

WORLD NEUROLOGY

THE OFFICIAL NEWSLETTER OF THE WORLD FEDERATION OF NEUROLOGY

WFN, WHO Take on ICD-10 Revisions

BY DONNA C. BERGEN, M.D.

Chair, Public Relations and WHO Liaison Committee, WFN

Collaboration between the World Federation of Neurology and the World Health Organization has moved into the important area of disease classification.

Although systems of disease classification were begun as early as the 18th century, since its founding in 1946 the WHO has been responsible for preparing and updating the International Lists of Diseases and Causes of Death (ICD). In fact, the ICD is more than 100 years old, making it older than the WHO. One of the WHO's earliest official actions was to approve the ICD-6.

Since then, the WHO has periodically revised the ICD codes. The current ICD-10, which is being used in most countries, was approved in 1990 by the World Health Assembly, which consisted of the health ministers of the WHO member states. The codes are used as universally recognized diagnostic labels by clinicians, by epidemiologists charting disease prevalence and incidence, by researchers, and by public health officials and health care planners responsible for resource allocation and training programs. Ministries of health use the code when reporting causes of death and disease rates to the WHO, and some health systems use the disease codes in reimbursement for health care. (Some countries, notably the United States, still use the ICD-9 version.)

In June, the ICD-11 Committee was convened in Geneva by Dr. Shekhar Saxena and Dr. Tarun Dua of the WHO's Programme for Neurological Diseases and Neuroscience, Department of Mental Health and Substance Abuse, the WHO division that is responsible for disorders of the nervous system. The meeting was chaired by Dr. Raad Shakir of Imperial College, London. Representatives from a range of international neurological organizations participated, including Alzheimer's Disease International, the International



COURTESY DR. DONNA BERGEN

The WFN's Dr. Donna Bergen and Dr. Johan Aarli (front, 3rd and 5th from left) with representatives from international neurological organizations at a meeting of the WHO's ICD-11 committee in Geneva. Dr. Raad Shakir (front, 3rd from right) was the chair. The meeting was convened by Dr. Shekhar Saxena (front, 5th from right) and Dr. Tarun Dua (front, 4th from left) of the WHO.

Brain Research Organization, International Child Neurology Association, World Federation of Neurosurgical Societies, International Neuropsychological Society, International League Against Epilepsy, International Headache Society, Multiple Sclerosis International Federation, World Stroke Organization, and Movement Disorder Society. Dr. Johan Aarli represented the WFN. The revision will include three versions: for primary health care workers,

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The capital city of this remote Siberian region is a hub of research, clinical practice, and training for neurologists.

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Going Global

The Multiple Sclerosis International Foundation and the World Stroke Organization have plans for raising worldwide awareness of the diseases and promoting research and clinical collaboration.

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Neurological Complications Seen in 4 Children With H1N1

BY MIRIAM E. TUCKER
Elsevier Global Medical News

Pandemic influenza A(H1N1) virus should be considered in the differential diagnosis for children who present with influenzalike illness accompanied by unexplained seizures or mental status changes.

That recommendation was made by the U.S. Centers for

Disease Control and Prevention (CDC) in a report of four children with neurological complications associated with H1N1 influenza virus infection seen in Dallas County, Texas, U.S.A., during May 2009. All four children, who were aged 7-17 years, were admitted with signs of influenzalike illness (ILI) and seizures and/or altered mental status. Three of

the four patients had abnormal findings on electroencephalography. In all four patients, H1N1 influenza viral RNA was detected in nasopharyngeal specimens but not in cerebrospinal fluid, the CDC said (MMWR 2009;58:773-8).

The four children were among a total of 405 persons with confirmed pandemic flu seen at all hospitals in Dallas

County since April 22, including 44 who were hospitalized. There were no deaths reported. Of all the confirmed cases, 83% were in patients who were younger than 18 years of age. Of seven possible cases of neurological complications, three were excluded either because they were found to have alternative etiologies or because they did not meet the case definition.

