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Viewpoint

Report From a U.S. Conference on Essential Tremor

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Abstract: Seventy researchers met in Washington, DC, on 20–21 October 2005 to identify and discuss the most pressing research issues in essential tremor (ET). The conference attendees concluded that the following six objectives are of immediate and overriding importance: (1) a collaborative network of research centers; (2) an international committee for developing a standard protocol for the diagnosis and quantification of ET; (3) the identification of one or more genes for ET; (4) a centralized repository of DNA and, ideally, immortalized cell lines from well-characterized ET families and healthy controls; (5) a reliable and efficient repository of optimally prepared and categorized brain samples for hypothesis-driven neuropathological examinations in well-characterized ET patients; and (6) animal models of ET for screening promising drugs. The conference attendees hope that this statement from the United States will engender international collaboration in finding a cure for ET. © 2006 Movement Disorder Society

Key words: essential tremor; pathophysiology; genetics; clinical trials; clinical neurophysiology

Historically, essential tremor (ET) has attracted relatively little interest because it is often mistakenly viewed as being a benign disorder that usually causes little or no disability. Few grants have been successfully submitted to the National Institutes of Health (NIH) for research in ET, and future research will require collaborative efforts and better communication among established and potential investigators. To this end, the Tremor Research Group organized a conference on essential tremor, which was held at the Embassy Suites Hotel Chevy Chase Pavilion in Washington, DC, on 20–21 October 2005.

This conference was funded by grants from the National Institute of Neurological Disorders and Stroke (1 R13 NS52017-01), International Essential Tremor Foundation, U.S. Army Medical Research and Materiel Command, Medtronic, Jazz Pharmaceuticals, Advanced Neuromodulation Systems, and Merck, and it was endorsed by the Movement Disorder Society. In addition to 13 representatives from these sponsors, the conference was attended by 25 invited speakers, 10 junior investigators nominated by chairs of neurology departments in the United States (letters soliciting nominations were sent to all chairs), 12 established investigators, and 10 researchers from the NIH. The 25 speakers were assigned to six workgroups devoted to the following general topics: diagnosis, epidemiology, pathophysiology, genetics, measurement and clinical assessment, and treatment. The remaining attendees were assigned to a general workgroup. Following the presentations of the 25 speakers, the workgroups met for 1 hour to summarize the most pressing research issues in ET. The workgroups then reconvened for the presentation and final discussion of these issues, which are now summarized for the benefit of all interested parties. The first draft of this summary was written by Rodger J. Elble and submitted to all conference attendees for feedback and revision. The revised summary was then submitted to all attendees for final revision and approval.

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Diagnosis and Clinical Characteristics of ET (Speakers: Jankovic, Juncos, Sethi, and Watts; Group Leaders: Sethi and Watts)

The typical patient with ET exhibits no neurological abnormalities other than action tremor (postural or ki-

netic) in both upper limbs (approximately 95% of patients) and less commonly in the head (approximately 34%), face (approximately 5%), voice (approximately 12%), tongue (approximately 30%), trunk (approximately 5%), and lower limbs (approximately 30%).[1,2] Patients with advanced ET often have crescendo tremor as the hand approaches its target, resembling cerebellar intention tremor,[3] and many of these same patients have subtly impaired eye movements[4] and impaired tandem walking without any other disturbance of gait.[5] Subclinical cognitive deficits have been found in six studies of patients with ET,[6–11] and inconsistent reports of mild olfactory impairment have been published.[12–15]

The extent to which other mild neurological signs may occur in ET has been a topic of debate[16,17] and was discussed extensively at the conference. Some patients with long-standing ET later develop rest tremor and other parkinsonian signs.[16] Increased risk of parkinsonism in some patients with ET is also suggested by the co-occurrence of ET and pathologically proven PD in some families,[18] mildly low striatal dopamine transporter (DAT) activity in some ET patients,[19] and Lewy body pathology in some patients with ET.[20,21] However, misdiagnoses are common[22] because the clinical characteristics of ET in the upper limbs are nonspecific. Identical action tremor can be the sole presenting symptom in patients with Parkinson's disease,[23] hereditary spinocerebellar ataxias,[24] fragile X–associated tremor/ataxia syndrome (FXTAS),[25] and dystonia.[26–29]

