
EDITORIAL

The Twenty-Fourth Annual Meeting of the International Tinnitus Forum 2006: Translational Research in Tinnitus Therapy II

Attendees to the Twenty-Fourth Annual Meeting of the International Tinnitus Forum (ITF) 2006 (Translational Research in Tinnitus Therapy II) experienced a positive glimpse into the future both from basic science and neuroscience and from its clinical translation for tinnitus patient diagnosis and treatment. The high level of interest in the presentations was reflected in the attendance, audience participation in the discussions, and CME comments.

The presentations were scheduled to introduce the audience to three new theoretical concepts that have provided a clinical translation for both tinnitus diagnosis and treatment in the clinical experience of the presenters. This was followed by clinical reports of translational tinnitus treatment results with electrical stimulation and medication. Though interference in the personal appearances and presentations occurred owing to Prof. C.-F. Clausen's recovery from recent surgery and a last-minute scheduling conflict involving Professors A. Stracher and M. Hamid, their abstracts are summarized for our readers in this account of the meeting.

Prof. C.-F. Clausen's abstract of a neurotological classification system of tinnitus, submitted for this meeting, is included in the summary of the meeting. It delineates between bruits, both endogenous and exogenous, and renders possible a better understanding of the underlying pathological mechanisms of tinnitus that may be curable by different approaches and methods in attempting tinnitus relief. In bruit patients, the complaint is of noise within the head that can be recorded as a physically existing sound in the skull and is heard by affected patients. Endogenous tinnitus can be treated by external masking to suppress noise within the ears. In exogenous tinnitus, patients seek to avoid any outside noise or sounds, and they report that tinnitus decreases as soon as they go, for instance, into the cellar of a house or other soundproof place.

Dr. Abraham Shulman presented a theory—the tinnitus dyssynchrony-synchrony theory (TDST)—conceived in 1979. It was presented at this time owing to recent neuroscience reports of brain function, the availability of objective evidence from nuclear medicine imaging and electrophysiology of metabolic and electrophysiological

correlates of central-type tinnitus, and a theory of consciousness that is considered to support the original theory. The theory was presented in the context of historical background, supportive objective evidence, and clinical application for both tinnitus diagnosis and treatment.

The TDST considers tinnitus to be an abnormal, auditory, conscious percept originating as an initial dyssynchrony in pre- and postsynaptic neuronal transmission within the peripheral or central nervous system. Its origin is either cortical or subcortical (or possibly both). By interference in the excitatory and inhibitory process or processes involved in maintaining homeostasis for brain neural function, in multiple neural substrates, it acts as an aberrant auditory stimulus to express this dysfunction via the auditory system. The conscious auditory percept for tinnitus is hypothesized to reflect a clinical summation of synchronous activities of neuronal activity recordable from multiple neural substrates at brain cortex. The transformation of the dyssynchrony from aberrant auditory stimulus to that of synchrony and individual brain function of perception, affect, somatosensory response, and consciousness is clinically considered to be a final common pathway for tinnitus.

The clinical application of the TDST has been highlighted by a paradigm change in clinical thinking. Now the focus is on brain function response to an aberrant auditory stimulus (i.e., consciousness) rather than on brain responses to the psychophysical and psychoacoustic characteristics to the aberrant auditory signal: tinnitus.

The clinical translation of the TDST to identifying (through nuclear medicine imaging) neural substrates in patients with severe disabling tinnitus, reported since 1989, has provided increasingly accurate diagnosis of the tinnitus complaint by isolating a metabolic correlate and a biochemical marker, the GABA-A receptor.

The quantitative electroencephalography (QEEG) identification of an electrophysiological correlate—the thalamo-fronto-temporal circuit—for tinnitus patients with severe disabling tinnitus was reported. This finding renders possible an in-office method for objective electrophysiological recording in a tinnitus patient, thereby improving the accuracy of the tinnitus diagnosis and ensuring monitoring to objectively record treatment effi-

cacy. QEEG provides data that reflect brain function in affected patients. The clinical interpretation of the QEEG is based on theories of a neuroanatomical homeostatic system for brain function that regulates baseline levels of local synchrony in multiple neuronal assemblies and the concept of consciousness. This introduces a basis for recommending a paradigm switch in the clinical understanding of the symptom of tinnitus and an application for tinnitus diagnosis and treatment. Specifically, attention focuses on brain function response (i.e., consciousness) to an aberrant auditory stimulus, tinnitus, rather than to psychophysical and psychoacoustic characteristics of tinnitus.