Two of the children—a 17-year-old black male and a 10-year-old Hispanic male—had been previously healthy. The older child was admitted with a fever, cough, headache, dizziness, and weakness and later developed disorientation and confusion. The younger child had had a 3-minute tonic-clonic

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EDITOR IN CHIEF'S COLUMN

Neurologists at the Movies

Neurologists are people, too, and often go (or should go) to the movies for entertainment and fun. Sometimes the movies have medical or even neurological themes. In these circumstances, we might well have a special interest. How are the patients that we see portrayed on the big screen? In addition, of course, our friends, colleagues, and even our patients may well want to know what we do think about a particular movie. Lay groups are often excited about movies that illustrate their disease; the movie makes their problem better known and increases sympathy for the symptoms they have.

What's the advantage of a movie review? The review lets us know about the film, to help us make a decision as to whether we want to go. If we don't go, then we are at least somewhat knowledgeable about the film. In addition, we can get an expert's viewpoint on the film. That sort of education can certainly increase our understanding of the disorder that is being portrayed, point out subtleties that we might miss, and increase our enjoyment overall. On page 19 of this issue of World Neurology, we have two movie reviews by experts: John Halperin reviews a movie on chronic Lyme disease, and Don Gilbert reviews a movie on Tourette syndrome.

The movie on chronic Lyme disease, "Under Our Skin," is a documentary by

advocates of the idea that many chronic, often vague, neurological symptoms may be due to a chronic Lyme infection. No use that the American Academy of Neurology and the Infectious Disease Society of America, upon careful and detailed review of all the evidence, have concluded that Lyme disease is generally not responsible for the symptoms complained about. Physicians are portrayed as nonsympathetic and the scientific method as misguided. This is an important area to know about. Many patients feel very strongly that their symptoms are due to chronic Lyme disease, and this movie will strengthen their belief. Proper treatment of the patient will require taking

this belief into account. Often somatization is the underlying disorder.

The movie on Tourette syndrome, "Phoebe in Wonderland," is an enjoyable story, but the lead character seems to have mainly obsessive compulsive disorder and impulsive behaviors. In fact, although the diagnosis of Tourette syndrome is made, the patient does not have any tics! Again, the movie maker has the wrong diagnosis, and the moviegoers may well be misled. So for both movies, the neurologist has an opportunity, and, perhaps even a responsibility, to correct any misconceptions these movies might create.

We watch so you don't have to—but you may well want to, anyway. ■



BY MARK HALLETT, M.D.

WCN 2009

First Advocacy Session Is Planned for Bangkok

The World Federation of Neurology will offer the first session of its kind on advocacy training on Oct. 29 at the 2009 World Congress in Bangkok.

Course faculty will include the president of the World Neurology Foundation, Dr. Michael Finkel, Dr. Mohammad Wasay, Dr. Man Mohan Mehndiratta, Dr. Wolfgang Grisold, American Academy of Neurology staff, and international graduates of the AAN's Palatucci Advocacy Leadership Forum.

They will present a structured program that will teach attendees how best to advocate for their patients and

our specialty based on the conditions in their home countries and how to present one's original project to representatives of media and government.

The course is a Scientific Session and does not require preregistration or additional charges.

It will be very useful to individuals as well as national societies that wish to follow the example of the Indian Academy of Neurology and establish a section on advocacy.

Questions regarding the session can be directed to Dr. Finkel at mfinkel@worldneurology.org or Melissa Larson at mlarson@aan.com. ■



DR. MICHAEL FINKEL, M.D.

Council of Delegates Meeting: Register if You Want to Vote

The 2009 Council of Delegates will be held in Bangkok during the World Congress of Neurology on Oct. 25 from 10:00 a.m. to noon, followed by a lunch from noon to 1:00 p.m.