Therefore, the conference attendees recommend that research studies utilize the skills of a movement disorder neurologist in diagnosing ET and normal controls, and they concur with the diagnostic criteria developed at the 1997 International Tremor Conference in Kiel, Germany. Definite ET is defined as abnormal action tremor of both upper limbs or isolated head tremor with no abnormal posturing, dystonia, or other neurological signs.[30,31] Cogwheeling in the absence of rigidity is common, and mildly unsteady tandem gait with no other disturbance of walking is seen in some advanced patients.[5] Some investigators regard isolated head tremor as possible ET[2] because such patients often prove to have tremulous cervical dystonia.[32]

The Kiel criteria do not specify how to distinguish mild ET from enhanced physiological tremor. Therefore, many investigators supplement the Kiel criteria with tremor amplitude requirements.[33,34] These amplitude requirements specify that hand tremor must be rhythmic and present in multiple activities (e.g., pointing and pouring), with an amplitude of approximately 0.5 to 1.0 cm (see the WHIGET criteria of Louis and colleagues[34,35]). These conservative criteria will exclude patients with very mild ET. This is not a problem in clinical studies of therapeutic agents for disabling tremor, but the exclusion of patients with very mild ET is not desirable in genetic studies.

There is no foolproof method of distinguishing very mild ET from physiological tremor in any age group, but electrophysiological tests have some value.[36–38] The sine qua non of ET is an abnormal entrainment of motor units at the frequency of tremor, which is classically 4 to 8 Hz. The frequency of motor unit entrainment changes less than 1 Hz when large inertial loads are attached to the limb. This frequency-invariant motor unit entrainment can be demonstrated in the forearm with surface electromyography, recorded with and without at least 300 g attached to the horizontally extended hand.[36–40] For patients with at least moderate tremor, the concordance between clinical diagnosis and electrophysiological diagnosis is nearly perfect.[36,41] By contrast, only 61% of people, age 70 to 91, with questionably abnormal postural or kinetic hand tremor (i.e., barely visible wrist tremor, causing the entire hand to shake) exhibit frequency-invariant motor unit entrainment.[42] Consequently, many patients with very mild or questionable ET will remain undiagnosable, despite the use of electrophysiological testing.

Only 8% of young (ages 20–40) and elderly (ages 70–92) controls exhibit prominent frequency-invariant motor unit entrainment in the absence of fatigue and tremorogenic drugs.[43] The frequency of this tremor is always 8 to 12 Hz in the young controls but is often 4 to 8 Hz in the elderly. Therefore, the presence of frequency-invariant motor unit entrainment at less than 8 Hz can be used as supporting evidence for ET in young adults with mild or questionably abnormal tremor. Patients with very early ET may exhibit this phenomenon when clinically the amplitude of tremor is only questionably abnormal.[44] However, the significance of an 8–12 Hz central neurogenic tremor is uncertain, and 4–8 Hz tremor can be seen in other conditions such as dystonia, Parkinson's disease, and possibly normal aging, so frequency-invariant EMG activity is not specific for ET.[40,41]

In summary, there is no completely reliable neurophysiological test or biological marker for diagnosing ET. Conservative diagnostic criteria (e.g., the Kiel criteria) should be used until a good laboratory test is developed. Electrophysiological tests may be used adjunctively.

Epidemiology of ET (Speakers: Louis and Tanner)

ET may begin in early childhood,[45–47] but its prevalence and incidence increase with age. Prevalence estimates from previous studies vary greatly due to the high rate of undiagnosed individuals with mild tremor, vari-

ability in diagnostic criteria, lack of a reliable diagnostic test, and frequent ascertainment bias.[34] The prevalence estimates from published community-based studies range from 4 to 39 cases per 1,000, and for people age 60 and older, the estimates range from 13 to 50 per 1,000.[48] At least 5% of people 65 years and older have ET, and ET occurs in all ethnic groups.[42,49–52] There are only two published incidence studies,[53,54] and virtually nothing is known about the effect of comorbidities.

Many cases are hereditary, but the proportion of hereditary versus sporadic cases is uncertain. First-degree relatives of ET patients are 5 times more likely to develop the disorder than controls, and they are 10 times more likely to develop ET if the proband's tremor began before age 50.[55] Tanner and colleagues[56] found a 60% concordance in monozygotic twins. Lorenz and colleagues[57] found a 77% concordance, which increased to 93% when they restricted their analysis to monozygotic twins with definite and probable ET.[2] These differences illustrate the importance of carefully defining ET for research purposes.

