malfunction is open to speculations.

It has been suggested (e.g. Hazell, 1995; Hinchcliffe and King, 1992; also in the sections 1.1.2 and 1.2.3), on the basis of circumstantial evidence, that the occurrence of tinnitus in many cases was related to the stress and various psychological phenomena. Given the extent of the connections between the auditory and other parts of the central nervous system (section 1.2.6), particularly those responsible for emotional states and adaptation to stress (e.g. limbic system and hypothalamus) and the variety of neurochemical responses (1.2.7), it is possible that the emergence of tinnitus in such cases could be based on an imbalance in the central inhibitory/excitatory mechanisms and/or the alterations in the neurochemistry, without structural lesions. As a result, an alteration in cochlear function, through the neural multisynaptic efferent (1.2.5.2), and/or humoral (1.2.7) systems, may occur, with further consequences on the auditory function.

Dysfunction (disinhibition) in the efferent control may create a physiological basis for some auditory phenomena. In a similar way, as described in the previous study (4.2), tinnitus could be explained by the altered excitatory input to the afferent system by increased gain in the cochlear activity. Likewise, the difficulty in listening against background noise may be due to reduced ability for fine frequency tuning, “focusing” of sound, the characteristic attributed to the OHCs, whose activity is modulated through the MOC system. Physiological basis for some other auditory complaints, such as sound distortion, “echoing sounds”, or “beats”, could be created by mutual interaction between SOAE components (distortion products), as well as their interaction with external sounds (e.g. synchronisation, phase locking). These phenomena, which will be further elaborated in the next study (4.4.1), may give another dimension to the feedback process between the cochlea and the central nervous system.

As mentioned above, the majority of the subjects with tinnitus in this study had other auditory symptoms, including difficulty in hearing in background noise. In the absence of an identifiable auditory lesion, at least by the methods used in this study, some of these cases could have been diagnosed as a condition referred to as an entity and termed “King-Kopetzky syndrome” (King, 1954; Kopetzky, 1948) or “obscure auditory dysfunction” (OAD) (Saunders and Haggard, 1989). However, using OAE methods as described above, it would be possible, in some cases, to obtain information suggesting cochlear (auditory) dysfunction, in the context of the above hypothesis for explanation of the auditory phenomena in subjects without apparent lesions.

Otoacoustic emissions may help either detect a subtle structural cochlear lesion, which may lead to secondary, ascending changes in the auditory system (described in the next study, 4.4.2), or to identify functional changes with an increased gain in cochlear micromechanics, resulting from the descending effect of the CNS changes, which are suspected to underlie tinnitus and other auditory symptoms in patients of this study. Either of these mechanisms may be related to the generation of tinnitus in subjects with normal hearing, as judged by the standard pure tone audiometry.

4.4 TINNITUS FOLLOWING NOISE EXPOSURE

Noise is an environmental factor which interacts with the cochlea in a very complex and specific manner (Chapter 1, 1.2.2/ 1.2.3). Cochlear mechanics may interact directly with noise well below a hazardous level, without causing a significant cochlear pathology, and this interaction could be a basis for the perception of tinnitus. However, when noise exceeds the physiological working range of the cochlea, causing irreversible pathological alterations in the cochlea and other parts of the auditory system, tinnitus may result from more complex, direct and indirect interactions.

Therefore, two studies have been undertaken to examine the relationship between cochlear mechanics and noise, and their relevance to tinnitus:

- I. A study in subjects with normal/ near normal hearing in whom tinnitus could be triggered, or if present, aggravated by environmental noise, by which normal subjects are unaffected (4.4.1)

- II. A study on tinnitus in subjects with noise-induced hearing loss (4.4.2)

4.4.1 Noise-related tinnitus in subjects with normal hearing

4.4.1.1 Introduction

The interaction between cochlear mechanics and external noise, leading to the perception of tinnitus, is probably related to the presence of “overactive” cochlear elements (i.e. sections of individual amplifier with increased gain), of which spontaneous otoacoustic emissions (SOAEs) are the most likely expression. SOAEs can be the basis for “spontaneous” tinnitus in a small proportion of tinnitus population (about 4%; reviewed in the section 2.1.1), but can also be responsible for “mechanical”, sound-evoked, tinnitus. The latter is the subject of this study.

The phenomenon of the interaction between external and hypothetical “internal” sounds had been known long before SOAEs were demonstrated (Kemp, 1979).

In 1931, in his classical paper on tinnitus, following experiments on his own tinnitus, Wegel described a perceptual experience of “beats” on the introduction of a test tone. Flottorp (1953) and Ward (1955) have also demonstrated that external pure tone can elicit sensation of “beats” when a single tone near the frequency of the “idiotone”, presumably SOAE, was presented, and that the beat rate depended on the intensity of the external tone. Flottorp, therefore, concluded that “idiotone makes itself known by interfering with the stimulus tone”.

Following the introduction of otoacoustic emissions (OAEs), Zurek (1981) in his experiments, also experienced “beats”, but he was able to demonstrate acoustically the temporal variation of the “beats”, *synchronised* SOAE, by changing the sound pressure of the acoustic input at the frequency of his own SOAE.

Wilson (1980) and Wilson and Sutton (1981) have demonstrated that the synchronisation may occur following pure tone, click, or tone-burst stimuli, at relatively low level of stimulation (around 25 dBSL) and that SOAE “would be forced to oscillate at the same frequency as the stimulus, i.e. its frequency would be ‘pulled in’”. At a stimulus intensity level just below this, phase-locking will occur for certain period; then, influences such as noise, change in sensitivity etc., will allow the emission to escape control and to oscillate at its natural frequency until phases are sufficiently close for locking to be re-established.

This process repeats in an irregular manner and explains why beats between tinnitus and an external tone are irregular and slower than would be usually expected for independent oscillations”.

Flottorp (1953) and Ward (1955) have described a condition in which a pure tone does not sound ‘pure’, but elicits a sensation of multiple tones. This distortion was apparent at low sound pressures, but above an upper limit, which depended on the frequency of tone, the sensation was no longer distorted, and was that of a pure tone. The multitonality that arises from single-tone stimulation (monaural diplacusis) can now be understood as being *combination tones (distortion products)*, resulting from two tones, primaries, at closely-spaced frequencies f_1 and f_2 , one corresponding to the SOAE and the other to an external tone, as described the section 1.3.4.3. Zurek (1981), again, in addition to his perceptual experience, was able to demonstrate this phenomenon acoustically, as distortion products, generated through the interaction of the external tone and his SOAE.

In his experiments with brief exposure (16-30 seconds, 100-110 dB SPL) to tones just below the SOAE frequency, Kemp reported (1982) systematic changes in SOAE frequency (shifting) and amplitudes - a biphasic effect, with a brief period of inhibition, followed by an enhancement, which coincided with the perception of tinnitus. These observations showed that noise can produce a temporary state in which cochlear mechanical activity (and hence cochlear mechanical tinnitus) can be *suppressed* or *enhanced*. *Sustained oscillations* which might be due to mechanical instability, have been demonstrated by recording emissions in post-noise-exposure tinnitus.

It is apparent that a multitude of possible interactions of “overactive” cochlear elements and external noise may occur. Some other forms of interactions, such as contralateral effect of noise, are not discussed at this point. Binaural exposure to noise in normal environmental conditions is assumed, and additional contralateral effects of noise make the relationship between the external noise and cochlear mechanics even more complex. It is also very likely that a perceptual experience corresponding to the interaction of external sounds and “overactive” elements in tinnitus patients, in whom an altered spontaneous auditory activity and/or imbalance in inhibitory/excitatory mechanisms may exist, could be even more pronounced. These phenomena may help to understand why some subjects are affected by environmental noise, well below a hazardous level, leading

to the complaints such as induced or prolonged tinnitus, sound distortions, or “echoing” tinnitus.

Therefore, the aim of this study is to identify the characteristics in cochlear dynamics, which would make some individuals more susceptible to different, low-level (non-hazardous) noise-related auditory complaints.

4.4.1.2 Material and methods

Subjects

This study included subjects with self-reported tinnitus, triggered or aggravated by external noise, at a level which does not cause a significant cochlear damage, as demonstrated by normal/near normal hearing, judged by the pure tone audiometry (≤ 25 dBHL). Some of them have reported additional auditory complaints, such as “distortion”, “beats”, or “echoing” sounds. They were compared with the control group, which included normal subjects without tinnitus or other auditory complaints, matched for gender and age (Table 4.4.1).

Table 4.4.1: Subjects included in the study

<i>Subjects</i>	<i>number</i>	<i>age (years)</i>
With tinnitus triggered/aggravated by noise:	27 (18F, 9M)	36 \pm 9
Normal subjects:	26 (17F, 9M)	35 \pm 10

As the information on noise exposure and auditory complaints was obtained from the subjects, a direct, objective effect of noise exposure on either group could not be evaluated. However, the comparison between the groups may be useful to identify possible difference in cochlear dynamics, which would make some subjects more susceptible to the noise-related auditory experience.

All subjects included in the study complied with the general inclusion criteria (3.1). The strict criteria for hearing normality, as in the two previous studies, were not applied here. There were also no aetiological consideration with respect to tinnitus in these patients.

Protocol

The subjects underwent the protocol as described in the section 3.2.2, which included:

- Pure tone audiometry
- Impedance measurement
- OAE recording : - TEOAEs
 - Click-synchronized SOAEs
 - Olivocochlear suppression test

All tests were performed in the manner described in the Chapter 3 (3.3).

Data considered:

- TEOAE: - The presence and the amplitude of overall response
 - The level of noise
- SOAE: The prevalence of SOAEs per ears/subjects in the groups of subjects
- Medial olivocochlear (MOC) suppression, as a reduction in TEOAE response under contralateral stimulation

4.4.1.3 Results

Tympanometry

Subjects of both groups had normal tympanometric measurements and results were comparable between the groups (Table 4.4.2).

Table 4.4.2: Tympanometric measurements in subjects with tinnitus and controls

	<i>Mean middle ear pressure (daPa)</i>	<i>Compliance (ml)</i>	<i>Ear canal volume (cm³)</i>
Subjects with tinnitus	3.9 ± 8	0.6 ± 3	1.1 ± 0.3
Normal subjects	2.7 ± 8	0.7 ± 3	1.3 ± 0.3

Otoacoustic emissions

In subjects with tinnitus, significantly higher TEAOE response amplitudes, in the presence of comparable noise levels, were recorded, with higher prevalence of SOAEs than in normal subjects (Table 4.4.3).

Table 4.4.3: TEOAEs, noise levels and SOAE prevalence in tinnitus and normal subjects

	<i>Mean TEOAE (dB SPL)</i>	<i>Noise (dB SPL)</i>	<i>SOAE prevalence per ears/subjects (%)</i>
Tinnitus	13.6 ± 4 *	0.6 ± 0.3	85**/ 96
Normal subjects	10.9 ± 3	0.7 ± 0.4	56 / 65

significant, *(Mann-Whitney U-test, p = 0.0027) **(χ^2 – test, p = 0.0012)

Medial olivocochlear suppression test showed reduced/absent suppression (<1dB) in 62% subjects with tinnitus, while in all normal subjects suppression was found to be normal (≥ 1 dB) (Table 4.4.4).

Table 4.4.4: TEOAE suppression values in subjects with tinnitus and controls

<i>Suppression ≥ 1 dB (%)</i>	<i>per ears</i>	<i>per subjects</i>
Subjects with tinnitus	52*	38
Control subjects	100	100

* significant (χ^2 – test, p = 0.0000)

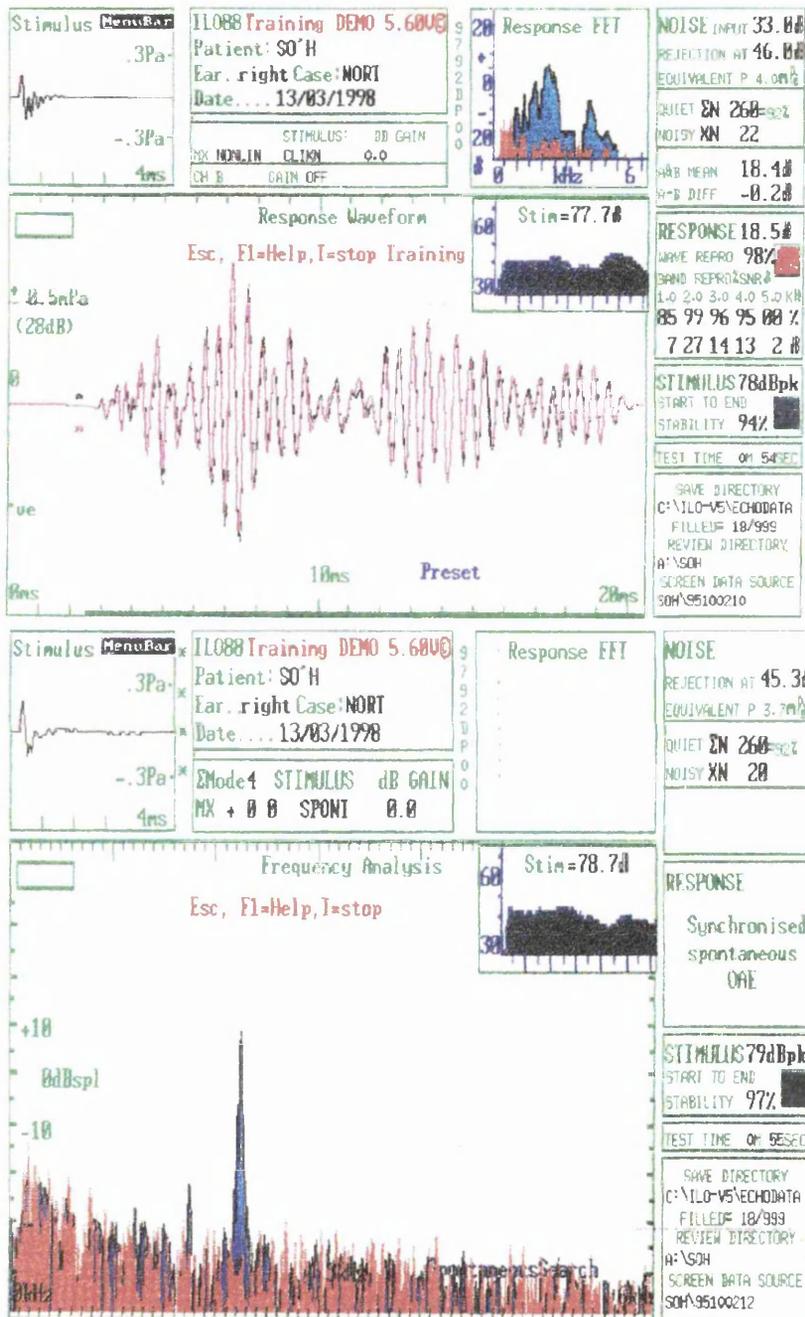
As an example, in Figure 4.4.1, otoacoustic emissions of a 36 years old man, with enhanced tinnitus and a sensation of “echoing” in noisy environment, in whom strong SOAE and large TEOAE responses, with entrained “beats” were recorded, are presented. In this subject with a reduced MOC suppression, normal audiometric thresholds and tympanometric measurements were obtained (Table 4.4.5).