The results of cochlear implantation in 18 patients were reported by Dr. Katrien Vermiere for Dr. Paul Van de Heyning and Dr. Dirk De Ridder. The study examines attempts at reducing tinnitus loudness and suffering in patients with a unilateral profound hearing loss provoked by incapacitating tinnitus. Implantation was performed in the deaf ear in all 18 patients in whom tinnitus was perceived. Selection criteria were (1) unilateral tinnitus due to profound sensorineural hearing loss; (2) incapacitating tinnitus refractive to conservative treatment modalities (tinnitus retraining therapy); (3) absent to moderate hearing loss in the contralateral ear; and (4) adult age and informed consent with the study according to the institutional review board. All patients received implants of the Med-el-multichannel cochlear implant (CI). The CIs were used by the patients daily for 12 months. Significant tinnitus reduction was reported by 17 of the 18 patients. The degree of improvement of the hearing did not correlate with the degree of tinnitus control. No conflict was reported between the hearing with the CI and the hearing in the opposite ear. The results are considered to support the hypothesis that tinnitus is a deafferentation-type sensation in affected patients and that this pathophysiological mechanism is reversible. Significant is that in this study, all patients with the severe, disabling-type tinnitus reported significant tinnitus relief with electrical stimulation.

Dr. Michael Hoffer discussed the Hear Pill (American BioHealth Group, San Diego, CA) and its rationale based on antioxidant use for prevention and treatment of noise-induced hearing loss and its potential for tinnitus relief. He reviewed the role of oxidative stress and antioxidants established in noise-induced hearing loss, the prevention of impulse noise-induced hearing loss with antioxidants, and age-related hearing loss and its association with reactive oxygen species and mitochondrial DNA damage. The results have provided a basis for treatment directed at prevention and maintenance of hearing.

Two mechanisms of inner-ear trauma have been reported to include depletion of glutathione and mitochon-

drial damage in the inner ear. Significant was the past report of the reduced permanent hearing loss due to acute trauma from continuous noise after use of acetyl-L-carnitine, a mitochondrial protectant.

The acetyl-L-carnitine was given to patients before and after acute noise trauma as a preventive and definitive modality of treatment. A combination therapy is projected for attempting tinnitus relief. The Hear Pill, a preparation using a technology licensed from the Navy to prevent and treat hearing loss based on an antioxidant rationale, may influence tinnitus. A report as to its efficacy for hearing loss and tinnitus relief is in preparation.

Dr. Abraham Shulman presented material prepared by Albert Stracher. It reviewed past efforts directed at identifying amino acids underlying biochemical processes involved in protein synthesis and protein degradation. It also highlighted a drug-targeting strategy directed initially at neuromuscular diseases and expanded to include neurodegenerative disease, bone loss, retinal degeneration, rheumatoid arthritis, hearing loss, and tinnitus. Calpain, a normal intracellular cytosolic protease, has been identified in neurodegeneration and noise-induced hearing loss. In animals exposed to noise-induced trauma, the drug Leupeptin (a calpain antagonist) has demonstrated neuroprotective action. The biochemical complexities involved in a final common pathway for tinnitus are hypothesized to include calpain. The future for tinnitus control includes plans to design neuroprotective medications that target genes involved in the neurochemistry of cochleovestibular and central nervous system function. (A Center for Drug Delivery Research has been established as a joint effort between SUNY Downstate Medical Center and Polytechnic University under the directorship of Dr. Stracher, SUNY Distinguished Professor and former chairman of biochemistry.) Its goal is the development of new drug delivery technology for advancing new therapeutic agents for the treatment of neuromuscular diseases, neurodegenerative disease, cancer, cardiovascular disease, bone loss, retinal degeneration, rheumatoid arthritis, hearing loss, and tinnitus. The approach is multidisciplinary and involves Dr. Shulman (otology and neurotology) to focus on drug development and delivery for hearing loss and tinnitus.