Only a few studies have looked for environmental factors in ET. Two recent epidemiological studies have implicated environmental β-carboline alkaloids and lead in ET.[58,59] Exposure to organochlorine pesticides is not a risk factor.[60]

The conference attendees identified the following epidemiological studies for future consideration: health care costs produced by ET; the natural history of ET (progression prospectively over time); prospective case–control studies of mortality; study of incident cases to explore associations; and studies of environmental risk factors, genetic factors, and their interactions.

Pathophysiology of ET (Speakers: von Sattel, Perlmutter, Lenz, and Thach; Group Leader: Elble)

Many observations suggest that ET emerges from abnormal oscillation within thalamocortical and olivocerebellar loops. Lesions in the cerebellum and thalamus greatly reduce ET.[61] Tremor-correlated neuronal discharge occurs in the ventrolateral thalamus, especially in the nucleus ventralis intermedius (Vim),[62] and electrophysiological studies have demonstrated enhanced cerebrocortical rhythmicity.[63–65] Contralateral limb tremor is greatly suppressed by ablation, high-frequency stimulation, and muscimol microinjection of Vim.[66–68] PET studies have produced data suggesting bilaterally increased olivary glucose utilization[69] and bilaterally increased blood flow in the cerebellum, red nucleus, and thalamus.[70] Functional MRI studies have disclosed increased blood flow bilaterally in the cerebellar hemispheres, dentate nucleus, and red nucleus and contralaterally in the globus pallidus, thalamus, and primary sensorimotor cortex.[70] Magnetic resonance spectroscopy revealed a reduced *N*-acetyl-L-aspartate to creatine ratio in the cerebellar cortex, consistent with neuronal loss or dysfunction.[71,72]

However, published neuroimaging and electrophysiological studies have significant limitations. Increased cerebellar blood flow and Vim thalamic rhythmicity occur in other forms of tremor, so the pathophysiological interpretation of data from PET, EEG, MEG, and intraoperative recordings is uncertain.[61,73,74] Only one study has suggested hyperactivity (increased glucose consumption) in the vicinity of the inferior olives.[69] Furthermore, published neuroimaging studies did not consistently monitor motor behavior during scans, so it is possible that the reported bihemispheric cerebellar hyperactivity at rest was an artifact of occult tremor during incomplete muscle relaxation. All studies have been limited by small numbers of patients, resulting in low statistical power with marginal statistical significance of many results. Therefore, additional neuroimaging studies should be done with careful behavioral monitoring of subjects during imaging (e.g., with EMG), adequate numbers of patients for appropriate statistical power, and proper statistical analyses with appropriate correction for multiple comparisons. In this way, we can determine whether there are truly abnormalities of cerebellar pathways in the resting state.

If bihemispheric cerebellar hyperactivity at rest truly exists, as measured with PET imaging, it would suggest that cerebellar afferents or intrinsic interneurons are hyperactive at rest. However, intraoperative electrophysiological recordings have revealed abnormal oscillation in the ventrolateral thalamocortical loop only during voluntary muscle contraction and not when the limb is at rest.[62] Therefore, if oscillations or some other form of hyperactivity does exist in the cerebellum at rest, it is transmitted to the thalamus only during voluntary muscle activation. Voluntary muscle activation could produce Vim oscillation via corticothalamic input, with or without oscillatory drive from cerebellar circuits.[62] Thus, the interaction and relative importance of olivocerebellar and thalamocortical pathways in tremorogenesis are still unclear.

Vim has a significantly higher proportion of tremor neurons than does the principal somatosensory nucleus (ventral caudal, Vc) and a pallidal recipient thalamic nucleus (ventral oral posterior, Vop),[62] but the involvement of all three nuclei suggests that the pathophysiology of ET may not be limited to pathways mediating the cerebellar control of movement. Indeed, subthalamic DBS has been found to suppress ET.[75–77] The critical

target in the subthalamic area could be the zona incerta and prelemniscal radiation, which carry cerebellar and somatosensory afferents to the ventrolateral thalamus, or it is possible that basal ganglia pathways participate in tremorogenesis.