If necessary, the Council will reconvene for a second session on Oct. 29 from 2:00 p.m. to 4:00 p.m.

All delegates are required to complete a delegate attendance form and

return it to the WFN head office as soon as possible. If you have not yet received such a form, please contact the head office at info@wfneurology.org.

Please also note that if you fail to register your society for the Council of Delegates meeting or to ensure that your dues payments are fully up to date, your delegate will be ineligible to cast a vote at this year's elections. ■



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World Federation of Neurology
Hill House, Heron Square
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Tel: +44 (0) 208 439 9556/9557 Fax: +44 (0) 208 439 9499
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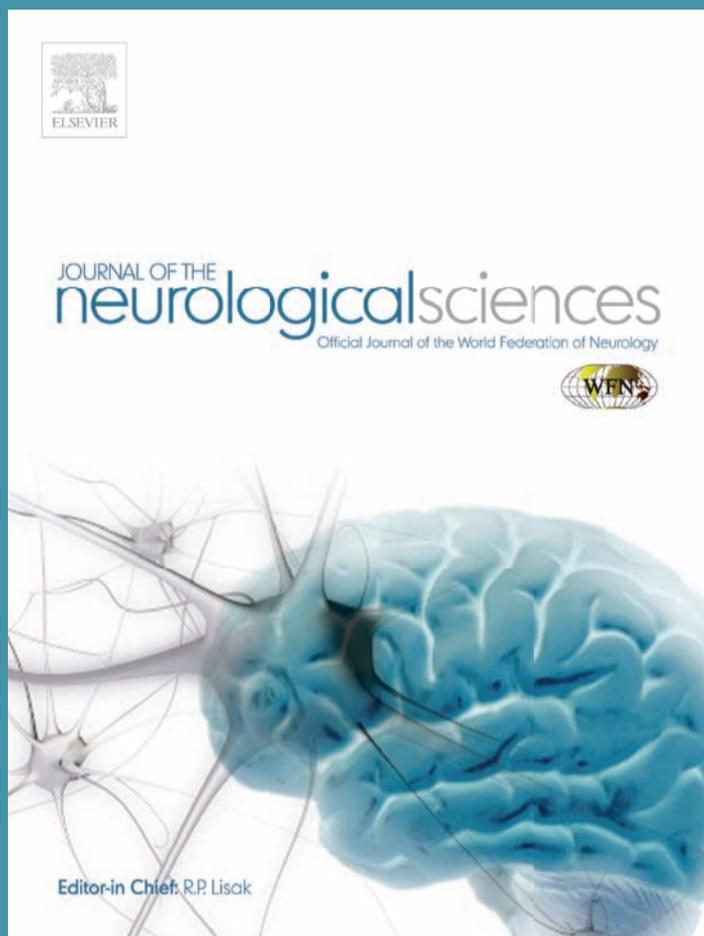
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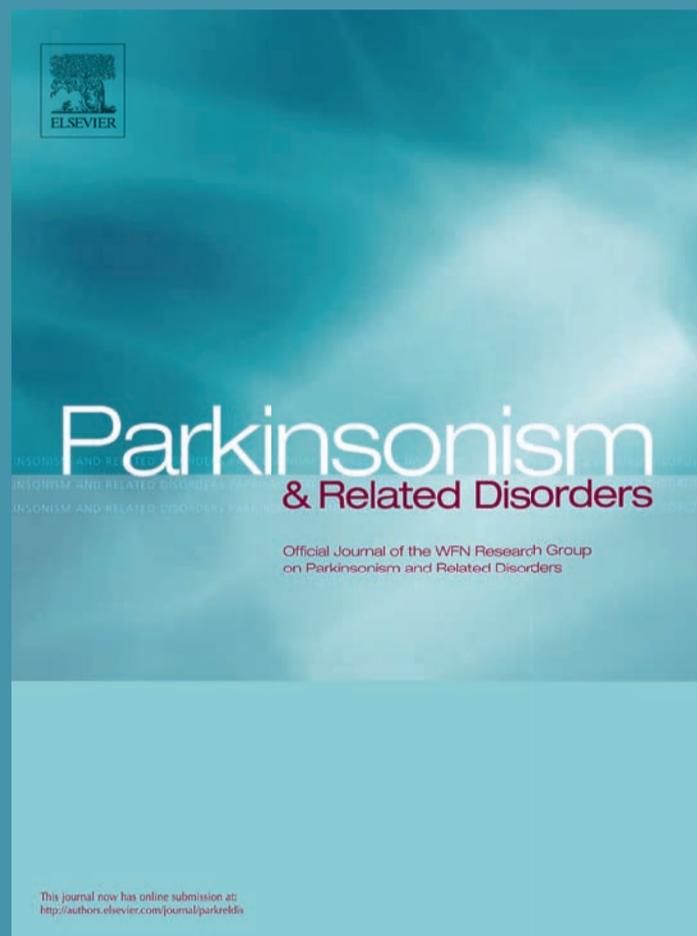