Table 4.4.5: PTA thresholds, tympanometric measurements and TEOAE suppression values in a patient with enhanced tinnitus and a sensation of “echoing” in a noisy environment

<i>PTA thresholds (dB HL)</i>	<i>0.25</i>	<i>0.50</i>	<i>1</i>	<i>2</i>	<i>4</i>	<i>6</i>	<i>8 kHz</i>
Right ear	15	10	-5	0	0	5	10
Left ear	5	5	5	-5	5	0	-5

<i>Tympanometric measurements:</i>	<i>Canal volume (cm³)</i>	<i>Middle ear pressure (daPa)</i>	<i>Compliance (ml)</i>
Right ear	0.9	0	0.4
Left ear	1.1	15	0.5

Medial olivocochlear suppression (dB): Right ear: 0.7
 Left ear: 0.7



4.4.1: Otoacoustic emissions (only in the right ear shown), with sustained oscillations of TEOAE response and strong SOAE in a subject with the sensation of enhanced, “echoing” tinnitus in noisy environment

4.4.1.4 Discussion

In subjects with tinnitus triggered/aggravated by noise, a significantly higher prevalence of SOAEs, higher TEOAE response amplitudes and reduced/absent suppressibility of TEOAE under contralateral stimulation in comparison with normal control subjects, were found. These findings may be indicative of cochlear hyperactivity, which may be due to disinhibition of efferent suppression, and the presence of “overactive” cochlear elements, expressed as SOAEs, and/or large TEOAE responses. Therefore, it appears that subjects with these findings are more susceptible to different auditory perceptions caused by noise, which otherwise does not cause any measurable damage to the cochlea.

Patients with tinnitus and other auditory symptoms affected by external noise, have exhibited OAE features suggestive of altered signal processing at the level of the cochlea (i.e. reduced ability to attenuate external sound was demonstrated in a significant number of subjects in tinnitus group (62%) and due to an higher gain in the cochlear amplifier, may lead to an enhanced afferent excitation. Tinnitus induced by noise and enhanced tinnitus in subjects who already had tinnitus, or other auditory sensations, may arise due to interaction between “overactive” elements and external noise. The noise may act as a source of energy to set the cochlea into a state of mechanical instability and sustained oscillations of the “overactive” elements, in a similar way as suggested by Kemp (1982), with the corresponding perception of tinnitus. Direct interaction between “overactive” elements may lead to the sensation of “beats” or “sound echoing”, as the perceptual correlates of the synchronisation/phase-locking of SOAE by external sounds. A perception of sound distortion (monaural diplacusis), may result from the frequency intermodulation of SOAE and external sound, as discussed in the introduction to this study.

The perceptual phenomena in subjects presented in this study, during/following noise exposure, when active cochlear elements directly interact with external noise, could be, therefore, explained within the framework of “mechanical” tinnitus (1.1.4.1).

The recognition of these phenomena may have practical implications in the treatment of some patients with tinnitus: their active cochlear elements may interact with external

noise, and, therefore, they may not be good candidates for the application of tinnitus masking devices. Another practical aspect in identifying these cases is the value of positive counselling, as a surprisingly good effect can be achieved by the appropriate explanation of these phenomena to the patient.

4.4.2 Tinnitus following noise-induced hearing loss

4.4.2.1 Introduction

A number of studies have demonstrated that noise exposure produces morphological and functional changes at different levels of the auditory system (Borg et al., 1995), and therefore, both, peripheral and central mechanisms, which may lead to the generation of tinnitus, will be considered. Owing to the mechanical force of noise exposure, the most extensive morphological changes are expected to occur in the cochlea. As it will be discussed later in this introduction, there is evidence that noise exposure alters cochlear mechanics, either directly or through the complex feed-back mechanisms, involving the medial olivo-cochlear efferent system, in such a way to precipitate the emergence of overactive cochlear elements, spontaneous or evoked, which may be a basis for perception of tinnitus.

Epidemiology of tinnitus following NIHL

Some reports on the epidemiology of tinnitus suggest that exposure to excessive noise is the most common cause of tinnitus. According to Axelsson (1992), in 411 consecutive tinnitus patients, tinnitus was attributed to noise-induced hearing loss (NIHL) in 28% of cases. Furthermore, in a study by Penner (1990), noise exposure was the most frequently suspected cause of tinnitus, in 42% cases (n = 96).

Different factors may influence the incidence of noise-related tinnitus, such as the level of threshold shift, duration or type of noise exposure (impulse vs. continuous noise), or age of an individual. The reports on age as a risk for the occurrence of tinnitus following noise exposure are controversial. In a study by Coles (1984), which did not control hearing loss, it was found that a history of noise exposure carries a 1.7 risk factor of accompanying tinnitus and this risk factor is raised to 2.0 for subjects over 40. However, Chung et al. (1984), in a study conducted only among male subjects, concluded that tinnitus is associated with age because of its association with hearing loss and that age *per se* is not a factor in tinnitus. These authors considered hearing thresholds to be most

important factor with respect to presence of tinnitus and reported that an increasing hearing threshold is followed by an exponential increase of tinnitus presentation.

The practical implication of the association of tinnitus and noise exposure is in the occurrence of tinnitus in subjects exposed to occupational noise. According to McShane et al.(1988) the prevalence of tinnitus in industrial hearing loss complainants is reported to be 34% in a population exposed for up to 10 years, and about 50% in those exposed to noise 11-30 years. This may be a consequence of cumulative effect of the total noise exposure, but it may also be attributed to the aging effect, and/or various additional aetiologies. Beside the length of time of noise exposure, there are indications that the type of noise to which subjects are exposed may be of importance for the prevalence of tinnitus: tinnitus is found to be more common following exposure to impulse than to continuous noise (Man and Naggan, 1981). It may be assumed that this difference in tinnitus prevalence results from a higher risk for hearing loss from impulse than continuous noise and consequent difference in hearing thresholds. However, Alberti (1987) has found that in subjects with similar audiometric patterns, tinnitus occurred in 63-70% of subjects exposed to impulse noise and 47-57% of subjects exposed to continuous noise. An interesting hypothesis to explain the higher prevalence of tinnitus following impulse noise has been suggested by Møller (1984). Namely, impulse noise, which exerts a greater direct mechanical effect than continuous noise, may cause structural damage to the sensory epithelium which in turn causes breakdown of the electrical insulation between the hair cells without necessarily damaging them. This leads to abnormal communication between the hair cells, synchronisation of their activity and, subsequently, tinnitus. The selective damage of electrical insulation of the hair cells (or auditory nerve fibres) without their damage, may also be an explanation for the presence or absence of tinnitus in subjects with the same audiometric thresholds.

Epidemiological studies by Coles et al., (1990) suggest that there is a *growing* number of subjects complaining of permanent tinnitus as a result of long-term exposure to occupational noise. However, the question whether there is a *real* increase in the number of individuals with tinnitus or it is the case of increased *awareness* of tinnitus, remains unanswered.

The results of extensive investigations (Luz and Hodge, 1971; Henderson et al., 1974; Cody and Johnston, 1980; Henderson et al., 1994), suggest that the effect of impulse noise on the cochlea differs considerably from that of continuous (steady-state) noise exposure, and there is a general view that impulse noise exerts a more direct mechanical effect, whereas the effect of steady-state noise may be more related to metabolic factors. This difference may constitute a higher risk to hearing from impulse than continuous noise of corresponding total sound energy, and that the hazard of impulse noise does not follow the “equal energy rule”, i.e. equal noise energy produces the same hearing loss, which is applicable to continuous noise (Henderson et al., 1974; Nilsson et al., 1980; Dieroff, 1980; Henderson and Hamernik, 1986; Price, 1989). The physical characteristic which makes impulse noise more injurious is the very high sound pressure level (160-190 dB SPL), in firearms shots (Ylikoski, 1989) of very short duration, resulting in a corresponding power spectrum with its peak in the high frequency (Brüel, 1980). Beside peak sound pressure level and duration, other factors, such as frequency spectrum, energy content, presentation manner (number of impulses, inter-impulse intervals), reverberation factor, individual susceptibility, are of importance in impulse noise exposure.

There is evidence from animal histological studies, that impulse noise causes greater loss of outer hair cells (OHCs) in comparison with the inner hair cells (IHCs) (Henderson et al., 1974; Hamernik et al 1980; Henderson et al., 1994, etc.), and that there are sharply demarcated, focused on OHCs, lesions (Cody and Johnston, 1980; Price, 1989). Similar selective changes may occur in the human cochlea, which can be explored using otoacoustic emissions (OAEs), known to be the only objective and non-invasive means of studying active cochlear mechanics and OHC activity. Conventionally, noise trauma is quantified by auditory threshold shifts and, therefore, subclinical cochlear lesions have not been identified.

In the auditory system, the cochlea demonstrates the most extensive morphological changes secondary to noise overexposure. The active cochlear mechanisms, involving outer hair cells (OHCs) are particularly vulnerable to the mechanical effect of the noise, which may be exerted to a greater extent in impulse, than in continuous noise, as discussed above. Consequently, the predominant lesion is in the OHCs, in comparison with the IHCs, may lead to dysfunction of cochlear mechanics and, possibly, contributes to the generation of tinnitus.

In a number of studies, OAE findings have confirmed the vulnerability of OHCs, providing early evidence of a cochlear lesion, even before any demonstrable audiometric changes. This is manifest by the reduction or absence in OAE responses, affecting primarily frequencies > 2kHz, thus narrowing the frequency spectra of evoked emissions (Hotz et al., 1993; Reshef et al., 1993; Prasher et al., 1994b; Ceranic et al., 1995b).

There is also evidence to suggest that noise exposure, may alter cochlear mechanics of the remaining “intact” OHCs, secondary to the OHCs lesion. This is expressed by the presence of “overactive” cochlear elements, spontaneous emissions and enhanced evoked emissions, in the frequency region corresponding to the point of onset of noise-induced hearing loss (NIHL) (Wilson and Sutton, 1981; Wilson, 1987), and sustained oscillations following transient stimuli (Norton et al., 1990), which are characteristic of the subjects with tinnitus. These “overactive” elements may correlate to the perception of tinnitus and could result from the heterogeneous activation of the efferent system or the “edge effect” following localised cochlear damage, alteration in the efferent activity in general, or even reduction around tinnitus frequencies (Hazell, 1987; Chéry-Croze et al., 1993; Attias et al., 1996a).

Noise exposure may also be responsible for “pathological” SOAEs, induced experimentally by impact noise (in chinchilla, Zurek and Clark, 1981; Powers et al., 1995). This allows further speculations on the practical implication of noise-related SOAEs on tinnitus.

However, the presence of overactive cochlear elements in subjects with tinnitus, who have been exposed to noise, has been demonstrated in individual cases, or in small groups of cases (Wilson and Sutton, 1981; Wilson, 1987; Norton et al., 1990). Several larger studies (see below) have failed to identify evidence to support the view that noise

exposure causes SOAEs or enhanced EOAEs in significant number of subjects. On the contrary, a low prevalence (about 7%, n=40, Penner, 1990; 14%, n= 48, Ceranic et al., unpublished data) or absent SOAE (n= 13 , Probst et al., 1987) has been found in subjects with NIHL. Similarly, several studies (Hotz et al., 1993; Prasher et al., 1994b; Reshef et al, 1993) have demonstrated a reduction in EOAE responses in subjects, who had been exposed to an unspecified type of noise, in comparison with the control group. Nevertheless, a small study (n=20) including an homogenous group of subjects exposed to impulse noise only (Ceranic et al., 1995b), showed a 40% prevalence of subjects with recordable SOAE. Another study by Collet et al. (1991), which included subjects with NIHL (n=109), with no reference to the type of noise exposure, showed *greater* intensity of EOAE than in subjects with sensorineural hearing loss (SNHL) of different (unspecified) origin. This may be an indication of the possible difference in the cochlear mechanics between subjects exposed to impulse and continuous (or mixed) noise, and between NIHL and high-frequency SNHL of different, e.g. genetic origin.

Efferent control of cochlear mechanics in NIHL

It has been speculated that functional dissociation of OHCs and IHCs, following damage of OHCs (Spoendlin, 1987) due to noise exposure, may trigger heterogeneous activation of the efferent system (Hazell et al., 1985), as suggested in the previous section. This finds support in the common observation that tinnitus pitch corresponds to the slope of hearing loss (Penner, 1980; Hazell, 1987).

Several studies on the function of the efferent system (VeUILlet et al., 1991; Chéry-Croze et al., 1994a,b; Graham and Hazell, 1994) have suggested a dysfunction of the medial olivocochlear efferent system in tinnitus patients, predominantly disinhibition, specifically around the frequency of tinnitus pitch (Chéry-Croze et al., 1993). A recent study by Attias et al. (1996a), which included NIHL (n=14) and normally hearing (n=8) subjects with tinnitus, in some cases demonstrated an *increase* of transient evoked otoacoustic emission levels under contralateral acoustic stimulation, particularly at lower intensities, in comparison with subjects of similar groups without tinnitus. It was proposed that this finding might reflect a global efferent dysfunction, rather than a specific medial olivocochlear system abnormality.

Retrocochlear findings following NIHL

Different morphologic and neurophysiologic changes in the central auditory system, following noise exposure, have been observed (Salvi et al., 1992). These changes, which may be of relevance in the generation of tinnitus, do not simply mirror peripheral damage. Noise-induced cochlear lesions alter the activity in the *auditory nerve* and increase excitability of the *cochlear nucleus, inferior colliculus (IC)* (Willot and Lu, 1982; Salvi and Ahroon, 1983) and *medial geniculate body* (Gerken, 1979). Since the IC is the obligatory relay for the ascending auditory pathway (Huffman and Henson, 1990) this may cause an imbalance between excitatory and inhibitory mechanisms, mediated by the neurotransmitters of auditory pathways, such as glutamate, glycine, acetylcholine or GABA.