Harmaline-induced tremor in laboratory animals emerges, at least in part, from tremorogenic rhythmicity in olivocerebellar pathways. Studies of octanol in this model[78] led to pilot clinical trials in ET with promising results,[79,80] and Martin and colleagues[81] recently proposed a harmaline mouse model for preclinical screening of candidate medications for ET. Moreover, Kralic and colleagues[82] recently described a $GABA_A$ receptor α_1 subunit knockout mouse with tremor that resembles ET, and this animal model might be useful for drug screening. Neither animal model may be a true replica of ET pathophysiology,[83] but this does not preclude their utility in drug screening.

Surprisingly few autopsies have been performed, considering the high prevalence of ET. Rajput[84] found no consistent abnormalities, but Louis and colleagues[20,21] have found brainstem Lewy bodies in some patients and increased Bergmann gliosis and axonal torpedoes in the cerebellum of other patients. Thus, ET may be a pathologically heterogeneous disorder. Younger patients and multiple affected people from the same family must be studied to avoid attributing spurious or coincidental pathology to ET.

The conference attendees believe a reliable and efficient repository of optimally prepared and categorized brain samples is needed for hypothesis-driven neuropathological examinations in well-characterized ET patients. To this end, Louis and von Sattel at Columbia University have established a centralized brain bank for ET (http://www.essentialtremor.org/research/brain_bank.php) and have worked to establish collaborative relationships with brain banks and neuropathologists at other institutions. Brains are processed so that biochemical, molecular biology, and proteomic studies can be performed by interested investigators. In conjunction with this brain bank, a collaborative network of investigative centers sharing data, analyses, and suggestions is needed.

In summary, our understanding of the pathophysiology of ET is still inadequate. Whether ET emerges from a localized site of abnormal oscillation (e.g., the thalamocortical loop or olivocerebellar loop) or from a more widespread disturbance of motor control (as in the $GABA_A$ receptor α_1 subunit knockout mouse) is unknown. The conference attendees believe the identification of one or more genes for ET is a necessary step toward deciphering ET pathophysiology. Identification of ET genes would enable the development of neurohistochemical markers that could be used to search for nervous system pathology.

Genetics of ET (Speakers: Higgins, Goldfarb, Gwinn-Hardy, and Singleton; Group Leader: Jankovic)

ET is often inherited in an apparent Mendelian dominant fashion. However, manifestations may not occur until age 65 or later, and penetrance may not be complete at advanced ages.[33,85] Studies of autosomal dominant pedigrees have identified a disease locus on chromosome 3q13 (*ETM1*)[86] and on chromosome 2p22-p25 (*ETM2*).[87–89] Suggestive linkage to 6p23 and 11p15 chromosomal regions was identified in large American pedigrees.[90] Thus, three or more genes may be involved, despite a remarkably consistent phenotypic expression of ET among families studied.[87,88,91,92]

It is disappointing that no gene for ET has been identified despite the efforts of several collaborative groups. A nonsynonymous variant (828C>G) in the *HS1-BP3* gene was recently identified in two American families with ET.[93,94] The 828C>G variant causes a substitution of a glycine for an alanine residue in the HS1-BP3 protein (A265G), which is normally highly expressed in motor neurons and Purkinje cells and regulates the Ca^{++}/calmodulin-dependent protein kinase activation of tyrosine and tryptophan hydroxylase. However, other studies have concluded that this variant may represent a normal polymorphism in the *HS1-BP3* gene, with no pathogenicity for ET.[95,96]

Thus, genetic heterogeneity in ET is very likely, and given the high prevalence of ET, large families with dominantly inherited ET could contain a second gene or phenocopy that would confound genetic linkage studies. Polygenic or digenic inheritance is another possible reason for failing to find an ET gene. The conference attendees recommend the following actions to facilitate the identification of ET genes.

One, focus on families with clear Mendelian inheritance of definite (monosymptomatic) ET, excluding those families with additional motor disturbances such as parkinsonism, dystonia, and myoclonus.

Two, develop a centralized repository of DNA and, ideally, immortalized cell lines from well-characterized ET families and healthy controls to allow sharing and pooling of resources.

Three, identify and study founder families in geographically isolated populations.

Four, perform a complete analysis of all genes in known loci (3q13.1, 2p24.1) and recent candidate loci (6p23, 11p15). Recently reported candidate polymor-

phisms (e.g., *HS1-BP3*) should be replicated in other families and in controls.

Five, when confirmed, the effects of mutations on mRNA and protein expression should be determined.

