

EDITORIAL

International Tinnitus Forum, Twenty-Third Annual Meeting: Translational Research in Tinnitus Therapy

The Twenty-Third Annual Meeting of the International Tinnitus Forum (ITF), titled “Translational Research in Tinnitus Therapy,” was concluded in Los Angeles on September 24, 2005. The goal of the meeting was to present to the attendees a take-home awareness of state-of-the-art methods for introducing into clinical practice basic “bench” science advances. These advances include improved accuracy of tinnitus diagnosis, increased efficacy of existing means of therapy, and new modalities attempting tinnitus relief.

The theme of the meeting was translational medicine and tinnitus: how basic science advances are integrated and adapted into clinical medicine for workable applications to benefit tinnitus patients.

In general, the presentations, reflective of translational research, increased the understanding, diagnosis, and treatment of the clinical course of tinnitus (particularly of the severe disabling type) toward achieving tinnitus relief. The presentations included processes underlying basic mechanisms at a cellular level involved in apoptosis-inflammation and neurodegeneration; diagnostic audiological testing methods of ultra-high-frequency audiometry and vestibular cranio-corpography; treatment methods of sound-wave shift and ultra-high-frequency acoustic stimulation; and clinical reports of tinnitus in whiplash injury and the atretic ear.

“Transitional and Translational Research” (presented by M.E. Hoffer) are the processes by which research moves from the bench to treatment of patients. Translational medicine examines how the industry is optimizing the impact of translational research activities into workable applications. Hoffer’s presentation traced how basic scientific work with noise exposure and hearing loss was transitioned and translated to human use and how the use of antioxidants can be and is being applied to the treatment of tinnitus. Translational research involves a paradigm switch from the old (i.e., identifying the basic mechanism of what I am studying) to the new (i.e., how what I am studying applies to the clinic). This switch involves new processes and techniques. Hoffer voiced caution against abandoning other research types.

In his presentation, “Antioxidants and Their Role in

Tinnitus,” B.J. Balough presented a summary of pharmacological and nonpharmacological approaches to tinnitus: past, present, and future. A critique of past studies centered on nonrandomized and noncontrolled trials and on low numbers reported. In addition, he discussed the lack of uniform patient criteria in differentiating various clinical types of tinnitus and the attendant lack of uniform reporting. Balough emphasized the need to respect the reported placebo effect of up to 40% in evaluating efficacy of therapeutic modalities attempting tinnitus relief, and he cited the lack of and need for developing basic science models. He recommended that the placebo effect be considered in reported results for tinnitus relief for “existing drugs,” “supplements,” and future pharmacological approaches attempting tinnitus relief. His review of drugs and the publications describing the basic and clinical science of these agents included tricyclic antidepressants, GABA-active drugs, prostaglandins, vasodilators, and the supplements zinc, *Ginkgo biloba*, B vitamins, and antioxidants. Currently, no large human trial for noise-induced hearing loss or tinnitus has been reported. For the future, Balough called for linkage of basic science with clinical studies of sufficient power and clarity.

These excellent presentations served as a follow-up and addition to previous ITF meetings in 2003 and 2004 having as their theme tinnito-pharmaco-proteogenomics. The development of such biopharmaceuticals is exceedingly complex and formulation development must be an integral part of the processes involved in drug production. Achieving the goal of successful manufacture of recombinant biopharmaceutical drugs for clinical testing and commercialization depends on input from knowledgeable clinicians and tinnitus patients and on high production yields, efficient purification schemes, and stable formulations. Lack of formulation development, particularly with regard to new proteins, may cause significant delay, thereby increasing the time required for agents to reach clinical trials or the market. Chromatographic and spectrographic characterizations are a requisite for formulation development and are an integral component of discovery, process development, and specification selection.

Tinito-pharmaco-proteogenomics formulations should include such considerations as stability, safety, and scalability and such factors as material contact, quality of raw material, and manufacturability and cost—all a continuum—in tinnitus drug development. A seamless interface must be created among neuroscience, biophysiology, and clinical otology, neurootology, and audiology, allowing each group the time, resources, and information to develop its contribution to a tinnitus drug and to expedite quality and cost-effectiveness. Time is of the essence, particularly for patients with severe disabling tinnitus.

P.G. Loyzaga reported the results of animal experimentation in the inner ear: "The Role of Serotonergic Innervation of the Inner Ear." Recent findings observed during cochlear blockade of serotonin transporters strongly suggested that this neuroactive substance has an important turnover within the auditory receptor. Although serotonin seemingly is not involved in cochlear neurotransmission or neuromodulation during auditory processing, serotonergic fibers are hypothesized nonetheless to play an important role in the auditory receptor, probably related to the general control of the sensory receptor.

The discussions that followed these presentations were highlighted by interesting considerations. First, participants debated medical-audiological tinnitus patient protocols, stressing the need for tinnitus professionals to develop protocols that provide for a differentiation between different clinical types of tinnitus. The consensus was that this would increase the accuracy of the tinnitus diagnosis both for treatment selection and reporting of efficacy for tinnitus relief. No longer can tinnitus be considered a unitary symptom.