Studies of the auditory *cortical neurons* have indicated changes in their frequency selectivity. Reduced afferent input, due to noise-induced cochlear lesions, initiates a sequence of changes in the relative levels of excitatory and inhibitory inputs to the primary auditory cortical neurons. This leads to expansion of the receptive field (located in the cochlea, adjacent to the damaged region) of the cortical neurons (Rajan, et al., 1992), which in turn raises the threshold sensitivity and broadens frequency selectivity. Restricted noise-induced damage to the cochlea also produces a tonotopic reorganisation of the *receptor surface in the primary auditory cortex*. The area in the auditory cortex deprived of its characteristic frequency peripheral input acquires a new characteristic frequency, of that at the edge of the region of cochlear damage (Robertson and Irvine, 1989; Schwaber et al., 1993). In other words, noise-induced changes to the cochlea lead to an expansion of the cortical representation of a restricted frequency band adjacent to the region of the cochlear loss. Such plasticity of frequency selectivity and auditory maps may alter perceptual function, and, therefore, may contribute to the emergence of tinnitus.

Information processing in the CNS has been shown to be affected in patient with tinnitus following NIHL, as measured by auditory and visual event-related potentials (Attias et al., 1993b, 1996b; Attias and Bresloff, 1997), contingent negative variation (Hoke and Hoke, 1997), neuromagnetic fields (Hoke et al., 1989; Shiomi et al., 1997b) etc. (section 1.1.5.2, Recording of tinnitus-related neural activity).

The study aim

This study was aimed at examining cochlear mechanics in tinnitus following NIHL. First, an attempt was made to identify general characteristics of cochlear mechanics following impulse, as oppose to, predominantly continuous noise. Second, the subjects with tinnitus were compared with those without tinnitus, to find potential differences which may result from the altered cochlear mechanics following exposure to noise, as well as the differences which may arise due to the type, impulse or continuous, of noise. Specifically, the presence of “overactive” elements, enhanced TEOAEs and SOAEs, in the slope of the power spectrum, near the suspected noise-induced cochlear lesion, has been systematically investigated.

4.4.2.2 Materials and methods

Subjects

This study has included subjects with NIHL, with and without tinnitus, who were further divided into two subgroups: subjects who had been exposed to impulse noise (military or recreational shooting) and those predominantly exposed to continuous noise (industrial noise). The control group comprised normal subjects. The summarised data were presented in Table 4.4.1.

All normal subjects complied with the general inclusion criteria (section 3.1).

Subjects with NIHL had an “island” of normal hearing, which was defined as audiometric thresholds with at least one test frequency within normal range.

Tympanometric measurement were normal in all subjects.

Table 4.4.6: Summary data on the subjects with impulse and steady noise-induced hearing loss and normal subjects

	<i>Number of ears</i>	<i>Age (years)</i>
Subjects with NIHL and tinnitus (37)	59	45±9
<i>impulse noise</i>	28	.
<i>continuous noise</i>	31	
Subjects with NIHL and no tinnitus (36)	58	42±9
<i>impulse noise</i>	30	
<i>continuous noise</i>	28	
Normal subjects (30)	60	43±10
Total number of subjects exposed:		
- to impulse noise (29)	58	
- to continuous noise (32)	59	

Male subjects dominated in all groups: 90% in normal, 100% in impulse and 93% in continuous noise group.

Methods

A routine protocol, as described in Chapter 3 (3.2.2) was applied in this study.

Otoacoustic emissions, TEOAEs and SOAEs were recorded using standard procedures (section 3.3.3).

Data analysis

The analysis of the data was performed in three directions:

- I. Subjects exposed to impulse versus continuous noise vs. normal subjects
- II. Subjects with NIHL: tinnitus versus non-tinnitus
- III. Subjects with tinnitus: impulse versus continuous NIHL

The following data were analysed:

- TEOAE and noise overall responses (Analysis I, II, III)
- TEOAE - 1/3-octave band analysis of the power spectra from 1 to 4 kHz (Analysis I)
 - Responses in the last four 1/3-octave bands of the power spectrum, nearest to the slope in the TEOAE power spectrum, with the points B1, B2, B3 and B4, as the centres of the bands, exemplified in Figure 4.4.2 (Analysis II, III)
- SOAE - Prevalence (Analysis I, II, III)
 - 1/3-octave band analysis (Analysis I)

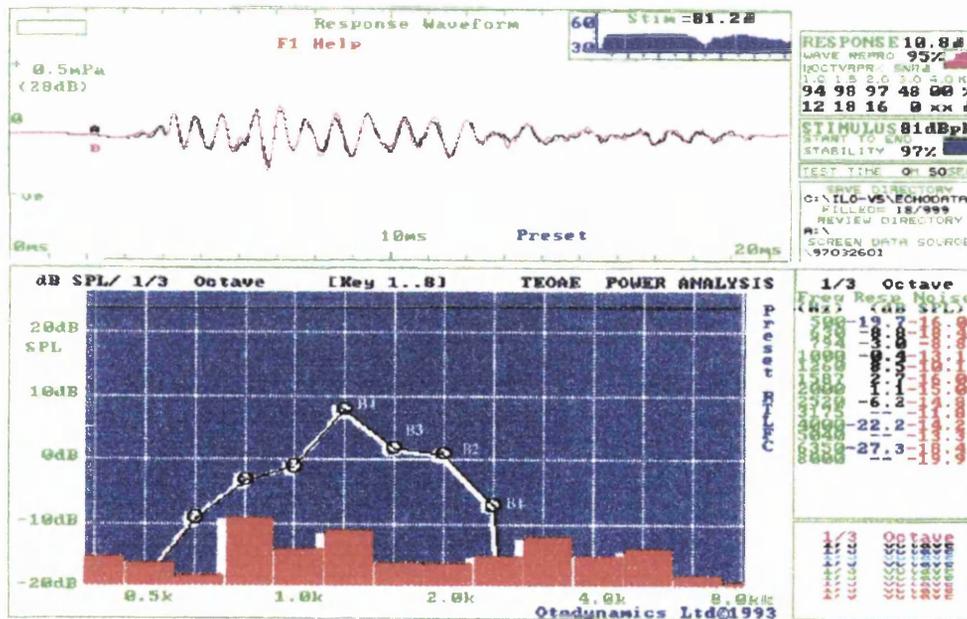


Figure 4.4.2: Spectral analysis of the slope in TEOAE power spectra, near suspected noise-induced cochlear lesion, using 1/3 octave bands centered at B1, B2, B3 and B4

4.4.2.3 Results

I. Subjects exposed to impulse v. continuous noise v. normal subjects

Pure tone audiometry

Results of PTA confirmed normal threshold levels in subjects of the normal group. Subjects in the noise groups exhibited a characteristic NIHL audiometric pattern with the presence of an “island” of normal hearing at lower frequencies, as illustrated in Figure 4.4.3.

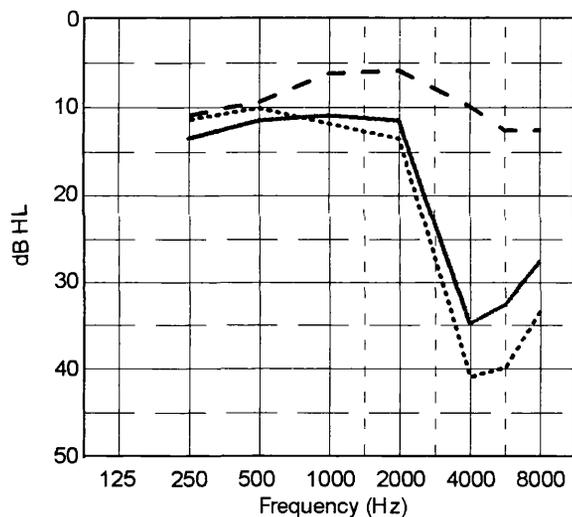


Figure 4.4.3: Mean audiometric thresholds for normal subjects (interrupted line) and, impulse (dotted line) and steady (green line), noise-induced hearing loss groups

Transient evoked emissions (TEOAEs)

TEOAE responses were recorded in all subjects in the control group, but absent in 7 ears (12%) in the impulse and in 1 ear (1.7%) of subjects in the continuous noise group, with the mean amplitude 7.8 ± 4 dB SPL, 7.0 ± 4 dB SPL and 5.6 ± 3 dB SPL, respectively, (ANOVA, $p=0.0103$), in the presence of comparable noise levels (ANOVA, $p=0.1015$).

Spectral analysis of TEOAE responses per 1/3-octave bands are presented in Table 4.4.2

Table 4.4.7: TEOAE analysis by 1/3-octave bands in normal subjects and subjects exposed to impulse and steady noise

<i>1/3 octave analysis 1 - 4 kHz</i>	<i>TEOAE responses (dBSPL)</i>		
	<i>Normal</i>	<i>Impulse</i>	<i>Steady</i>
1000	-0.6± 5	0.2± 5	-1.0± 4
1260	-0.2± 5	0.5± 6	-0.6± 4
1587	-1.5± 5	-2.7± 6	-3.4± 4
2000	-3.0± 5	-3.1±17	-6.8± 5
2520	-5.1± 5	-3.7±18	-7.9± 4

3175	-3.9± 6*	-8.1±5	-5.7± 4
4000	-5.8± 5**	-9.0±3	- 6.7± 3

Significant, *(ANOVA, p = 0.004); **(ANOVA, p = 0.0554)

The comparison of TEOAEs between the groups by 1/3 spectral bands, showed a high variability of responses. There was, in general, a tendency of greater responses in impulse group in comparison with continuous noise group, but this tendency reversed at the frequencies 3175 Hz and 4000Hz. The significance was reached only for the normal group in 3175Hz- and 4000Hz-bands, as indicated in Table 4.4.2.

The absence of the responses was observed for the noise groups, particularly in the frequency bands ≥ 2 kHz, as illustrated in Figure 4.4.4.

Spontaneous otoacoustic emissions (SOAEs)

The prevalence of SOAEs was greatest in the normal group, slightly less in impulse, but significantly lower in the steady noise group (Table 4.4.8).

Table 4.4.8: SOAE prevalence in normal, impulse and steady noise groups

<i>SOAE prevalence (per ears):</i>	<i>Normal group</i>	<i>Impulse noise</i>	<i>Steady noise</i>
	46 (31)%	41 (27)%	*18 (13)%

* Significance (χ^2 - test, p = 0.054)

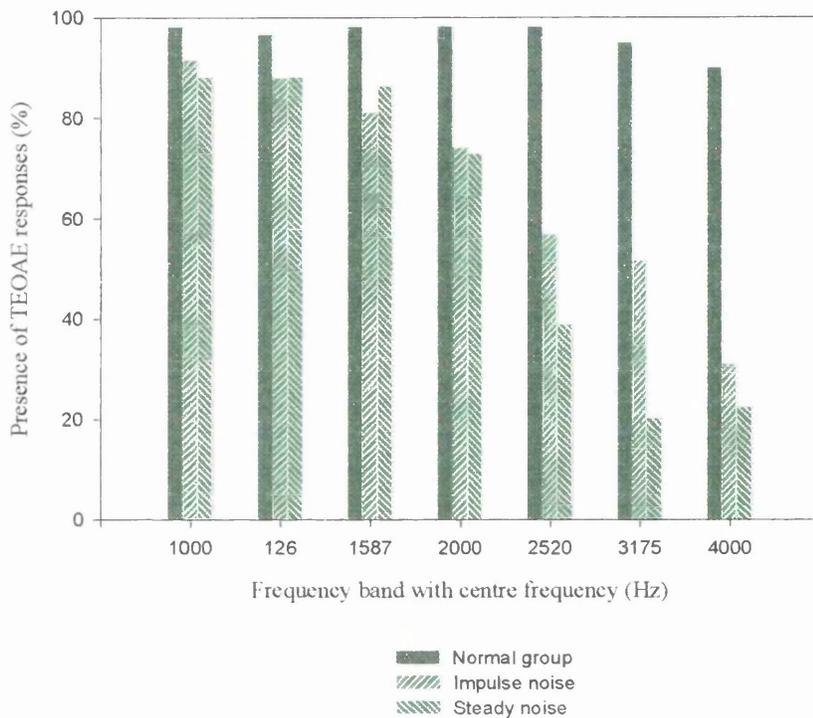


Figure 4.4.4: Spectral analysis of TEOAE responses in all three groups: 1/3-octave band analysis from 1 to 4 kHz

A spectral analysis of SOAEs per 1/3 octave bands is presented in Figure 4.4.5, indicating a higher prevalence of SOAEs in the ears of impulse than those of steady noise group, with notable absence of spectral peaks for both noise groups in the frequency bands over 2520Hz.