Six, conduct multicenter international studies of sib-pairs, monozygotic twins, and nuclear families (proband, both parents, and one affected sibling or child) with monosymptomatic ET and no evidence of bilineal transmission. A subset of centers involved in multicenter genetic studies should use electrophysiological tests to distinguish enhanced physiological tremor from very mild ET.[37,43,44]

Seven, search for chromosomal abnormalities (e.g., deletions, translocations) in patients with definite ET.

Eight, publish negative results of genetic linkage studies. This might consist of a brief report or abstract in a Medline journal, with a hyperlink to a full-length report on the Internet.

Nine, genetic mouse models with an ET phenotype (e.g., $GABA_A$ receptor α_1 subunit knockout) should be pursued and studied.

Measurement and Clinical Assessment of ET (Speakers: Tintner, Lyons, Elble, and Goetz; Group Leaders: Tintner and Lyons)

The 1997 Kiel conference on tremor spent little time addressing the problem of quantifying tremor for diagnosis and assessment in clinical trials. The published literature contains numerous rating scales, similar to the Fahn–Tolosa–Marín scale,[97] which were never validated. The WHIGET scale[35] and the scale of Bain and colleagues[98] are two notable exceptions. The Tremor Research Group is developing a scale specifically for ET that has good concordance between raters and excellent correlation between live and video and repeat assessments.[99]

ET interferes significantly with employment, activities of daily living, and social function,[100] with approximately 75% of patients reporting significant disability.[101] A valid reliable questionnaire for assessing disability and a performance-based rating scale were recently developed by Louis and colleagues,[102,103] and Lyons and colleagues[104,105] developed a quality-of-life assessment scale that is sensitive to the problems of ET. Existing generic quality-of-life assessments, such as the Sickness Impact Profile, are not sensitive to the impact of ET.

The conference attendees recommend the development of a unified tremor rating scale that is suitable for research studies and routine office assessments. This scale should measure motor function (tremor), activities of daily living, and quality of life. An international committee on tremor scales is needed to review the assets and deficiencies of existing scales to determine if an existing scale is ideal. If not, a group of candidate scale items could be decided on and an algorithm for validation should be agreed on. The committee should include scale developers, statisticians, and clinicians.

The extent to which rating scales should be supplemented with accelerometry and other motion transducers is still debated.[106,107] Tablets, accelerometers, and other motion transducers provide linear measures of tremor, but rating scales do not, which is predicted by the Weber–Fechner–Stevens laws of psychophysics.[108] The relationship between typical five-point rating scales and linear precision measures of tremor with accelerometry and digitizing tablets is logarithmic, such that a one-point increase in the Tremor Rating Scale (TRS) corresponds to roughly a 216% increase in tremor amplitude, and a one-point decrease in the TRS is a 68% decrease in amplitude. Similarly, the ratio of tremor amplitudes is 3.16 for a one-point worsening in TRS and 0.316 for a one-point improvement in TRS.[109] This poor resolution and nonlinearity may be unacceptable in many clinical trials of tremor therapy.

The conference attendees strongly encourage the further development of objective devices such as digitizing tablets, accelerometry, and EMG, with consideration given to devices that can be used by patients in their homes. Because of diurnal variation in tremor amplitude,[110] continuous accelerometric[111] and electromyographic[112] recordings should be considered for use in clinical trials. Data reduction should be done at a central facility when these devices are used in multicenter trials.

Treatment of ET (Speakers: Ondo, Comella, Pahwa, Hallett, and Fahn; Group Leaders: Ondo and Pahwa)

Only 2 of 159 published surgical and pharmacological treatment trials (Medline: 1966–2003) included more than 50 patients (median = 15). Nearly all were performed by single investigators, and so many ad hoc study designs and measures of efficacy were used that it is impossible to compare the results among most studies accurately.[113] Standards for performing therapeutic trials and strategies for identifying and testing new treatments are needed.

Many drugs have been used to treat ET, but only a few have proven efficacy.[113] Beta-adrenergic blockers and primidone are the mainstays of pharmacotherapy, but only about 50% of patients with ET benefit from one or both of these medications, and the average reduction in tremor is only about 50%. Topiramate was recently shown to have similar efficacy.[114] The beneficial effect of all drugs is largely limited to hand tremor, although

this impression may reflect, to some extent, weaknesses in our ability to measure head and voice tremor.