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PRESIDENT'S COLUMN



BY JOHAN A. AARLI, M.D.

Bangkok 2009 and Beyond

I hope that this column reaches the WFN membership in time for the World Neurology Congress that opens on Oct. 25. All of us are deeply indebted to the Neurological Society of Thailand for its hard work in preparing for this important event.

More than any previous WCN host society, the Thai organizers have had their share of unexpected obstacles in the planning of the congress. Global air travel has fallen off as the financial crisis has hit economies around the world. Passenger volumes have declined, and meetings and international conventions have taken the hardest hit, though this is now slowly improving. We have seen some political unrest, but law and order have been restored. And as if this was not enough, the WHO declared the influenza A(H1N1) a pandemic, but considers the overall severity of the pandemic to be moderate. This means that most people recover from infection without the need for hospitalization or medical care. There is no reason to assume that the risk of contracting influenza is higher in Thai-

land than in the home country.

Nevertheless, the Thai neurologists have managed to prepare for this world's largest scientific event in neurology in a professional, open, and well-balanced way. Most participants have already bought their tickets and made hotel reservations for this unique week in Bangkok. Hopefully, many guests will also have the opportunity to explore this exotic, beautiful, and cultured country.

The congress presents a unique possibility for neurologists from all regions of the world to receive information and be updated on developments in the neurosciences. The main topic themes are stroke, multiple sclerosis, epilepsy, dementia, movement disorders, and pain. There will be plenary lectures, named lectures, debate sessions, invited lectures, industry-sponsored satellite symposia, free papers, poster sessions, and the 3rd Tournament of the Minds.

The WCN 2009 will also be a meeting ground for discussions on the relationship between neurology and public health. I would like to prepare the participants for debates on the role of WFN in joining WHO's work on the development of clinical neurology.

The WHO Mental Health Gap Action Programme, starting almost simultaneously with the Bangkok congress, clearly

signals the need to scale up medical services for mental, neurological, and substance use disorders. The program is designed for low- and lower-middle-income countries. By doing this, the WHO has taken an important step to show its responsibility for the great global burden of neurological disorders.

The WHO and WFN have clearly demonstrated that there are inadequate resources for patients with neurological disorders living in low-income or developing regions. Most patients still have no access to a neurologist. They may see general practitioners, nurses, or health care workers who may have some or no training in diagnosis and care of common neurological disorders. A lack of reliable diagnostic and therapeutic tools adds to the problem.

If there is no neurologist available, it is our mission to see that the available health workers also have a basic training in neurology. But to do that, we need a comprehensive system of neurological care at the primary care level, including training of primary health-care workers. We need general practitioners and health workers to find out what neurology is and is not.

Such training in diagnosis and management of common and treatable neurological disorders for health providers is essential. We are not talking about in-

frequent disorders. We are talking about some of the most common disorders, such as epilepsy, stroke, migraine, peripheral neuropathies, and Parkinson's disease. A general practitioner has to be updated on these disorders.