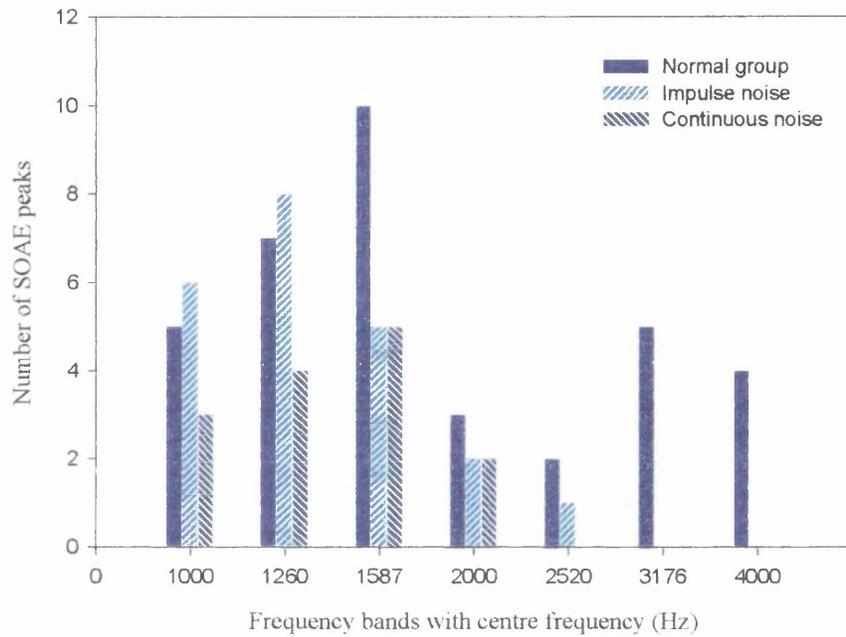


Figure 4.4.5: Spontaneous otoacoustic emissions: 1/3-octave band analysis for all three groups

II. Subjects with NIHL: tinnitus versus non-tinnitus

Pure-tone audiometry

The mean audiometric thresholds for subjects with and without tinnitus are presented in Figure 4.4.6:

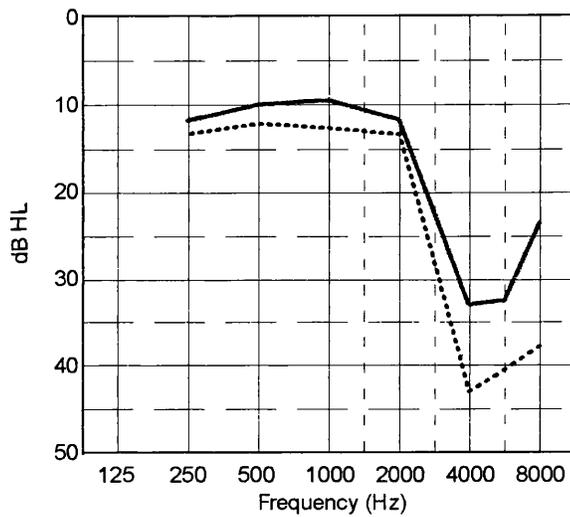


Figure 4.4.6: Mean audiometric thresholds in subjects with noise-induced hearing loss, with (dotted line) and without tinnitus (green line)

Otoacoustic emissions

The comparison of the results of TEOAE overall responses between subjects with tinnitus (mean: 6.7 ± 3 dB SPL) and those without tinnitus (5.7 ± 4 dB SPL) was not significantly different (t-test, $p = 0.278$).

The analysis of the power spectra, four bands (B1, B2, B3 and B4) on the slope near NIHL, showed a tendency of greater responses in tinnitus group, but the significant difference was reached only in B3 (Table 4.4.3).

Table 4.4.9: TEOAE responses: 1/3-octave band analysis of the slope in the power spectra in subjects with and without tinnitus

<i>1/3 octave bands centered at B1-B4 of the slope</i>	<i>TEOAE responses (dBSPL)</i>	
	<i>Tinnitus</i>	<i>No tinnitus</i>
B1	-5.3 ± 5	-7.4 ± 3
B2	-2.3 ± 5	-4.4 ± 4
B3	-0.8 ± 5*	-3.5 ± 5
B4	-1.8 ± 5	-1.9 ± 5

* significant (Mann-Whitney U-test, p = 0.0058)

The prevalence of SOAEs in subjects with tinnitus was significantly higher in those without tinnitus (Table 4.4.10).

Table 4.4.10: SOAE prevalence in subjects with NIHL, with and without tinnitus

	Tinnitus (n=59)	No tinnitus (n=58)
<i>SOAE prevalence (per ears):</i>	(19) 32%*	(5) 8%

* Significant (χ^2 -test, p = 0.0015)

III. Subjects with tinnitus: impulse versus continuous NIHL

Pure-tone audiometry

The mean pure-tone audiometric thresholds in subjects with tinnitus and NIHL, following exposure to impulse and predominantly steady-state noise were presented in Figure 4.4.7.

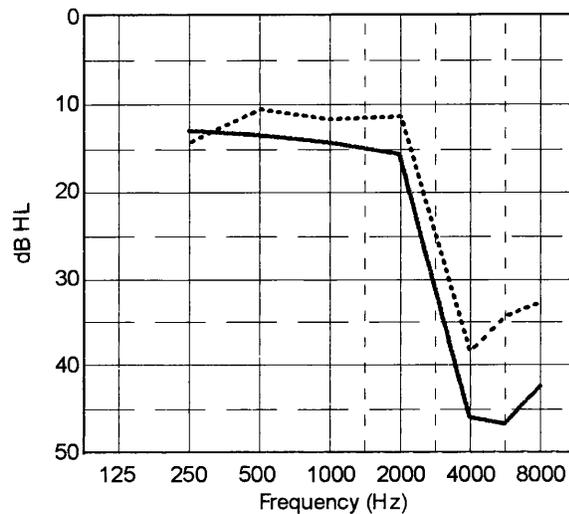


Figure 4.4.7: Mean pure-tone audiometric thresholds in subjects with tinnitus and noise-induced hearing loss: impulse (dotted line) vs. steady-state noise (green line)

Otoacoustic emissions

The overall TEOAE responses between the subjects with tinnitus following impulse noise exposure (7.8 ± 4 dB SPL) and those following predominantly steady noise exposure (5.8 ± 3 dB SPL) were significantly different (Mann-Whitney U-test, $p=0.046$). TEOAE responses in four 1/3-octave bands near noise-induced cochlear lesion (B1, B2, B3 and B4) these two groups were highly variable, without reaching a significant difference.

SOAE prevalence (per ears) was higher in the impulse (39%) than in the steady-state noise group (25%), but without statistical significance (χ^2 -test, $p=0.268$).

4.4.2.4 Discussion

Subjects in the normal group showed the highest prevalence (100%) of TEOAE responses and the greatest overall amplitudes, in comparison with subjects with noise-induced (impulse and steady noise) hearing loss, although a high variability in response amplitudes was observed in all groups. This is in agreement with previous studies.

In subjects with NIHL, there was no significant difference in TEOAE responses between those with and without tinnitus. However, among subjects with tinnitus, those with hearing loss induced by impulse noise have demonstrated significantly higher TEOAE responses (7.8 ± 4 dB SPL) than those following steady-state noise (5.8 ± 3 dB SPL), in the presence of comparable pure-tone audiometric thresholds, tympanometric measurements and noise levels.

Spectral analysis of TEOAEs by 1/3 octave bands from 1 to 4 kHz showed significantly higher response amplitudes at 3175 Hz and 4000 Hz in normal subjects, with the decline in the presence of responses, as well as the amplitudes, for the frequency bands with centre frequencies over 2000 Hz, in the groups with NIHL. However, subjects with hearing loss following impulse noise exposure exhibited greater responses up to 2520 Hz, and lower above 2520 Hz, than subjects with hearing loss following predominantly continuous noise, which may suggest a sharper contrast in OHCs lesion between these two groups and more demarcated OHCs lesion following impulse noise, as demonstrated in histological animal studies (as described in the Introduction, section 4.4.2.1).

There was a similar observation following the comparison in SOAE prevalence between the groups. The highest prevalence, as expected, was found in the normal group (46%), corresponding to those previously reported in normal subjects. However, slightly lower prevalence was found in impulse (41%), but significantly lower (18%) in subjects with NIHL following predominantly continuous noise, with notable absence of spectral peaks in the frequency bands ≥ 2000 Hz in steady-NIHL group, and in frequency bands ≥ 2520 Hz in impulse-NIHL group. These findings further support the hypothesis of a more localised cochlear lesion following exposure to impulse noise, and are consistent with the histological findings in animal studies.

The comparison of TOAEs between subjects with and without tinnitus have demonstrated a high inter-individual difference, without reaching statistical significance,

although analysis of the power spectra in four 1/3-octave bands (B1, B2, B3 and B4) of the slope showed a tendency for greater responses in the power spectrum near the suspected noise-induced OHCs lesion, in the tinnitus group, with a significant difference in one of the four bands (B3). However, the prevalence of SOAEs was significantly higher in subjects with tinnitus (32 % in tinnitus and 8 % in non-tinnitus ears), thus providing support for increased OHC activity in tinnitus.

These findings could be suggestive of “overactive” elements in the frequency bands near a noise-induced cochlear lesion, which are more pronounced in subjects with tinnitus following impulse noise. In this group, there were greater overall TEOAE amplitudes and SOAE prevalence than in tinnitus following steady-state noise exposure. These findings could be the consequence of altered efferent activity, in response to traumatic noise exposure, [as has already been suggested (Hazell, 1985; Attias et al., 1996)], in which more demarcated cochlear (IHC and OHC) and/or discordant OHC lesions, may result from the exposure to impulse noise.

To summarise, there is evidence to suggest that impulse noise may cause more localised cochlear damage than continuous noise, and that the “intact” region may be subjected to altered motor control, leading to overactivation of cochlear elements of relevance to the perception of tinnitus.

With the prevalence of SOAEs significantly higher in impulse- versus continuous- NIHL in tinnitus versus non-tinnitus subjects, and the higher prevalence in subjects with tinnitus following impulse-NIHL versus continuous-NIHL, it appears that SOAEs are a more sensitive indicator of changes in cochlear dynamics than TEOAEs. The resulting practical implication is that subjects with NIHL and recordable SOAEs, may be predisposed to the occurrence of tinnitus.

Nevertheless, the significance of the difference between impulse and continuous noise could be more academic than practical, as the subjects with exclusively impulse-NIHL represent a small proportion of the overall population of subjects with NIHL. Noise exposure is most likely to be mixed, with components of impulse/impact and continuous noise. Consequently, the likelihood of recordable SOAEs is rather low, and therefore, in practice, their importance in assessment of the patients with NIHL and tinnitus should not be overestimated. The same hypothesis may be applied to TEOAEs, and OAEs in

general, and it is most likely that TEOAE responses will be small or absent, even in the presence of “islands” of normal hearing.

In conclusion, it appears that in subjects with NIHL, OAEs may be useful in the assessment of the degree of a cochlear lesion, as their spectral width and characteristics depend on the spatial pattern of the OHCs lesion. If OAEs are recordable, then their relevance for the perception of tinnitus could be explored further as outlined above, particularly with a view to defining the potential dysfunction of efferent control. However, due to the fact that the most extensive lesions following noise exposure occur in the cochlea, with extensive OHC lesions, and consequently absence of OAE responses, their overall practical importance is limited. Other methods, in which the altered central auditory activity in response to the cochlear lesion, as reviewed in the introduction of this study (4.4.2.1), could be of much greater importance, e.g. the detection of tinnitus-related neural activity, using new techniques, based on sophisticated modern technology (1.1.5.2, Recording of tinnitus-related activity), has provided encouraging results.

4.5. TINNITUS AND MENIÈRE'S DISEASE

4.5.1 Introduction

Tinnitus is one of the cardinal symptoms in patients with Menière's disease. Therefore, a separate study of changes in cochlear mechanics which occur in Menière's disease has been undertaken.

Definitions of Menière's disease versus endolymphatic hydrops

Patients with a classical triad of episodic symptoms: tinnitus, diminished hearing and vertigo, as described by Prosper Menière in 1861 (Hawkins, 1996), are presumed to suffer from a *clinical entity*, termed as Menière's disease. Endolymphatic hydrops is a *histopathological condition* that is considered to underlay Menière's disease. Hence, these two terms are often used interchangeably, although, up to date, it has not been proven beyond doubt that Menière's disease and endolymphatic hydrops are the same phenomena.

Current concepts on aetio-pathogenesis of Menière's disease, hearing loss and tinnitus

The aetiology of Menière's disease is unknown and remains the subject of controversy. A number of factors have been proposed to be responsible for Menière's disease, including genetic abnormalities, autonomic imbalance, vascular irregularities, dietary factors, allergic phenomena, endocrine disturbance, psychosomatic disorder or autoimmune mechanisms (Merchant et al., 1995). Endolymphatic hydrops is thought to be the fundamental morphological alteration seen in histopathological studies of Menière's disease (Hallpike and Cairns, 1938), although it had been found in people who were not known to have exhibited the symptoms of Menière's disease during their lifetime (a review, Kiang, 1988).

Endolymphatic hydrops may arise as a result of the destabilisation of the natural regulation of the endolymph through its overproduction and/or decreased outflow from the endolymphatic space.

The water component of the endolymph is derived from the perilymph and it is thought that the unique composition (high K^+ , low Na^+ and low Ca^{++}) of endolymph is maintained by active homeostatic mechanisms located in the stria vascularis (Fig. 1.2). The specific chemical composition of endolymph and the generation of the transepithelial positive potential (1.2.3) are considered to be regulated by a membrane-bound Na^+/K^+ activated adenosine triphosphatase (Na^+/K^+ -ATPase) in the marginal cells of stria vascularis and the dark cells of the vestibular labyrinth (Kuijpers and Bonting, 1969). A variety of hormonal and secretory factors that can regulate Na^+/K^+ -ATPase activity in the kidney (Mc Donaough and Farley, 1993). One of these factors is the mineralocorticosteroid aldosterone, which plays a role in regulation of extracellular volume and is a major regulator of potassium metabolism (Williams and Dluhy, 1994). In animal experiments it has been demonstrated that strial Na^+/K^+ -ATPase levels increase as a result of enhanced aldosterone levels by low-sodium, high-potassium diet. Aldosterone levels may also be increased by emotional stress, which has been suggested to precipitate Menière's disease (Williamson and Gifford, 1971), and which may lead to an increased secretion of adenocorticotrophic hormone (ACTH) from the hypothalamus, and subsequent adrenocortical production of hormones such as aldosterone. The strial Na^+/K^+ -ATPase activation by aldosterone may result in an increased secretion of K^+ in the endolymphatic compartment (section 1.2.1.2, Fig. 1.2) and *overproduction* of endolymph.

The endolymphatic sac (ELS) is considered to be responsible for the production of glycoproteins, which create an osmotic gradient in the endolymph and a longitudinal flow in the direction of the ELS (Claes and van de Heyning, 1997). The ELS, which is immunologically active, is also involved in absorption of the endolymph and its metabolites. The abnormality of the ELS, therefore, may also contribute to the pathogenesis of endolymphatic hydrops, by affecting the endolymph flow and/or by reducing the absorption.

The resulting *endolymphatic hydrops* is thought to lead to the distention of the endolymphatic space, which may further lead to a rupture of Reissner's membrane or a transient endolymph leakage due to permeability increase of the membranes lining endolymphatic space (e.g. tight junctions in the reticular lamina or Reissner's

membrane). It is assumed that this causes the attack itself, leading to a mixture of endolymph and perilymph, which entrails a breakdown of the normal electrical potential and a potassium (K^+) intoxication of the sensory and neural tissue in the cochlea, which is thought to be the essence of the Menière's attack. In an experiment with a cochlear explant (isolated living OHCs of a guinea pig), using K^+ perfusion (Zenner et al., 1994), the exposure of the lateral and basal membrane parts of OHCs to increasing K^+ concentration, led to a non-physiological transient depolarisation and accompanied by longitudinal shortening of the OHCs. This produced a temporary electrical and mechanical effect on OHCs, with concomitant compression of the organ of Corti. A similar effect has been assumed to occur in vivo in humans. Nevertheless, it would be noteworthy that no menieriform attack has ever been observed in any animal model of endolymphatic hydrops (a review, Merchant et al., 1995).