Attendees also discussed the need for total cochleovestibular system evaluation, both peripheral and central, with a view to establishing an accurate tinnitus diagnosis and selection of treatment modality and the identification of the medical significance of the tinnitus complaint. Additionally, discussion centered on establishing objectivity in nuclear medicine imaging (i.e., brain single-photon emission computed tomography or positron emission tomography [or both]) and in electrophysiological functional imaging (i.e., quantitative electroencephalography) for patients with severe disabling tinnitus.

Our guest of honor was Dr. John House, a true Californian—born, raised, and educated in a tradition of equality, fairness, and respect for family and community. It was fitting that he be our guest of honor here in Los Angeles at this Twenty-Third Annual Meeting of the ITF. His presentation, "Tinnitus: 30 Years' Experience and Frustration," reviewed a 30-year history that included attempts for tinnitus relief with instrumenta-

tion and medication. It was a positive summary of basic science and clinical efforts and future expectations. Emphasis was placed on (1) the need to obtain a complete history and to explain to affected patients what is known of the tinnitus symptom and (2) on the availability of multiple modalities of instrumentation and medication for attempting tinnitus relief. From his many contributions to otology and neurootology, Dr. House stressed at this meeting the significance of identifying and attempting treatment of the affect tinnitus component (i.e., the behavioral response of patients with severe disabling tinnitus to anxiolytic-antidepressant medication). He also updated results for tinnitus relief, which focus on controlling anxiety and depression manifested by many patients; Dr. House initially presented this area of inquiry at the First and Second International Tinnitus Seminars in New York City in 1979 and 1981, respectively, and at the Ciba Symposium in London in 1981.

"Vestibular Testing and the New Technique of Craniocorpography," a presentation by Dr. C.-F. Clausen, allows clinicians to identify the psychomotor component of the tinnitus symptom. Clinically, this technique is recommended not only as a screening test for vestibular diagnosis but as a monitor for efficacy of therapy modalities attempting tinnitus relief. Dr. Clausen introduced a classification of tinnitus to differentiate between exogenous and endogenous tinnitus.

M.D. Seidman chose to present "Direct Electrical Stimulation of Cortex" for attempting tinnitus relief and reported positive results. Notwithstanding that the study was limited to two single cases, the report was exciting. He outlined a concise review of the history of direct cortical electrical stimulation and the method of patient selection. All attendees congratulated Dr. Seidman for this translational clinical effort and presentation.

The discussion that followed included other interesting highlights. Concerning method, C.-F. Clausen informed the attendees of the history of stereotaxic surgery [1] and urged them to consider less invasive surgical approaches that may result in similar results for tinnitus relief. Also to be considered for direct electrical stimulation of cortex are several recent publications. Cheung et al. [2] reported significant and sizeable A_1 frequency distribution and area₁ content map variations in squirrel monkey primary auditory cortex. Discussion of clinical application of this study included its consideration for tinnitus patient selection and the evaluation of tinnitus relief results. Specifically, it suggested that direct electrical stimulation of cortex attempting tinnitus relief is probably highly individual and variable. The report in this study—that " A_1 frequency maps have striking variations in the highest CF isocontour"—is considered to be particularly significant

for high-frequency tonal tinnitus. A. Shulman suggested that the workup for patient selection for this procedure should include nuclear medicine imaging (positron emission tomography [PET] or single-photon emission computed tomography [SPECT]), quantitative electroencephalography, and ultra-high-frequency audiometry. Another study, by Zuo et al. [3], reported substantial decrease in the number of synapses in the mammalian brain from the late postnatal period until the end of life. At distinct stages of life, apparently the more experience one has, the more synapses will be lost in the brain. The results emphasize the importance of childhood experience in sculpting neuronal connectivity while the brain is up to the task.

Discussion included the consideration that the sensory experience for all sensations is significant for tinnitus relief with direct cortical stimulation. Although sensory deprivation can be reversed in adolescents, it cannot be reversed once spines are stabilized in adulthood. Interestingly, the dendritic spines are postsynaptic sites of the majority of excitatory axodendritic synapses in brain, and their activity serves as an indicator of synaptic plasticity. Chronic blockade of N-methyl-D-aspartate receptors with the antagonist MK801 decreases the rate of spine elimination and accelerates after blockade withdrawal. The issue in direct cortical stimulation for tinnitus becomes one of understanding synaptogenesis and synaptic plasticity. The "timing" of the sensory experience becomes significant and is reflected in brain function by the integration of experience, learning, and memory. To be considered in relation to that study is the hypothesis of a final common pathway for tinnitus (i.e., the transformation of a sensory to an affect behavioral response), the initial process being the establishment of a paradoxical memory for the aberrant auditory sensation of tinnitus. A. Shulman pointed out that patient selection for direct electrical stimulation of cortex for tinnitus relief should consider multiple factors based on what little is known of brain function. Also, for the future, a combination of direct cortical stimulation and direct drug application may increase the efficacy of this therapeutic modality.