Neurology needs a better contact with primary health care. Rural community health centers may develop into the critical link only if they have contact with neurological centers. This could form the backbone of a national program for neurology care.

But there are many medical schools that have no neurologist to give medical students even basic training in neurology. What then about the training of nurses and auxiliary health personnel?

To establish adequate neurological care, three sets of critical elements are essential: basic public health service and primary health care, neurology training at all medical schools, and a national neurology service system. The three are interwoven and depend upon each other. Basic public health service and primary health care is essential to develop modern neurology in countries lacking a medical infrastructure. Thailand is a good example of a once developing country that has developed into a modern highly developed nation. I look forward to meeting you in Bangkok. ■

Develop Rational Plan for Managing Chronic Pain

BY BETSY BATES

Elsevier Global Medical News

Pain and depression are common bedfellows, entwined in a complex relationship of situational and neurophysiological connections that are not yet fully understood.

Numerous studies point to frequent comorbidity, yet physicians treating patients who present with one condition often fail to assess for the other.

It is unknown whether depression is the "cause or the consequence" of chronic pain in some circumstances. This emphasizes the need for a patient with chronic pain to be comprehensively assessed for both conditions, said Dr. Charles E. Argoff, professor of neurology and director of the Comprehensive Pain Program at Albany (N.Y.) Medical College.

But this is challenging to do in the real world because "so much of taking care of people is based on the last 1,000 people you have taken care of and what your experiences have been in addition to your textbooks and the mentorship you receive during training."

Neurologists can manage patients' depression and anxiety if they feel comfortable doing so or refer the person for treatment in the community. Depression and anxiety that remain untreated will limit the usefulness of any pain treatments, Dr. Argoff said in an interview.

That does not necessarily mean, however, that treating a depressed patient with chronic diabetic neuropathy will only require prescribing a serotonin-norepinephrine reuptake inhibitor such as duloxetine.

"The point is that there are many considerations to be made, but there is no clear-cut, routine, easy, slam-dunk solution," Dr. Argoff said. If someone is depressed, has migraines, and is obese, "I wouldn't necessarily put them

on a tricyclic antidepressant because of the side effect of weight gain, despite its efficacy in chronic headache."

Some medications can have multiple effects that are particularly useful in treating certain patients, such as those with diabetic neuropathy who are already taking a selective serotonin reuptake inhibitor (SSRI) agent such as fluoxetine for depression. In this case, a pain specialist may want to switch the patients' SSRI to the serotonin-norepinephrine reuptake inhibitor duloxetine, which is U.S. Food and Drug Administration-approved for the treatment of painful diabetic neuropathy, depression, generalized anxiety disorder, and fibromyalgia. Another option, the anticonvulsant pregabalin, an agonist of the alpha 2 delta subunit in voltage-gated calcium channels, is indicated for diabetic neuropathy and in Europe may be used for generalized anxiety disorder.

Dr. Michael Clark, a psychiatrist who directs the Johns Hopkins Pain Treatment Program in Baltimore, said he is "pretty nonbiased when it comes to drug selection and pretty pragmatic with regard to a person's individual situation." By the time patients see him, they may have been prescribed an array of the newer, more expensive drug choices, so he may turn to a tricyclic antidepressant (such as amitriptyline or doxepin) or an antiseizure medication such as divalproex or lamotrigine.

"Often, no one else has tried these medications in these patients, and I'm comfortable with using them," Dr. Clark said, explaining that rare side effects, careful titration, and blood monitoring are not daunting, once one has familiarity with them.

Dr. Jon Mark Streltzer, professor of psychiatry at the University of Hawaii, Honolulu, maintains that the controversy surrounding long-term, high-dose opioid use for chronic pain is a matter of difference among individuals, rather than a specialty-specific perspective.