The auditory symptoms, *hearing loss* and *tinnitus*, associated with Menière's disease, have been explained within the context of this hypothesis.

To recapitulate briefly the bioelectrical events related to the process of transduction, associated with normal process of hearing (more details in 1.2.3): the apical channels (towards endolymphatic space) allow K^+ influx into OHC along the electrochemical gradient (see section 1.2.2/1.2.3), resulting in OHC depolarisation (i.e. receptor potential). K^+ channels in the lateral cell membrane (facing the cortilymph, a perilymphatic compartment between lateral walls of the OHC), which are gated by the cell potential and Ca^{++} concentration, allow the efflux of K^+ from the OHC cytoplasm into the cortilymph, contributing to the repolarisation phase of the transduction process. In physiological situation this is possible due to the low K^+ concentration in the perilymph. However, in pathological situation, such as is in Menière's disease, with the raised K^+ in the perilymph, K^+ efflux is inhibited, leading to a long-lasting depolarisation and prolonged contraction of the OHC (Zenner, 1986), that interferes with mechanical transduction (Zenner et al., 1994). The prolonged depolarisation impairs OHCs ability to react to sound stimuli, thus contributing to the *hearing loss*. Beside this electro-mechanical cause of hearing loss, there could be the other, more mechanical causes, such as a static shearing displacement between the basilar and tectorial membrane and partial decoupling of the OHCs from the tectorial membrane, due to shortening (longitudinal contraction) of OHCs, with compression of the organ of Corti, which interferes with the cochlear amplifier. The mobility (elasticity) of the basilar membrane is

also impaired (reduced) due its distention, thus affecting the basic structural property required for the generation of the traveling wave. The displaced, over-distended basilar membrane may display vibratory saturation at lower stimulus than a membrane under normal pressure.

Within the framework of the above hypothesis, *tinnitus* may also be explained by pathological depolarisation of the hair cells. Depolarisation is the fundamental event following a physiological (acoustic) stimulus, essential for the process during which a signal is transferred from the OHCs to the nerve ending. The pathological, “spontaneous”, prolonged depolarisation of OHC in Menière’s disease, which occurs in the absence of an external stimulus, therefore, leads to the perception of sound, tinnitus. Prolonged depolarisation of IHCs, with the excess of released excitatory aminoacids (glutamate), leads into pathological firing of the afferents (Zenner et al., 1994). The compression of the organ of Corti due to longitudinal contraction of the OHCs and the subsequent shearing movements of the stereocilia and/or decoupling stereocilia from the tectorial membrane, is another (or additional) proposed mechanism of tinnitus generation in Menière’s disease (Tonndorf, 1980).

Diagnosis of Menière’s disease

Menière’s disease is a clinical diagnosis. It has been defined by the Committee on Hearing and Equilibrium, AAOO (1995) and the diagnosis is based on the characteristic clinical history, a documented sensorineural hearing loss shift on pure-tone audiometry and/or reduced speech intelligibility using word recognition score test, and the exclusion of specific causes (such as post-traumatic and post-infectious endolymphatic hydrops, otosyphilis or Cogan’s syndrome).

The role of electrocochleography in diagnosis of Menière’s disease

Given the similarity in the characteristics of cochlear microphonics and OAEs, due to which OAEs were termed as “acoustic emission cochleography” (Kemp et al., 1986),

characteristic findings in electrocochleography (EcochG) will be discussed. Like OAEs, the cochlear microphonics can be altered by stimulating the MOC system: by electrical stimulation of the olivocochlear bundle (OCB), the cochlear microphonics are increased (Fex, 1959).

EcochG is a technique for recording cochlear potentials (section 1.2.3) and has been applied in the diagnostics of Menière's disease. The cochlear microphonic (CM) is an alternating-current (ac) response, which mimics the waveform and polarity of the stimulus and is known to be the receptor potential of the OHCs. The summation potential (SP) appears as a positive and negative shift from the CM baseline. The action potential (AP) is an algebraic sum of the action potentials from the spiral ganglion and cochlear nerve.

EcochG demonstrating an enlarged SP/AP amplitude ratio and a shift of SP amplitude in the negative direction, has been most used in identifying Menière's disease (Ferraro and Krishnan, 1997), especially in the early stages of the disorder. An enlarged SP has been attributed to the displacement of the BM towards the scala tympani due to hydrops. An enlarged amplitude (Ge et al., 1997) and a prolonged "after-ringing" of the CM (Morrison et al, 1980) have also been attributed to endolymphatic hydrops. Despite the lack of specificity for various otological disorders, which makes the overall clinical utility of the CM limited, the use of the CM in the assessment of patients with Menière's disease seems to have undeservedly received very limited attention. Of particular importance could be the finding of a raised CM in patients with Menière's disease, in comparison to non-Menière's patients (Ge et al., 1997). This makes it likely that the hearing loss in Menière's disease is not caused by hair cell loss, as it occurs in patients with sensorineural (cochlear) hearing loss of different aetiologies (e.g. noise-induced hearing loss). Furthermore, the CM amplitude is not correlated to the degree of hearing loss. Therefore, the finding of a raised CM amplitude in Menière's disease could be convincing evidence that permanent structural damage of the OHCs has not occurred.

Thus, the CM has potential value in the assessment of cochlear status. More recently, a high-pass masking technique to obtain derived frequency-specific CM from subtracted waveforms to rarefaction and condensation stimuli, has been proposed by Ponton et al., 1992, allowing the assessment of hair cell integrity in the basal and the apical regions of the cochlea.

There have been a number of studies in which OAEs have been used for evaluation of Menière's disease.

The majority of previous studies have applied TEOAEs (Kubo et al., 1995) and DPOAEs (Horner and Cazals, 1989; Lonsbury-Martin et al., 1993) for the frequency analysis and the site-of-lesion testing to track the pattern of OHCs damage, with responses usually absent at lower frequencies. DPOAEs seemed to have been a subject of more interest, due to the responses being more frequency-specific. Beside the interest in frequency-specific responses, the overall responses were also recorded, with the finding of significantly lower responses in patients with Menière's disease (Harris and Probst, 1992).

The results between the studies vary and no consensus in the significance of OAE application in evaluation of Menière's disease has been reached. The OAE responses would, obviously, depend on the stage of Menière's disease (at the early stage, with no structural OHC lesions, or advanced, when permanent OHC lesions are more likely to occur), as well as whether responses were obtained during the exacerbation or remission of Menière's disease.

OAEs were also studied to assess the effect of substances known to alter cochlear status and, therefore Menière's symptoms. For instance, in a study with i.v. application of Lidocaine (a local anaesthetic which suppresses spontaneous depolarisation and reduces abnormal hyperactivity in the auditory system), an improvement (disappearance or decrease) in tinnitus (in 94% of patients), accompanied by the alteration in the TEOAE amplitude levels, have been observed (Haginomori et al., 1995). In another study (Uziel and Bonfils, 1989), following the administration of an hyperosmolar solution, glycerol, which may relieve tinnitus temporarily by causing osmotic withdrawal of water from the scala media, an improvement in the TEOAE amplitudes has been demonstrated.

Comparing the effects of experimentally induced endolymphatic hydrops in rabbits (Martin et al., 1988), it was demonstrated that behavioural thresholds were considerably more elevated than the corresponding DPOAEs. The subsequent study on cochlear nerve-fibre activity in hydropic rabbits, exhibited reduced sensitivity and frequency selectivity, significantly more than that of DPOAEs, which was suspected to imply that

the reduced hearing sensitivity comes from the deficit *proximal* to the cochlear hair cells (Lonsbury-Martin et al., 1989).

The otoacoustic emissions (TEOAEs) technique, with a simultaneously applied low-frequency tone, similar to the technique evaluating the CM (see above), has been proposed for the diagnosis of Menière's disease (Nubel et al., 1995). With this technique, patients with hydrops were identified by the absence of the TEOAE amplitude modulation (due to the basilar membrane reduced mobility), which would be normally caused by the low-frequency tone.

Aims of this study

The objective of this study is to assess cochlear status and dynamic changes in cochlear mechanics in patients with Menière's disease. To achieve this, TEOAEs and SOAEs have been recorded in two sessions. Ideally, this would be a session during the exacerbation, and a session during the remission of Menière's disease. However, in clinical practice, with prebooked outpatients' sessions and unpredictability of the course of Menière's disease, this would be difficult to achieve.

To assess in what way cochlear mechanics are affected by Menière's disease, TEOAE and SOAE characteristics in patients were compared with those in normal subjects.

Both TEOAEs and SOAEs have been extensively studied in normal population. TEOAEs are known to be present in almost all normally hearing subjects and they are characterised by the high inter-session intra-individual stability (sections 1.3.3 and 1.3.4.2). SOAE spectral peaks in normal subjects are also highly reproducible and they are known to be absent if audiometric thresholds exceed 20 dB HL. (section 1.3.4.1). Therefore, the characteristics of TEOAEs and SOAEs, including the prevalence and reproducibility in two sessions, were the subject of comparison between Menière's and non-Menière's subjects. The functional integrity of the MOC system was assessed by a standard procedure of recording of TEOAEs under contralateral acoustic stimulation.

A subpopulation of patients with Menière's disease, in whom relatively intact structurally OHCs were assumed, and including those often termed as "early endolymphatic hydrops", was targeted, not only to obtain recordable OAEs, but also to avoid possible

feedback effects due to the secondary, ascending CNS changes which may occur in response to the permanent OHC lesion (as discussed in the section 4.4.2.1). In patients with irreversible cochlear damage, the clinical presentation of auditory symptoms, hearing loss and tinnitus, may change, and may, therefore, be less typical for Menière's disease. It is expected that studying a subpopulation of patients with Menière's disease in whom OHCs are relatively structurally intact, will help to achieve a degree of homogeneity of the group, and thereby to obtain a meaningful variation in OAE responses, which would provide information on the mechanism of the generation of tinnitus and hearing loss in Menière's disease.

4.5.2 Materials and methods

Subjects

Two groups of subjects were included in the study (Table 4.5.1): patients with Menière's disease and normal subjects, matched for gender and age.

Table 4.5.1: Subjects included in the study

<i>Subjects</i>	<i>number: subjects/ears (gender)</i>	<i>age (years)</i>
Patients	24/38 (7M, 17F)	40 ± 7
Normal subjects:	20/40 (6M, 14F)	42 ± 12

The prevalence of Menière's disease in females (70.8%) was significantly higher than in males (χ^2 - test, $p < 0.000$).

Patients with Menière's disease (episodic tinnitus, hearing loss and vertigo) were selected to have normal hearing (≤ 20 dB HL) at one or more audiometric frequencies, in order to obtain otoacoustic emissions. The diagnosis was based on the characteristic clinical history (Committee on Hearing and Equilibrium, AAOO, 1995). A shift in audiometric threshold of more than 10 dB HL at two or more different frequencies was present in all

affected ears. All patients had tinnitus at the time they were tested. In addition to the above symptoms, they also complained (70%), during the attacks, of hyperacusis. Other diseases with similar symptoms were excluded using neuro-otological methods (1.1.5.1).

Protocol

All subjects included in the study underwent the protocol carried out in two sessions, separated by a time period of 10.3 ± 8 weeks in patients with Menière's disease and 8.9 ± 6 weeks in normal subjects, and included:

- Pure-tone audiometry (3.3.1)
- Tympanometry, to ascertain normal middle ear function and comparable middle ear pressure in two sessions (3.3.2.1).
- Otoacoustic emissions (3.3.3):
 - Transient evoked (TEOAEs)
 - Spontaneous (SOAEs)
 - Olivocochlear suppression test

Data analysis

The following procedures and analyses were performed:

- TEOAE (3.3.3.2):
- Comparison of the response amplitudes between the groups
 - Comparison of the difference in amplitudes in two sessions
 - The difference in the noise levels in two sessions

- SOAE (3.3.3.3):
- The prevalence
 - Reproducibility in two sessions, expressed as the number of SOAE peaks (%) present in both sessions (as detailed in the section 4.1.2),
 - Correspondence to the audiometric thresholds

Suppression test (3.3.3.4):

- TEOAE responses with and without contralateral suppression

4.5.3 Results

Pure-tone audiometry

Pure-tone audiometric thresholds in normal subjects were confirmed to be normal in the control group, with the mean better than 15 dB HL across frequency range, and the thresholds were characteristically elevated at lower frequencies in the Menière's group (Figure 4.5.1).

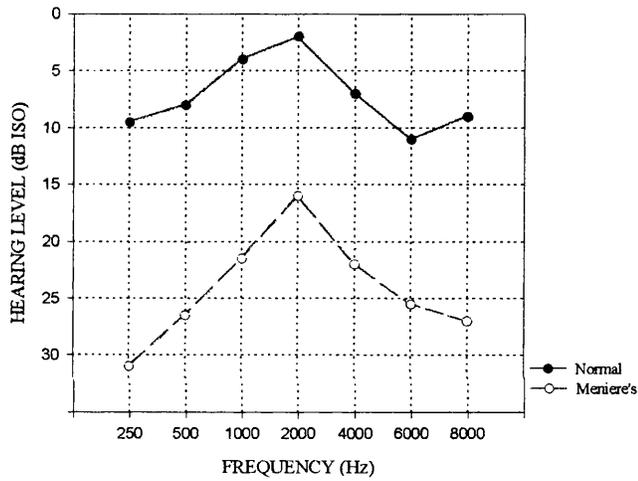


Figure 4.5.1: Mean pure-tone audiometric thresholds in Menière's and normal groups

Transient evoked otoacoustic emissions

In the presence of normal and comparable tympanometric measurements between the groups in two sessions (the mean difference in the middle ear pressure was 8.1 ± 7 daPa for the hydrops 6.5 ± 5 daPa for normal group; Levene's t-test, $p=0.24$), TEOAE amplitudes were significantly higher in the control group, and the difference in the two sessions, was significantly higher in the hydrops group (Table 4.5.2).