Significant for future tinnitus diagnosis and therapy would be information—obtained from cortical electrical stimulation—establishing the correlation among the tinnitus match, site of electrode placement, and reported tinnitus relief. We look forward to future reports of this effort for cortical electrical stimulation, both for tinnitus relief results and for understanding the basic neurophysiology of the auditory system and plasticity of the auditory cortex.

Muhlnikel et al. [4] demonstrated a reorganization in the auditory cortex of expansion in the tinnitus fre-

quency areas (more than doubled in size), with a suggestion of lower-frequency expansion below the expected frequency subsequent to the hearing loss.

Lenhardt [5] introduced us to ultra-high-frequency/ultrasonic (UHF/US) acoustical response. Clinically, metabolic alterations at a cortical level have been reported to correlate with the residual peripheral neuronal population in the cochlea and integrity of the cortex. That is, the alteration–neural reprogramming–plasticity at a cortical level does not appear to be a unitary phenomenon (limited to the cortex) [6].

The report that A_1 frequency maps have striking variations in the highest CF isocontour is considered to be particularly significant for high-frequency tonal tinnitus. It must be remembered that electrical stimulation and tinnitus relief were reported in 1801 [7]. Not surprisingly, a positive result for tinnitus relief has been reported with direct cortical electrical stimulation. A. Shulman warned that we must temper our desire to obtain a result with understanding of what is taking place at a cortical level in response to direct electrical stimulation in normal patients over time, in patients with different types of tinnitus, and with different residual neuronal populations in the cochlea.

The distribution of the branches of the middle cerebral artery (cortical and subcortical) are to be considered in electrode placement "at the auditory cortex (A_1)." In particular, as A. Shulman pointed out, attempts to increase access to A_1 by increasing visibility in the Sylvian fissure may result in cerebrovascular complications reflecting underlying neuronal substrates.

"A Frequency Mapping Approach for Tinnitus Relief" (S. Chandrasekhar) based on sound wave shift and "UHF Acoustic Stimulation for Tinnitus Relief" (B. Goldstein) are exciting reports. Both reports are positive for achieving tinnitus relief. Are both a clinical translation of the masking phenomenon, the basic science of which is not known? Is masking with the conventional frequencies of 250–8,000 Hz clinically suggested to be different from that in the UHF/US range? Is the "sound wave shift" a masking effect? The prediction of which tinnitus patient may benefit from ultra-high-frequency acoustic stimulation provides to professionals an objective basis for selection of a particular modality of therapy in attempting tinnitus relief.

A study of two case reports by Shulman et al. [8] focused on SPECT of brain demonstration of hypoperfusion in brain areas supplied by the middle cerebral artery on the side of an atretic ear, contralateral to the location of the reported tinnitus. Total evaluation of the cochleovestibular system (both peripheral and central) established in an affected patient that the medical significance of the tinnitus was one of cerebrovascular disease and a gradually increasing sensorineural hearing

loss. The ultra-high-frequency hearing loss was greater than expected for the age of the patient. A plan of therapy directed to the GABA_A receptor for one patient resulted in significant tinnitus relief. Questions raised are highlighted by determining the incidence of hypoperfusion in the brain in patients with congenital atresia of the external ear: Is the ultra-high-frequency hearing loss associated with the congenital atresia, and what is the incidence of cerebrovascular disease in this population? Total evaluation of the cochleovestibular system, both peripheral and central, is recommended in patients with severe disabling tinnitus to include nuclear medicine imaging (SPECT of brain), ultra-high-frequency audiometry, and electrophysiological functional imaging (quantitative electroencephalography).

All presentations at the meeting demonstrated the state-of-the-art translations of basic science into clinical applications for both diagnosis and treatment of cochleovestibular complaints. Resultant clinical observations are providing a feedback loop for future translation into research. Thus is created a "circle," a "continuum" of input, all for the benefit of tinnitus patients.

The efforts of Dr. Barbara Goldstein provided excellent coordination and arrangements for this meeting, efforts that contributed significantly to its success. An open invitation was extended to professionals. Those desiring to participate may submit abstracts to be considered for presentation at the Twenty-Fourth Annual International Tinnitus Forum, Toronto, Canada, September 16, 2006. Materials should be directed to Abraham Shulman, MD, Downstate/SUNY, 450 Clarkson Avenue, Box 1239, Brooklyn, NY 11203 (Phone: 718-773-8888; Fax: 718-465-3669; E-mail: metre@inch.com).

Those desiring to attend the Thirty-Third International NES Congress, Bad Kissingen, Germany, should contact Claus F. Claussen, MD, NES, Kurhausstrasse 12, Bad Kissingen, Germany 97688 (Phone: 0049-971-64832; Fax: 0049-971-68637; E-mail: claussenolog@t-online.de).

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