However, he generally prefers to manage chronic pain patients (where possible) on acetaminophen (1 g, 4 times daily) while using a program aimed at function, activity through functionally directed therapy, including cognitive-behavioral psychotherapy.

That said, acetaminophen "won't work on opioid-dependent patients," he warned. "Almost nothing will work until the dependence is treated."

Within the larger context of chronic pain, patients with generalized pain syndromes deserve special consideration, Dr. Clark said.

Central sensitization appears to be the common denominator among fibromyalgia, interstitial cystitis, diffuse low back pain, chronic fatigue syndrome, irritable bowel syndrome, and headache syndromes, with resulting amplified pain sensations.

"The most important thing is that you don't want to give these patients a little bit of everything and think that's the answer: a little bit of occupational therapy, a little bit of physical therapy, a little bit of psychotherapy and psychopharmacology. Throwing ingredients into a soup without a recipe is not the answer. These patients need to have someone design a rational plan for their care," Dr. Clark said.

Dr. Streltzer reported no relevant financial conflicts with regard to this story. Dr. Clark has served on the speakers bureau or as a consultant for Eli Lilly & Co., maker of duloxetine, and Pfizer Inc., maker of pregabalin.

Dr. Argoff has received grant support from several companies involved in pain therapeutics. He also serves on the speakers bureau and advisory boards and is a consultant to various companies in the field, including Eli Lilly and Pfizer. ■

Jeff Evans contributed to this article.

Honorees in the WCN 2009 Named Orations

A primary component of a World Congress of Neurology is the Named Orations. They are funded by donations from their colleagues, held in trust accounts managed by the World Neurology Foundation. The Foundation and World Neurology have worked with the families of these truly remarkable human beings to create brief biographies that explain why they are so honored by their colleagues. This year, all four speakers have donated their honoraria to the Foundation for the purchase of tool kits as part of the 2009 Tool Kits for Africa distribution for Uganda. The Foundation is seeking donations for its desired shipment to Nigeria for 2009.

Eddie Bharucha (b. 1916) and Pilo Bharucha (1917-2001)

Dr. Eddie Bharucha received medical degrees in Mumbai and London. He trained at Queen Square and Maida Vale in London, at the Neurological Institute



COURTESY BHARUCHA FAMILY

in New York under Dr. Houston Merritt, and in Boston under Dr. Denny Brown.

Dr. Bharucha established the first department of neurology in India in 1946. His contributions covered a spectrum of neurological disorders, including vitamin deficiencies, tuberculosis, epilepsy, cerebral palsy, and hereditary neuropathies. His descriptions of craniovertebral anomalies and the neurological manifestations of acute hemorrhagic conjunctivitis are seminal. He was a joint editor of the Handbook of Neurology, president of the Neurological Society of India, and a vice-president of the World Federation of Neurology. In 1970, he co-founded the Indian Epilepsy Association and was its secretary until 1991.

Dr. Pilo Bharucha trained as a pediatrician and obtained her medical degrees in Mumbai and London. She founded the department of pediatrics at the King Edward VII Memorial Hospital in Mumbai. Her interests were preventive pediatrics, child welfare, and immunization. Poliomyelitis immunization became her crusade. She revitalized the Indian Academy of Pediatrics and served as its president. She and Dr. Eddie Bharucha married in 1947, and had three sons. She was a persistent fighter for everything she believed in, whether it was the plight of ill children or animals, the welfare of the underprivileged, or the environment. Together with Eddie, she orchestrated an effort to repeal a law that linked epilepsy with insanity and provided grounds for nullifying marriage.

The 2009 Bharucha Oration will be given by THIRAVAT HEMACHUDHA, M.D., professor of neurology at the faculty of medicine, Chulalongkorn University, Bangkok, Thailand, on Oct. 26 at 9:15 a.m. His main research interest is human

rabies. He is a member of the WHO Expert Advisory Panel on Rabies and director of the WHO Collaborating Center for Research and Training in Viral Zoonoses.