Table 4.5.2: Results of TEOAEs in Menière's and control subjects:

	<i>Mean TEOAE (dB SPL)</i>	<i>Noise (dB SPL)</i>	<i>TEOAE inter-session difference (dB)</i>
Subjects with hydrops	4.2 ± 5	1.1 ± 2	3.24 ± 2.3
Control subjects	$11.3 \pm 3^*$	-0.6 ± 3	$0.63 \pm 0.6^{**}$

* Mann-Whitney U test, $p < 0.0000$

** Levene's t-test, $p < 0.000$

The inter-session difference in TEOAE responses was exemplified in Figure 4.5.2: the recovery of TEOAE responses in this patient implies the presence of structurally intact OHCs and reversible changes in cochlear mechanics due to Menière's disease, and this recovery in TEOAEs was parallel to the full recovery of audiometric thresholds. An example of TEOAE response power spectrum in a subject with Menière's disease, with the absence of the lower frequency components, which corresponds to the elevated PTA thresholds, was presented in Figure 4.5.3. This is a pattern with possible OHC damage at lower (≤ 1.5 kHz) frequencies, as repeated TEOAEs (in four sessions) over the period of one year fail to show recovery at lower frequencies.

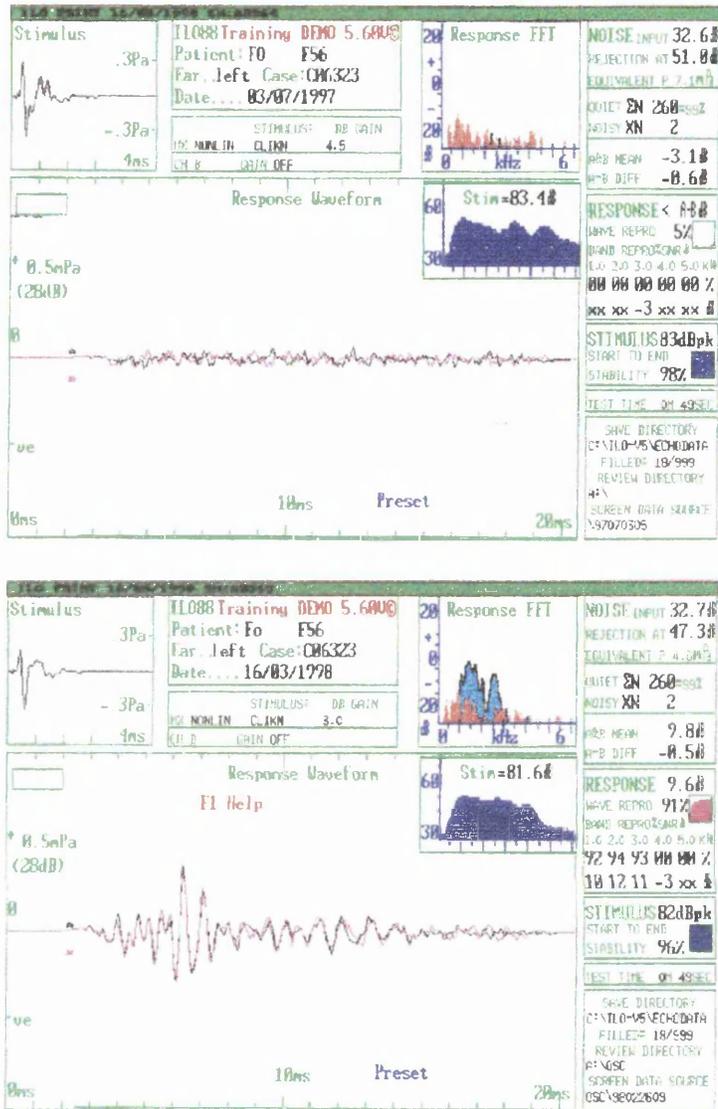


Figure 4.5.2: TEOAEs of a subject with Menière's disease, with a dramatic improvement in responses (from no response in the session I to 9.6 dB SPL in the session II)

In 4 patients in this study, it has been observed that significant inter-session changes in TEOAEs (≥ 2 dB) may occur even in the absence of changes in the audiometric threshold levels, implying that OAE are more sensitive for detecting changes in cochlear status than pure-tone audiometry.

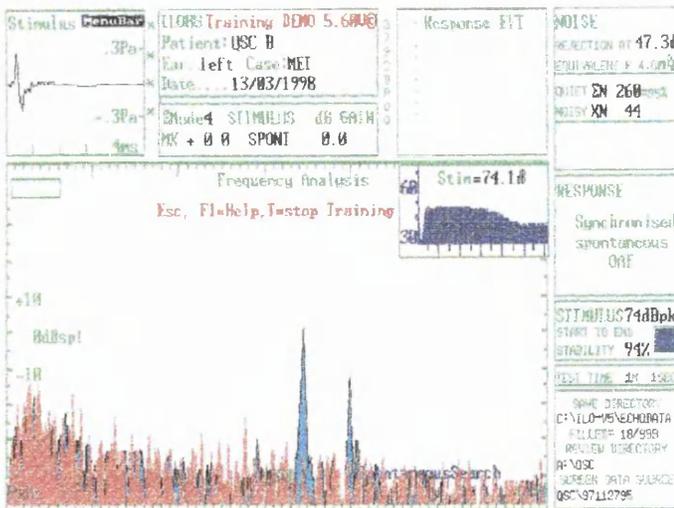
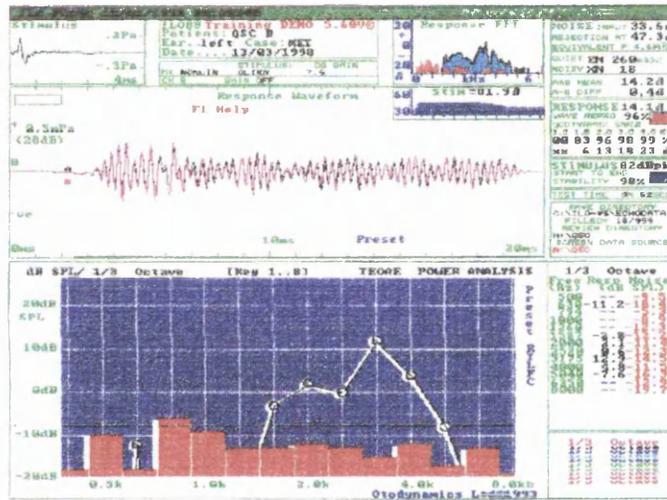
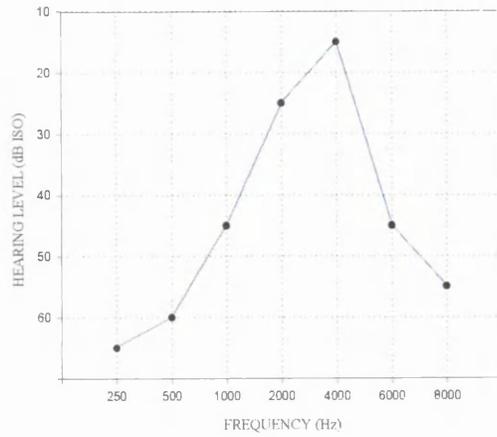


Figure 4.5.3: PTA, TEOAEs and SOAEs in a patient with Menière's disease: the lower frequency responses (≤ 1.5 kHz) of the TEOAE power spectrum were absent, in agreement with PTA. Strong, entrained TEOAE responses and OAE are suggestive of the enhanced gain in the remaining "intact" part of the cochlea.

Spontaneous emissions

Results of SOAEs (Table 4.5.3) show that the prevalence of SOAE in the Menière's group (66%), was higher than in controls (55%), despite elevated audiometric thresholds (Fig.4.5.3 and 4.5.4). The reproducibility of SOAEs in two sessions was significantly lower the Menière's group, 64% (33 of total 51 peaks) than in the controls, 96% of SOAEs (79 of total 82 peaks) (Levene's t-test, $p < 0.001$).

Table 4.5.3: Results of SOAEs in Menière's and control subjects

	<i>SOAE prevalence subjects/ears (%)</i>	<i>Total number of peaks</i>	<i>Reproducibility (%)</i>
Menière's patients	66 / 52	51	64
Control subjects	55 / 47	82	96

It was further observed that in normal subjects SOAE spectral components always corresponded to thresholds < 15 dB HL at homologous audiometric frequencies. However, in the Menière's group, in 6 (24%) patients, SOAEs were recorded at the frequencies which corresponded to the thresholds ≥ 30 dB HL at homologous audiometric frequencies, such as in the case illustrated in Figure 4.5.4.

Medial olivo-cochlear suppression

In all 15 patients with Menière's disease, in whom the suppression test was performed, a reduction of TEOAE amplitude under contralateral noise greater than 1 dB was found, as it was in all control subjects.

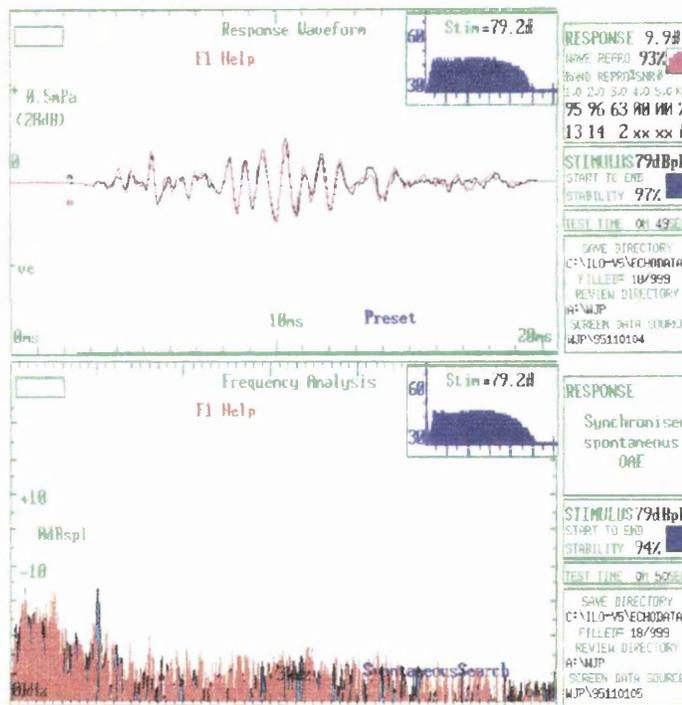
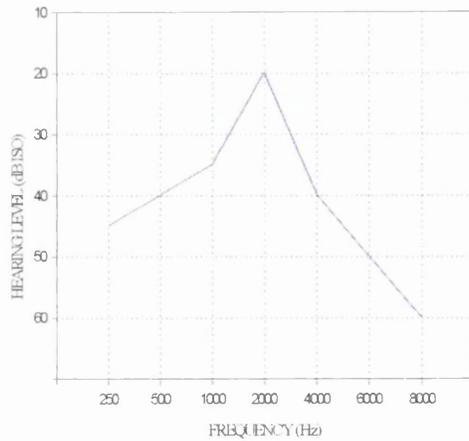


Figure 4.5.4: PTA, TEOAEs and SOAEs in a patient with Menière's disease: TEOAE responses and SOAEs were recordable despite the elevated audiometric thresholds. SOAE spectral component at the frequency 1001 Hz, corresponds to the threshold of 35 dB HL at the homologous PTA frequency

4.5.4 Discussion

Interpretation of OAE results

This study has demonstrated significant dynamic changes in cochlear mechanics in patients with Menière's disease, in comparison to normal subjects. A significant difference in the mean TEOAE responses was recorded in two sessions: inter-session difference in the Menière's patients was 3.24 ± 2.3 dB against 0.63 ± 0.6 dB in normal subjects. Similarly, the reproducibility of SOAE spectral peaks (their presence in two sessions) in the Menière's group (64%) was significantly reduced in comparison with normal subjects (96%). A high variability in the inter-session difference among patients with Menière's disease was noted, probably due to the fact that two sessions in some instances represented exacerbation and remission, with dramatic differences in TEOAE inter-session responses (e.g. from absent to 9.6 dB), while in other cases there was hardly any difference, as both sessions coincided with the exacerbation. The same situation also led to considerable variability in total TEOAE responses, from absent to as high as 17.4 dB SPL, in some cases with unexpected finding of very good TEOAE responses, considering audiometric thresholds. However, the mean TEOAE response amplitudes in Menière's group (4.2 ± 5 dB SPL) was significantly lower than in normal subjects (11.3 ± 3 dB SPL), implying that micromechanical processes, leading to the generation of OAEs had been impaired.

Fluctuation in TEOAE responses in two sessions was usually accompanied by fluctuation in audiometric thresholds, but in some cases changes in TEOAEs only were observed, thus suggesting that TEOAEs are more sensitive in detecting changes in the cochlear status than pure tone audiometry. Therefore, TEOAEs seem to be reliable indicator of changes in the cochlear status, even in the absence of significant change (< 10 dB) in audiometric thresholds.

The prevalence of SOAEs in the Menière's group (66%) was higher than in the controls (55%), despite the obvious differences in the audiometric thresholds (Fig.4.5.1). Furthermore, SOAEs were in some cases (24%) recordable even when the pure-tone

audiometric thresholds at homologous frequencies were equal or exceeded 30 dB HL. This relatively high prevalence of SOAEs in Menière's group could be an expression of the raised OHCs activity, which may correspond to the pathological, prolonged depolarisation, a prolonged excitatory state ("auto-stimulation") of the cochlea, leading to an increase in spontaneous activity of auditory neurons and, subsequently, a basis for the generation of tinnitus.

The finding of TEOAEs and SOAEs with concomitantly elevated audiometric thresholds is in agreement with the finding of raised cochlear microphonics (Ge et al., 1997) as discussed in the introduction of this study (4.5.1), and the finding of disproportionately elevated behavioral thresholds in comparison to DPOAEs (Lonsbury-Martin et al., 1989), which supports the hypothesis that hearing loss in patients with Menière's disease may not be due to structural hair cells damage. This relationship between OAEs and audiometric thresholds in the Menière's group suggests that the nature of the hearing loss differs considerably from other types of sensorineural hearing loss, in which the damage of OHCs corresponds to the findings of reduced/absent OAEs and cochlear microphonics (Probst et al., 1991; Ge et al., 1997).

These results clearly indicate abnormal micromechanical activity in patients with Menière's disease.

The relatively high SOAE prevalence and fluctuation of SOAEs and TEOAEs in Menière's patients, in view of the known influence of the efferent system on the OHCs through the medial olivocochlear (MOC) innervation (1.2.5.2, 1.3.5), could be an indication of involvement of the central nervous system mechanisms in the pathogenesis of this condition: the impaired efferent inhibition may be reflected by the presence of SOAEs, and the variations in efferent activity expressed in dynamic changes of cochlear mechanics and OAEs. The finding of normal MOC suppression in Menière's cases implies dysfunction above the superior olivary complex.