Dr. John R. Emmett was the guest of honor. His quiet, respectful attention to his patients and colleagues has earned him their respect. The response of his peers is reflected in positions of honor highlighted by the Centurions, Triological Society, American Academy of Otolaryngology-Head and Neck Surgery, and the American Tinnitus Association. His pride in family is a testament to the love and respect of his wife and children. Dr. Emmett was recognized for his pioneering work, together with John J. Shea and his colleagues at the Shea

Clinic, in introducing into the United States a lidocaine therapy in attempting tinnitus relief. His experience with the oral lidocaine preparation Topamax was investigated and reported in his presentation. It is a reference point for all professionals attempting tinnitus relief with lidocaine and other anticonvulsants. The presentation acknowledged the clinical problem of tinnitus and attempts toward its control. Significant was reference to past efforts with anticonvulsant therapy and lidocaine. Dr. Emmett made reference to B. L. Crue who, in 1970, considered tinnitus to be sensory epilepsy. Lidocaine therapy was recommended as a potent short-term anticonvulsant. In 1976, the Auckland Pain Clinic of New Zealand reported intravenous (IV) lidocaine as a diagnostic test in postherpetic neuralgia to differentiate between pain of central origin and peripheral origin. Some pain patients who also had tinnitus reported tinnitus relief. In 1978, Melding, Goodey, and Thorne reported the use of IV lidocaine and anticonvulsants in the diagnosis and treatment of tinnitus. Speculations as to the site and mechanism of action of lidocaine persist. The clinical use of tocainide hydrochloride (Tonocard), the oral, active amide analog of lidocaine, to provide tinnitus relief was aimed at overcoming the limitation of the short duration of relief with IV lidocaine reported by tinnitus patients having positive relief and at avoiding parenteral IV drug delivery. Its half-life is approximately 11 hours as compared to 1.5 hours for IV lidocaine. The results were reported in 1980. The dose recommended was 400 mg at bedtime, or two to four times a day. Significant side effects highlighted by gastrointestinal upset were reported in 1981 and 1984, and not all positive lidocaine responders experienced tinnitus relief with tocainide. The agent was concluded to be effective for tinnitus relief in a limited number of tinnitus patients. Dr. Emmett's personal approach in attempting tinnitus relief starts with the consideration of tinnitus as a symptom and the need to identify with affected patients and their tinnitus complaint. A treatment ladder is then followed with medication, including *Ginkgo biloba*, buspirone hydrochloride (Buspar), perphenazine (Etrafon), venlafaxine (Effexor), and intratympanic lidocaine and dexamethasone and IV lidocaine. Dr. Emmett's excellent presentation was appreciated by all. We recommend that the lidocaine experience of Dr. Emmett and Dr. Shea be reviewed and referenced by tinnitus patients considering lidocaine therapy and by professionals recommending lidocaine for tinnitus relief and for new delivery systems using lidocaine or other anticonvulsant therapy for such relief.

Dr. Mohamed A. Hamid reported that intratympanic perfusion of dexamethasone has become an accepted treatment for restoring hearing and controlling vertigo in patients with Ménière's disease. The treatment has

also resulted in tinnitus control in selected cases. The perfusion procedure is performed with local anesthesia and has no major side effects. Audiovestibular studies are essential in pre- and posttreatment management of such patients.

Dr. Robert J. Marchbanks was invited to present the theory of transcranial cerebral sonography and the technique that measures infrasound at frequencies of nominally 50 Hz or lower with a device known as the MMS-11 cerebral and cochlear fluid pressure analyzer. The device attempts to objectify abnormalities of intracranial fluid dynamics with inner-ear homeostasis disorders (i.e., inner-ear complaints of hearing loss, tinnitus, or vertigo). In addition, the data establish a basis for extrapolation for cerebrospinal fluid pressure. The transcranial cerebral sonography technique measures infrasound directly via a microphone sensitive to infrasound or in terms of tympanic membrane displacement using the cerebral and cochlear fluid pressure analyzer.

The link between abnormalities of intracranial fluid dynamics with inner-ear homeostasis disorders has been identified in the neurological disorder of Arnold-Chiari syndrome and pseudotumor cerebri. Clinically it is considered to be significant for identifying the etiology and mechanism of a subset of tinnitus in patients with the severe disabling type.