Botulinum toxin injections into the forearm muscles produce little if any improvement in most patients, and finger or wrist weakness is a common side effect.[115,116] Greater efficacy has been reported in occasional patients with disabling head tremor and voice tremor, but this experience is largely anecdotal.[113] Future studies of botulinum toxin and other injectables should be done separately for head, voice, and limb tremor. The study design should allow for individualized dosing and muscle selection.

Vim thalamotomy and deep brain stimulation (DBS) produce marked (>75%) or complete suppression of limb tremor in 70% to 90% of patients and is therefore the most effective treatment for ET.[115,116] Abnormal motor unit entrainment is dramatically reduced, making tremor more physiologic.[117] Thalamotomy and DBS are reserved for drug-resistant tremor that warrants the risks of surgery.[68,113,115,116,118,119] DBS is the procedure of choice at most centers because it is associated with fewer adverse events than thalamotomy, particularly when bilateral procedures are performed.[113] The improvement with Vim DBS has been maintained up to 7 years.[120]

Vim is the preferred stereotactic target in nearly all patients with ET. However, situations may exist when alternative targets are needed. Parkinson tremor and essential tremor in the same patient have responded to subthalamic DBS.[77] Furthermore, Murata and colleagues[75] reported promising results in eight patients with severe essential tremor involving the proximal muscles, and Plaha and colleagues[76] successfully treated four essential tremor patients with bilateral DBS in the subthalamic area. Therefore, targets other than Vim should be investigated in cases that are refractory to Vim DBS.

Several uncontrolled studies of gamma knife thalamotomy have produced favorable results,[113] but delayed complications have been reported,[121] and clinical improvement may take weeks to months to occur.[122] Controlled studies of gamma knife thalamotomy should be considered in advanced patients who are not surgical candidates.

Ethanol is a potent suppressant of ET in many patients, but ethanol has obvious limitations in the chronic treatment of ET. The mechanism of ethanol in tremor suppression is uncertain. Other alcohols appear to have similar efficacy. Octanol[79,80] and sodium oxybate[123,124] were beneficial in pilot studies, but larger double-blind placebo-controlled trials are needed to test the safety, tolerability, and efficacy of long-term treatment with these drugs. Sodium oxybate is approved and restricted in the United States for the treatment of cataplexy.

The conference attendees believe that the ideal study design for future clinical trials is a double-blind randomized parallel placebo-controlled study with an evaluation of tremor after at least 3 months of maintenance therapy. Investigators performing formal tremor assessments should be blinded to all other clinical assessments, including medication adverse events. Evaluation using a universally accepted battery of tremor, activity-of-daily-living, and quality-of-life assessment scales is needed to enable comparison of treatment effects across studies. Studies should focus on patients with definite ET, as defined by the Kiel consensus criteria.[30,31]

Proposed Research Strategy

The conference attendees believe the following six objectives are of immediate and overriding importance.

One, a collaborative network of research centers is needed for clinical trials, genetic studies, and neuropathological investigations.

Two, a standard protocol for the assessment of ET is needed to facilitate clinical diagnosis and tremor quantification in therapeutic trials. Therefore, the recommended formation of an international committee on tremor scales should be an immediate priority.

Three, the identification of one or more genes for ET is the pivotal step in finding a cure for ET. Multicenter international studies of sibpairs, monozygotic twins, and nuclear families (proband, both parents, and one affected sibling or child) with monosymptomatic ET and no evidence of bilineal transmission should begin as soon as possible. A subset of centers involved in multicenter genetic studies should use electrophysiological tests to distinguish enhanced physiological tremor from very mild ET.

Four, a centralized repository of DNA and, ideally, immortalized cell lines from well-characterized ET families and healthy controls.

Five, a reliable and efficient repository of optimally prepared and categorized brain samples is needed for hypothesis-driven neuropathological examinations in well-characterized ET patients. The ET brain bank at Columbia University (http://www.essentialtremor.org/research/brain_bank.php) should be enhanced by additional collaborative relationships with brain banks and neuropathologists at other institutions. A concerted effort should be made to obtain postmortem specimens from well-characterized ET patients and healthy controls. Multiple patients from the same family should be studied to control for phenocopies and coincidental comorbidities.

Six, animal models of ET should be developed so that pharmaceutical companies can screen for promising

drugs. Without these models and preclinical studies, pharmaceutical clinical trials will continue to be sporadic ventures with drugs approved for other purposes. The harmaline-tremor model has been the sole ET model for too long. More models such as the $GABA_A$ receptor α_1 subunit knockout mouse are needed.