The question of the possible role of the efferent system in the pathogenesis of Menière's disease, has already been raised in section 4.1.4. It has been suggested (LePage, 1989) that dysfunction of the efferent MOC system, through its capacity to modulate the osmotic forces internal to the OHCs, could lead to a failure of the local homeostasis, and, thus, hydrops. In that case, the efferently induced dysfunction of OHC ion channels would be the *primum movens* mechanism of Menière's disease, and the subsequent electrochemical and mechanical changes (prolonged depolarisation and the OHCs contraction, with altered mechanical properties of the basilar membrane, as the slow, tonic contraction of the OHCs is responsible for the basilar membrane position) could generate symptoms, even in the absence of endolymphatic hydrops. This may explain some cases diagnosed as "Menière's disease", without demonstrable endolymphatic hydrops post mortem (Berggren, 1949; Belal and Ylikoski, 1980) and would support the hypothesis that endolymphatic hydrops is an epiphenomenon (Kiang, 1988).

Fluctuant change in the osmolarity of the OHCs, due to the MOC-electromodulation of osmotic forces internal to the OHCs (electro-osmosis), could be one of the fundamental mechanism of Menière's disease: It has been demonstrated in vitro, that an hypo-osmotic solution induces fast contraction and hyper-osmotic elongation of the OHC (Dulon et al, 1987). The motility of the OHCs, which is caused by the change in the osmolarity of the OHCs, rather than acoustic stimulation, results in shearing of stereocilia which may give rise to tinnitus.

The MOC-electromodulation of the silent current (dc) and its influence on the Na⁺ and K⁺ pump mechanisms (1.2.3) may provide the environment in which normal or abnormal spontaneous discharge of the afferent cochlear nerve fibres may appear. The contraction of OHCs due to K⁺ intoxication would enhance spontaneous activity in the cochlea, or in other words, the cochlea in Menière's disease could be considered to be in a state of hyperactivity, hyperexcitability, reflected by the presence of SOAEs and the raised cochlear microphonics, which is conveyed to the IHCs and through the afferents to the CNS system. The Ca⁺⁺ influx raises the HC membrane potential (depolarisation) which releases the excitatory neurotransmitter (glutamate) and this in turn leads to a raise in the action potential in the afferent nerve and further to an increase in central neural activity and tinnitus. The displacement of the basilar membrane, which is the basis for an enlargement of the summation potential (5.1.1, The role of electrocochleography in the

diagnosis of Menière's disease), may be due to the MOC-electromodulation and not due to endolymphatic hydrops. This is supported by the finding of the displacement of the basilar membrane on stimulation of the MOC bundle (Gans, 1977).

That Menière's disease may result from the neural dysfunction, is supported by the finding that intravenous Lidocaine simultaneously suppresses tinnitus (in 73%) and alters the amplitude of TEOAEs in subjects with attack of Menière's disease (Haginomori et al., 1995) [N.B. Lidocaine is known to be a potassium-channel blocker, which operates most efficiently in nerves with high discharge rates (Møller, 1984)], as well as by the observation that vestibular neurectomy (with inevitable section of the efferent MOC bundle) stabilises, or even improves, hearing levels in patients suffering from Menière's disease (Scharf et al., 1994).

Neural mechanism involving the auditory efferent system, which may be a basis for impaired autoregulation in the OHC tonus and osmolarity (electro-osmosis), could be only in part responsible for the pathogenesis of Menière's disease. It is also conceivable that there is a feedback interaction between OHC-regulated osmotic forces and homeostatic mechanisms in the stria vascularis, which receives sympathetic, adrenergic innervation, and, therefore, is under direct control of the autonomic nervous system (1.2.4), or indirectly through the mechanism involving the hypothalamo-adrenocortical axis and hyperproduction of aldosterone, as discussed in the section 4.5.1 (Current concepts on aetio-pathogenesis of endolymphatic hydrops, hearing loss and tinnitus). The subsequent endolymphatic hydrops may further complicate the existing pathological state in the cochlea (electro-chemical and mechanical changes) by the raised hydrostatic pressure.

Possible causes and mediators of the abnormal modulation in efferent activity

There is a common view that alteration in physiological processes mediated by the autonomic nervous and endocrine systems may play a significant role in the pathogenesis of Menière's disease. The symptoms of Menière's disease often become manifest during periods of stress and are more common in professionals and management occupations (Watanabe et al., 1995). The ability to compensate for stress is directly dependent on the pituitary-adrenal axis, the dysfunction of which could contribute to the development

Menière's disease (Powers, 1978). Menière's disease is also more common in women, 70.8% in this study and 70% in n=953 (Watanabe et al., 1995), who are known to be more susceptible to hormonal imbalance than men.

Alteration in physiological processes can modulate the OHCs activity (dc movements) through the variety of neural connections and neurochemistry (1.2.6; 1.2.7). The control of OHCs is assured by the efferent MOC fibres which release acetyl-choline (Ach) and γ -amino-butyric acid (GABA) into the synaptic cleft at the basal pole of the OHC (1.2.7). Ach and GABA are suppose to counteract in the control of the cochlea. The reciprocal distribution of Ach and GABA receptors and their counteracting function (contraction vs. elongation) has an additional impact on the modulation of the OHC function. There is also cross-reactivity between GABA_A receptors and those of the nicotinic cholinergic family (Kujawa et al, 1994). Malfunction of the central GABA mechanisms (GABA is known as the main inhibitory neurotransmitter of the CNS) may affect cochlear homeostasis via efferent system at its apical part, were GABAergic receptors are predominantly located (Altschuler and Fex, 1986). Indeed, the low-pitch component of tinnitus and low-frequency hearing loss in Menière's disease (Nodar and Graham, 1965) could be the expression of an abnormality in the cochlear apex.

GABA secretion is stimulated by reproductive hormones (McGinnis et al.,1980; Perez et al., 1986). Fluctuation in levels of neuroactive steroids (e.g. progesterone), which are associated with the menstrual and pregnancy cycles, and are induced by stress in males, modulates GABA-receptors activity (Smith et al., 1998). An alteration in brainstem auditory evoked potentials during the menstrual cycle (Dehan and Jerger, 1990; Elkind-Hirsch et al., 1992) has also been observed, suggesting that female reproductive hormones influence inhibition and excitation in the brainstem auditory pathway. This may explain why Menière's disease is more common in women and why the onset in Menière's disease often coincides with the beginning of the menopause or with the change in hormone dynamics in general (Andrews and Honrubia, 1994). The GABA-mediated inhibition in the processing of auditory information by neurons of the inferior colliculus (Chen and Jastreboff, 1995) may explain the hypersensitivity to sound that many patient with Menière's disease experience.

Therefore, the dysfunction of the GABA-mediated inhibitory mechanisms, as a result of alteration in the autonomic and hormonal systems, may be responsible, at least in part,

for Menière's disease. The possible micromechanical changes, resulting from this dysfunction, are consistent with OAE findings in this study.

In view of that, pharmacological manipulation of GABA may be one of the options useful in treating this disorder in the future.

The summary of OAE findings which may have clinical implications

SOAEs and TEOAEs, with inter-session fluctuation, are sensitive in detecting changes in the cochlear status of patients with Ménière's disease in a very simple and objective manner and, therefore, can be successfully used in *monitoring* cochlear status in Ménière's disease.

The presence of OAEs when audiometric thresholds are elevated strongly suggests structurally intact OHCs, in a similar way as cochlear microphonics, and are indeed a probe for OHCs status in Ménière's disease. Therefore, they could be helpful in identifying those patients whose hearing loss may be reversible if the underlying pathological state can be corrected. Therefore, OAEs may have significant *prognostic* value.

The absence of TEOAE response in one session and good response in the other, implies that the absence of TEOAEs does not necessarily correspond to OHCs structural damage, which is the usual conclusion when TEOAEs are not recordable. This is an unique finding, characteristic for Ménière's disease, and not documented in the literature for any other type of sensorineural hearing loss. The finding of SOAEs and TEOAEs, in general, in the presence of elevated audiometric thresholds, together with characteristic symptoms, are suggestive of Ménière's disease, and therefore could be objective evidence to support the *diagnosis* of Ménière's disease.

Chapter 5: GENERAL DISCUSSION

5.1 SUMMARY OF MAIN FINDINGS

As discussed in the Chapter 2 (2.2, Study aims and hypothesis), this project has examined the peripheral (cochlear) manifestations of tinnitus-related changes in the auditory system, using otoacoustic emissions (OAEs) in groups of patients homogeneous with respect to aetiology and audiometric thresholds. Specifically, OAEs have been used to provide objective assessment of patients with tinnitus. The attempts have also been made, on the basis of the obtained data, to explain the mechanisms underlying tinnitus.

5.1.1 Group characteristics

Tinnitus following head injury

In patients of this group, tinnitus was considered to be of “central” origin, as there was no evidence of a “peripheral” (cochlear) lesion, as judged by the standard pure tone audiometry (PTA). Additionally, to demonstrate the “normality” of the cochlea, spectral analysis of OAEs was used, as a more sensitive method in identifying subtle cochlear lesions than the PTA. The findings of SOAEs in all subjects of this group and strong TEOAEs were interpreted as extracochlear phenomena, in which an increase in cochlear gain had resulted from the dysfunction of the efferent control of cochlear mechanics. A lesion of the central nervous system (CNS), may, thus, trigger “tinnitogenic” activity, including *descending* changes, the presence of which was supported by the finding of absent/reduced medial olivocochlear suppressive effect. The above findings of OAEs, therefore, appear to be the cochlear manifestations of tinnitus-related activity in the CNS.

Tinnitus and normal hearing without identified pathology

As in the above study, OAE spectral analysis, in addition to the conventional method of PTA, was applied to define the “normal cochlea”. The findings of SOAEs in a significant number of patient and greater TEOAE responses in comparison with normal subjects, have led to the conclusion of malfunction (disinhibition) in the efferent control of cochlear mechanics. In the absence of identifiable pathology, a hypothesis has been proposed that physiological alterations in the CNS, resulting from neuropharmacological

changes associated with the stress or psychological/emotional phenomena, may be responsible for the initiation of the “tinnitogenic” signal. The physiological basis for this hypothesis is provided by the variety of the inter-connections between the auditory and other parts of the CNS (section 1.2.6), particularly those responsible for emotional states and adaptation to stress (e.g. limbic system and hypothalamus), and a wide spectrum of neuroactive substances, which potentially may influence the auditory system (section 1.2.7).

Tinnitus related to noise

OAEs were evaluated in two groups of patients whose tinnitus was related to noise exposure: patients with normal hearing who complained of tinnitus precipitated or aggravated by noise and patients with NIHL and associated tinnitus.

In the first study (4.4.1), there was evidence of the presence of “overactive” cochlear elements, expressed as SOAEs and large TEOAE responses, whose interaction with external noise (e.g. synchronisation/phase locking, or SOAE frequency intermodulation) may provide a basis for the various auditory sensations, which, in addition to tinnitus, included sensations of sound “echoing”, “beats”, monaural diplacusis and/or sound distortion.

In the second study (4.4.2), the prevalence of SOAEs was found to be significantly higher in tinnitus than non-tinnitus patients, and particularly so in patients exposed to impulse noise, as opposed to predominantly continuous noise. This suggests that the pattern of OHCs pathology with an “audiometric edge”, (i.e. abrupt changes) may cause an excitatory/ inhibitory imbalance (e.g. increased excitability in the inferior colliculus, as demonstrated by Chen and Jastreboff, 1995) and tonotopic reorganisation at the higher levels of the central auditory system, e.g. primary auditory cortex (4.4.2.1, Retrocochlear findings following NIHL), with tinnitus as a consequence. Cochlear damage, therefore, initiates *ascending* changes and through the feedback mechanism(s), an “intact” neighbouring region may be subjected to altered efferent control.

Tinnitus and Menière’s disease

The finding of the relatively high prevalence of SOAEs and fluctuation of SOAEs and TEOAEs (Study 4.5), has led to the *de novo* hypothesis of the possible role of neural

mechanism(s) in the pathogenesis of Menière's disease. Impaired autoregulation of the OHCs tonus and osmolarity (electro-osmosis) due to dysfunction of the efferent system, particularly the GABA-mediated inhibitory mechanisms, may result in a state of raised cochlear excitability, and, consequently, tinnitus. Therefore, tinnitus may arise from a combination of effects, one of which is specific for Menière's disease (in the proposed hypothesis, efferent dysfunction, i.e. a *descending*, central effect) and other non-specific changes related to the structural lesion of the OHCs due to a sustained pathological process (i.e. an *ascending*, cochlear effect).

The variety of SOAE and TEOAE responses, could, therefore, be the consequence of a wide spectrum of different functional and morphological states:

- exacerbation or remission of Menière's disease
- the presence and severity of existing endolymphatic hydrops and
- the degree of structural damage of the OHCs.

The finding of SOAEs and TEOAEs in the presence of elevated audiometric thresholds is unique for Menière's disease, and it appears to be the only known condition with SNHL, in which OAE recordable despite the hearing loss. These characteristics could provide objective evidence to support a diagnosis of Menière's disease.

5.1.2 General characteristics

A common observation throughout these studies is of the finding of raised cochlear activity, expressed through the presence of SOAEs and enhanced TEOAEs, suggesting that tinnitus is hyperactive auditory disorder. This is in agreement with the hypothesis of disinhibition in the interneuronal pathways (systems), proposed by Chen and Jastreboff (1995), which was based on the finding of abnormal (raised) activity in the inferior colliculus of rats, whose behavioural pattern was suggestive of (salicylate-induced) tinnitus. These data support the neurophysiological concept of generation of tinnitus (Jastreboff, 1991; Jastreboff and Hazell, 1993; sections 1.1.4.3, 1.1.4.5), which assumes that tinnitus may originate at any level in the auditory system, leading to a sequence of events, involving all parts of the auditory system, as well as some other parts of the CNS (e.g. limbic and autonomic systems), which are not directly associated with auditory function. This hypothesis has further support in the finding of altered spontaneous

activity (hyperexcitability), demonstrated by the methods, at present only experimental, of recording tinnitus-related central nervous system activity (section 1.1.5.2).