Dr. Joel Lehrer presented preliminary data using the MMS-11 cerebral and cochlear fluid pressure analyzer in neurootological patients with the chief complaint of vertigo and diagnoses of Arnold-Chiari syndrome, perilymphatic fistulas, perilymphatic hypertension, and idiopathic intracranial hypertension. Tympanic membrane displacements can be classified as spontaneous when generated by arterial, venous, or respiratory pressures transmitted through the inner ear to the stapes with resultant tympanic membrane displacement. They are evoked when the stapedius reflex is generated in response to a sound, the movement of which results in movement of the tympanic membrane. The tympanic membrane displacement results were significant, suggesting a link between abnormalities of intracranial fluid dynamics with inner-ear homeostasis disorders in the cases presented and the potential advantage of this test to estimate cerebrospinal fluid pressures.

Dr. Carlos A. Oliveira presented the results of a comparison of transient and distortion product otoacoustic emissions in normally hearing patients with and without tinnitus. The tests were completed in 32 patients with tinnitus and pure-tone thresholds equal to or below 25 dB in the 500- to 8,000-Hz frequency range, and results were compared to 37 control individuals with normal hearing and no tinnitus. The age range was 20–45 years in both groups. A hypothesis of tinnitus production has been related to dysfunction of the outer hair

cells. The results of this study suggest a reduction in activity of the outer hair cells in the tinnitus group. Inclusion of otoacoustic emission testing is recommended for all patients with tinnitus and normal audiometry.

The summary of the presentations of the Twenty-Fourth Annual Meeting of the International Tinnitus Forum reflects significant advances in the discipline of tinnitology toward clinical translation for tinnitus patient diagnosis and treatment. The highlights include, for diagnosis, an understanding of tinnitus as seen in an integration of advances in basic auditory and neuroscience into a theory of tinnitus with a focus on brain function, not only of perception but of consciousness; identification of a tinnitus circuit in brain that can be objectified with QEEG; the hypothesis that abnormalities of intracranial fluid dynamics may link with inner-ear homeostasis disorders (i.e., inner-ear complaints of hearing loss, tinnitus, and vertigo and an ear-placed device for measurement); and confirmation of an audiometric test—transient and distortion product otoacoustic emissions—that provides objective test findings in normal hearing patients with tinnitus. For treatment, positive results were reported in a selected cohort of tinnitus patients with CI electrical stimulation, lidocaine therapy, and intratympanic dexamethasone tinnitus relief in tinnitus patients with and without Ménière's disease.

The future for tinnitus treatment will parallel developments now in progress worldwide and their clinical translation to tinnitus control. This includes the potential of a rationale of antioxidant therapy for noise-induced hearing loss, which may have application for a particular clinical type of tinnitus, drug development

targeting underlying processes of neurodegeneration, and neuroprotection in tinnitus patients. The establishment of a Center for Drug Delivery Research as a joint effort between SUNY Downstate Medical Center and Polytechnic University will focus on such approaches, including benefits projected for tinnitus patients.

The quality and state-of-the-art content of papers presented at meetings of the International Tinnitus Forum have, over the years (and in particular within the last 3–5 years), reflected a widening dynamic range of information sources from multiple disciplines all capable of clinical translation into tinnitus diagnosis and treatment. The *International Tinnitus Journal* (ITJ), the official journal of the International Tinnitus Forum, anticipated this dynamic development in the discipline of tinnitology from the time of the journal's inception. This realization was seen in its original and subsequently added editorial staff and organizational section. Readers of the ITJ, a state-of-the-art, peer-reviewed journal dedicated to tinnitus, can expect future journal additions that will embody the widening dynamic range of information sources from multiple disciplines and having clinical translation to tinnitus diagnosis and treatment.

Plans are in progress for the Twenty-Fifth Annual Meeting of the International Tinnitus Forum in Washington, DC, on September 15, 2007—our twenty-fifth anniversary. The title of the meeting will be Translational Research in Tinnitus Therapy III. Themes of the meeting will include neuroimaging and tinnitus. Details will follow. Plan to attend.

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