The Tremor Research Group is committed to the successful completion of these recommendations and objectives. We recognize that this conference was attended by only one person from a country outside the United States. We hope that this document will serve as a catalyst for international discussion and collaboration and for larger international meetings devoted to ET. Interested researchers may contact Rodger J. Elble (relble@siumed.edu), Kelly Lyons (lyons.kelly@att.net), or any other member of the Tremor Research Group.

APPENDIX

In Memory of William C. Koller (1945–2005)

This conference was dedicated to Bill Koller, who died unexpectedly a few weeks before the conference. Bill was a champion of ET research and clinical care. He was instrumental in organizing the Tremor Research Group and the International Tremor Foundation, which later became the International Essential Tremor Foundation. There is probably no better way to honor Bill's memory than to participate in ET research and clinical care.

Tremor Research Group

The Tremor Research Group (TRG) was established in March 2001 as a not-for-profit group of scientific investigators who are committed to cooperative planning, implementation, analysis, and reporting of controlled clinical trials and pathophysiological investigations in tremor disorders, with particular emphasis on ET. The current membership of TRG is Rodger J. Elble, president (Southern Illinois University School of Medicine); Ray Watts, past president (University of Alabama Birmingham); Kapil Sethi, vice president (Medical College of Georgia); Kelly Lyons, secretary/treasurer (University of Kansas); Cynthia Comella (Rush Medical School, Chicago); Stanley Fahn (Columbia University); Mark Hallett (NINDS, NIH); Joseph Jankovic (Baylor College of Medicine); Jorge Juncos (Emory University); Elan Louis (Columbia University); William Ondo (Baylor College of Medicine); Rajesh Pahwa (University of Kansas); Matthew Stern (University of Pennsylvania); Caroline Tanner (Parkinson Institute, Sunnyvale, CA); and Ron Tintner (Methodist Neuroscience Research Institute, Houston, TX). All members except Matthew Stern attended the conference.

Other Conference Attendees

Jomana Al-Hinti (University of Arkansas for Medical Sciences), Valerie Anderson (Oregon Health and Science University), William Bara-Jimenez (NIH), Kersi Bharucha (University of Oklahoma Medical School), James Boyd (University of Vermont), Helen Bronte-Stewart (Stanford University), Khalaf Bushara (University of Minnesota), Howard Chan (Medtronic), Jack Chen (Loma Linda University), Jorge Eller (Portland VA Medical Center), Mark Eller (Jazz Pharmaceuticals), Samuel Ellias (Boston University Medical Center), Leslie Findley (National Tremor Foundation, United Kingdom), Shari Finsilver (International Essential Tremor Foundation), Mark Foreman (Jazz Pharmaceuticals), Edwin George (Wayne State University), Christopher Goetz (Rush University Medical Center), Lev Goldfarb (NIH), Stephen Grate (U.S. Army Medical Research and Materiel Command), Katrina Gwinn-Hardy (NIH), Peter Hedera (Vanderbilt University), Joseph Herring (Merck), Joseph Higgins (Albany Medical College), William Houghton (Orphan Medical), Jay Huff (Jazz Pharmaceuticals), Suk-Yun Kang (NIH), Shana Krstevska (Wayne State University), Fred Lenz (Johns Hopkins University), Zoltan Mari (NIH), Masao Matsuhashi (NIH), Sabine Meunier (NIH), Hokuto Morita (Tremor Action Network), Fatta Nahab (NIH), Maria Ospina (Louisiana State University School of Medicine), Elizabeth Peckham (NIH), Delea Peichel (Advanced Neuromodulation Systems), Phil Perera (Jazz Pharmaceuticals), Joel Perlmutter (Washington University School of Medicine), Ian Reynolds (Merck), Catherine Rice (International Essential Tremor Foundation), Sarah Pirio Richardson (NIH), Heike Russmann (NIH), Nyamkhishig Sambuughin (NIH), Alex Shatunov (NIH), Holly Shill (Barrow Neurological Institute), Andrew Singleton (NIA), Frank Skidmore (University of Florida), Natividad Stover (University of Alabama at Birmingham), Yohei Tamura (NIH), Claudia Testa (Emory University), W. Thomas Thach (Washington University School of Medicine), David Vaillancourt (University of Illinois at Chicago), Jean Paul Von Sattel (Columbia University), Allan Wu (University of California at Los Angeles), and Rachel Wurzman (NIH).

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