Therefore, the data from this thesis, which are related to different pathologies and in which hypothetical “tinnitogenic” signal originates from different levels in the auditory system (central and peripheral), and represent “peripheral” manifestations of tinnitus, can be integrated within this hypothesis. Furthermore, an increased variability in cochlear mechanics, evident from an increase in frequency variability of SOAEs (reduced reproducibility and raised relative frequency shifting of SOAEs) (Study 4.1), in comparison with normal subjects, may be a reflection of variable, unstable CNS activity, associated with the perception of tinnitus.

The studies have demonstrated that tinnitus in subjects with normal hearing is often associated with other auditory symptoms, such as hyperacusis and difficulty in hearing in background noise (Studies 4.2 and 4.3). These symptoms have been explained as the consequence of disinhibition by the efferent mechanisms and therefore described and termed as “*the auditory disinhibition syndrome*”. This auditory dysfunction which constitutes the above syndrome associated with a normal auditory periphery, can be identified by undamped OAEs, robust TEOAEs and almost invariably recordable SOAEs. Some other auditory phenomena, such as “echoing”, “beats”, distortion, or/and monoaural diplacusis, (Study 4.4.1) may result from the interaction of SOAEs and external sounds, and can be recognised in some subjects with recordable SOAEs.

5.2 OBJECTIVE EVALUATION OF TINNITUS BY OAEs

Spontaneous otoacoustic emissions

SOAEs in these studies are considered as the pathophysiological *correlate*, not as the cause, of tinnitus, as in previous studies (2.1.1), on the basis of experimental data suggesting that SOAEs may, in part, reflect functional changes at the higher levels of the auditory system (2.2 ; 4.1.1). Their variability, which appears to be associated with tinnitus, as discussed above, can be used as an objective indicator of the presence of tinnitus in a subset of patients with recordable SOAEs, and the presence of variable SOAEs may increase the probability of a subject having tinnitus. SOAEs could also be a valuable tool for intrasubject monitoring of the functional and structural state of the cochlea (OHCs), as demonstrated in the study on Menière's disease.

Transient evoked otoacoustic emissions

The findings of TEOAE frequency dispersion (analyses of frequency spectra) strongly indicate that this technique is *sensitive* in detecting subtle structural changes in the cochlea. This technique was used in these studies (4.2 and 4.3) to extend the criteria of "normality" of the auditory periphery, while TEOAE amplitude was used to detect functional changes (clearly evident from the suppression test). However, TEOAE amplitude does not have *sufficient specificity* for differentiating individuals with pathology, in particular, the tinnitus from the non-tinnitus state. Due to high inter-individual differences in the normal population, it would be almost impossible to define a lower or upper limit in TOAE amplitude.

Of good diagnostic value, for individual patients, are TOAEs with a very high amplitude which could be classified as "abnormal", but a dilemma occurs when the value falls in the equivocal region. A more definitive value depends on the predictive value of the test, and the criteria on which the value of TEOAE depends are primarily the hearing status, age and the gender of an individual. To enhance specificity, all studies have used normative data from their own control group, strictly matched for gender, age and audiometric patterns.

Medial olivocochlear suppression

Medial olivocochlear suppression test is an emerging technique for the assessment of efferent activity, which controls cochlear mechanics. However, the lack of sufficient

baseline data and the lack of consensus in the definition of the normative values, make the interpretation of the results with a degree of reservation. The interpretation of the MOC suppression values requires even more caution in subjects with partial cochlear lesion, in view of the frequency selectivity in suppression (Moulin et al., 1993), being stronger for the lower frequencies of ipsilateral stimulation.

The TEOAE suppression value of >1 dB, adopted in this thesis, was considered normal on the basis of the findings in normal subjects, and is in agreement with similar values (typically of 1 to 2 dB) from other studies (Collet et al., 1990b; Ryan et al., 1991; Moulin et al., 1993; Williams et al., 1993). There is evidence to suspect that this test is not sensitive enough for detecting a wider range in the MOC control, probably due to the sound attenuation by the middle ear, but also due to the test methodology. This can be illustrated by electrophysiological measurements (Puria et al., 1994), which have demonstrated up to 10 dB difference in TEOAE amplitude, with and without contralateral stimulation, in comparison with acoustic measurements.

There is a need for further characterisation of the MOC effect, which depends on many factors, including the intensity of both, ipsi- and contralateral, stimuli, the frequency composition and the rate of presentation. The issue of latency both with respect the onset and the offset of the MOC effect; the possibility of adaptation to repetitive stimulation; the relationship with the acoustic reflex; the influence of age and gender; lateral asymmetry, and reasons for inter-individual differences, are yet to be clarified.

Nevertheless, this test at present provides general information on structural integrity of the medial olivocochlear reflex arc, and a glimpse into the modulation of cochlear mechanics by its stimulation.

Otoacoustic emissions in general

TOAEs are recordable in subjects with relatively intact OHCs morphology, and therefore can be used only in a limited number of patients with tinnitus, a subpopulation with relatively normal hearing. The application of SOAEs is further restricted to an even smaller population in which they can be recordable.

It is obvious from the data in this thesis, that application of OAEs is most useful in patients with normal hearing, specifically, in patients with CNS pathology.

However, despite of the practical importance of tinnitus associated with NIHL, as noise is considered by many authors to be the most common cause of tinnitus, (4.4.2.1., epidemiological data), among all the groups examined in this study, in patients with tinnitus following NIHL, OAEs seem to be the least useful, as the noise causes morphological lesion of the OHCs, often resulting in smaller or absent OAEs.

In view of the above, an important aspect to consider is that the identification of individuals with tinnitus from those without tinnitus on the basis of OAE findings alone may not be a reasonable expectation. However, they may provide a valuable information in conjunction with other tests, such as frequency selectivity - tuning curves, or recording spontaneous activity in the CNS, which may be developed in future.

Future application of OAEs in the objective assessment of tinnitus will be closely related to further technological advances of OAE techniques. The development of more sensitive recording systems for the extraction of the signal in noise, for both SOAEs and TEOAEs, and greater frequency resolution of SOAEs (currently ILO system provides frequency resolution of 12 Hz, which was inadequate to detect smaller frequency shifts), would improve the clinical use of OAEs.

Technology which would allow analysis of contralateral suppression in different parts of the response window, could be useful in the assessment of the MOC function in patients with partial cochlear damage.

5.3 CONCLUSIONS

Several conclusions can be drawn from the data obtained in this study:

A common observation throughout these investigations is of raised cochlear activity expressed by the presence SOAEs and enhanced TEOAEs, suggesting that tinnitus is hyperactive auditory disorder. The hyperexcitability in auditory pathways is, thus, reflected in the periphery. These findings support the neurophysiological concept for the generation of tinnitus.

OAEs are a sensitive technique for detecting subtle structural changes in the cochlea, which can be a basis for the generation of tinnitus, and functional changes relevant to the perception of tinnitus.

An increased variability of SOAEs is associated with the complaint of tinnitus in a significant number of subjects, and, therefore may provide objective evidence which increases the probability of a subject having tinnitus.

The association of SOAEs and TEOAEs with elevated PTA thresholds has been demonstrated in Menière's disease, and, this unique characteristic may have diagnostic value. The inter-session fluctuation of SOAEs and TEOAEs and relatively high SOAE prevalence have led to the *de novo hypothesis* of the role neural mechanisms in pathogenesis of Menière's disease.

It has been observed that complaint of tinnitus in patients with normal peripheral auditory function is often associated with other auditory complaints, such as difficulty in hearing in background noise and hyperacusis. These symptoms constitute a presentation of auditory dysfunction, described in this thesis as the "auditory disinhibition syndrome", with the finding of undamped OAEs, robust TEOAEs and recordable SOAEs, consequent upon central efferent auditory dysfunction.

Strong SOAEs and enhanced TEOAEs were also found in patients in whom tinnitus could be triggered, or, if present, aggravated by environmental noise, and in some of whom also reported other perceptual phenomena, such as "echoing", "beats", distortion

and/or monaural diplacusis. The physiological basis of these phenomena may be the interaction of external noise and SOAEs. The identification of these patients may have practical implications as they may not be good candidates for the application of masking devices.

The findings in this thesis suggest a complex feedback interaction between the auditory perceptual phenomena, physiological changes in the CNS precipitated by different pathologies, and external noise, the manifestation of which can be detected at the periphery of the auditory system, using OAEs.

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APPENDIX I

Letters of ethical approval obtained from both the Joint Medical Ethics Committee at the Royal National Throat, Nose & Ear Hospital and the National Hospital for Neurology & Neurosurgery.

LOCALLY ORGANISED RESEARCH SCHEME - GRANT APPLICATION FORM

1. APPLICANT (s)

Surname, qualifications and title: Prasher. PhD. Dr.
Luxon. BSc. FRCP. Professor

First name(s): Deepak Current post: Senior Lecturer, ILO
Linda Professor, ILO

Full postal address of
place of work: Royal National Throat, Nose & Ear Hospital
330 Gray's Inn Road, WC1

Telephone no: 071 837 8855 ext 4290

2. LOCATION where work would be undertaken:

Department: ILO Division of Audiological Medicine

Telephone no: x 4290

3. TITLE OF PROJECT: To seek objective evidence of the presence
of tinnitus

4. ABSTRACT OF RESEARCH:

Attempts to identify the mechanisms underlying tinnitus and to develop effective treatments have been thwarted previously, in part because no objective measure of tinnitus has been available. A study has been devised which will examine functional changes in the auditory pathway from the cochlea to the cortex which may occur as a consequence of tinnitus. This approach is adopted as the pathophysiology of tinnitus remains unclear and no single test is likely to encompass the diversity of factors responsible for tinnitus complaint.

5. PROPOSED DURATION: 3 years

PROPOSED STARTING DATE: April 1994

COST OF PROJECT: give total financial support requested over
duration of project:

Support requested for first year of project only £24648

7. OTHER SUPPORT

Is support being provided or sought from any other body? YES/NO
If YES please give full details.

Iron Trades Federation

8. STATEMENT OF APPROVAL BY HEAD OF DEPARTMENT

The proposed research work has my approval.
The work to be carried out can be accommodated and
administered in the department.

Name in full: Linda M Luxon

Signature:

Date: 25 February 1994

9. I shall be actively engaged in, and in day to day control of, this project.

Signature:

Date:

10. COLLABORATOR (s) N/A

Statement:

Name (s) in full:

Signature (s):

Date:

11. CLEARANCE BY ETHICS COMMITTEE:

(a) This project has been cleared by the District Ethics Committee

on 9.11.93 Yes

(b) Not applicable Yes/No

(c) Project Licence Number
(for work involving experiments on animals)

Signature:

Date:



THE NATIONAL HOSPITAL FOR NEUROLOGY AND NEUROSURGERY

Queen Square, London WC1N 3BG
Telephone: 0171 837 3611
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IFM/JAS
REF: 02/25/97

Extension 8799

24th June 1997

Professor L.M. Luxon,
N.H.N.N.

Dear Professor Luxon,

RE: TO SEEK OBJECTIVE EVIDENCE OF TINNITUS

I am pleased to inform you that the Joint Medical Ethics Committee approved your project at its meeting on 12th June 1997 subject to:-

Submission of the patient information sheet on headed note paper.

The Committee require copies of the following documents regarding this application:

- 1) A brief final report on completion of the study and a copy of any published results.
- 2) Immediate notification of any problems which may be identified during the study.
- 3) Notification that the project has been aborted should this be the case.

Would you kindly ensure that the points raised by the Joint Medical Ethics Committee are addressed before the commencement of this trial. Please send confirmation of copies of any amended correspondence to Mrs. J.A. Sullivan, Secretary to the Joint Medical Ethics Committee, Patient Services Department.

I would be grateful if you could ensure that the appropriate forms enclosed are completed

continued ...



The University College London Hospitals

University College London Hospitals is an NHS Trust incorporating The Eastman Dental Hospital, The Hospital for Tropical Diseases, The Middlesex Hospital, The National Hospital for Neurology and Neurosurgery, The United Elizabeth Garret Anderson Hospital and Hospital for Women, Soho, and University College Hospital.

24th June 1997
Professor Luxon (continued)
REF: 02/25/97

With best wishes.

Your sincerely,

A handwritten signature in black ink, appearing to be 'I.F. Moseley', written in a cursive style.

Dr. I.F. Moseley,
Chairman,
Joint Medical Ethics Committee

Encs.
Ethics/let1997/3rd/022597

**INFORMATION SHEET FOR SUBJECTS
INVOLVED IN THE RESEARCH PROJECT ON TINNITUS**

Tinnitus is the perception of a sound in the head or ears which has not been generated by an external source, and is a common symptom in many people with, or without, hearing loss.

The present research project aims to develop tests which will enable the presence of tinnitus to be measured rather than rely solely on the patient's report of his symptom. As this may allow us to understand better how tinnitus is generated, in the long term, we hope that this will result in the development of better methods of treatment.

If you consent to participate in our research project on tinnitus, you will undergo various hearing test. These tests rely on your hearing responses to sound stimuli and are recorded by means of ear phones. They include:

- Standard hearing test: quiet tones are presented through the ear phones, and you are required to respond by pressing the button**
- A test to assess middle ear function: a tone under mild pressure will be presented via rubber probe inserted in your ear. No active involvement is necessary for this test.**
- A series of several short tests (each lasting 1 to 3 minutes) for inner ear function: Clicking sounds are presented via foam probes inserted in your ears and responses recorded by the computer. This test also does not require your active involvement.**

These tests are entirely harmless and do not cause any discomfort.

Your participation in the trial is entirely voluntary. You are free to decline to enter or to withdraw from the study at any time without having to give a reason; if you choose not to enter the trial, or to withdraw once entered, this will in no way affect your future medical care. All information regarding your medical records will be treated as strictly confidential and will only be used for medical purposes. Your medical records may be inspected by competent authorities and properly authorised persons, but if any information is released this will be done so in coded form so that confidentiality is strictly maintained. Participation in this study will in no way affect your statutory legal rights.

Thank you in advance for your time, attention and, we hope, involvement.

Investigators:

Dr Borka Josifovic Ceranic, 0171 915 1590

Professor Linda M. Luxon, 0171 837 3611 ext. 3386 / 0171 915 1590

Dr Deepak K. Prasher, 0171 915 1590

CONSENT FORM
for participants in the research project on tinnitus

I have read the information sheet and have had the procedure explained to me by Dr Borka Josifovic Ceranic.

I agree to participate in the research project on tinnitus.

Signed.....
(name in capitals)

Date.....

Witness:

Name.....

Address.....

Date.....