B.S. Singhal, M.D. (b. 1933)

Dr. B.S. Singhal completed his medical training at Grant Medical College and Sir J. J. Group of Hospitals in Mumbai, and trained in neurology in London.

He has served as president of the Neurological Society of India and the Indian Epilepsy Association; established the Parkinson's Disease Foundation of India; is founder fellow of the Indian Academy of Neurology, the Association of Physicians of India, and the International Medical Science Academy; and is a member of the American Academy of Neurology, the American Neurological Association, the French Neurological Society, and the Association of British Neurologists. He has



served on the research committee of the World Federation of Neurology, and was regional director of the Asian-Oceanian Chapter of the WFN from 2005 to 2009. Dr. Singhal is the chair of neurology at the Bombay Hospital Institute of Medical Sciences in Mumbai. He is widely respected for his gentle style, positive approach, and incredible work ethic. He has contributed nearly 200 papers to national and international journals and recognized a form of leukodystrophy unique to the Indian subcontinent. His many awards include the Priyadarshini Academy National Award for Excellence in Medicine, the Wockhardt-Harvard Medical International Award for Neurology, and the Dr. B.C. Roy Indian National Award. Dr. Singhal is married to Dr. Asha Singhal.

The Singhal Oration was established by Dr. Sorab Bhabha to honor Dr. Singhal's lifelong contributions to neurological education and research, his clinical excellence, and his devotion to patient care. Dr. Bhabha was a neurologist, a friend and colleague of Dr. Singhal, and helped establish this lecture before his death from ALS in 2006.

The 2009 Singhal Oration will be given by SAMUEL F. BERKOVIC, M.D., on Oct. 28 at 8:00 a.m. He is Laureate Professor in the department of medicine at the University of Melbourne and director of the Epilepsy

Research Centre at Austin Health in Heidelberg, both in Australia.

Melvin D. Yahr, M.D. (1917-2004)

Dr. Melvin D. Yahr was a lifelong New Yorker. He received his undergraduate and medical degrees at New York University, a free education at that time. He admitted to playing the clarinet in a jazz combo to earn extra money, although he insisted that he played badly. After three years of military service, he joined the neurology department at Columbia-Presbyterian Medical Center. He was chairman of the department of neurology at Mount Sinai Hospital in New York from 1973 to 1992, and continued his clinical practice and research until his death in 2004 at the age of 86.



Dr. Yahr and colleague, Dr. Margaret Hoen

Based on research in the late 1950s showing that depletions of the chemical messenger dopamine could set off Parkinson's disease, Dr. Yahr conducted and published the first clinical trials of L-dopa in the late 1960s. These studies changed the outlook for people with Parkinson's disease. By 1972, barely 3 years after his study was published, about half of the nation's 1.5 million people with Parkinson's disease were taking it. Today, L-dopa, despite some side effects, is by far the most common treatment for Parkinson's. He was the first scientific director of the Parkinson's Disease Foundation.

In 1948, he married Felice Turtz, a marriage that lasted 44 years until her death in 1992. They had four daughters. His daughter Carol remembers that, no matter who the patients were, or how hopeless their situation seemed, her father was always engaged, positive, and supportive.

The 2009 Melvin D. Yahr Lecture will be presented by ROGER N. ROSENBERG, M.D., on Oct. 29 at 8:30 a.m. He is the Zale Distinguished Chair and professor of neurology and director of the U.S. National Institutes of Health's Alzheimer's Disease Center at the University of Texas Southwestern Medical Center at Dallas, U.S.A. He is a past-president of the American Academy of Neurology, a trustee of the World Federation of Neurology, and editor in chief of Archives of Neurology.

Richard Lambert Masland, M.D. (1910-2003)

Dr. Richard Lambert Masland was born in Philadelphia, U.S.A. He attended Haverford College and the Universi-

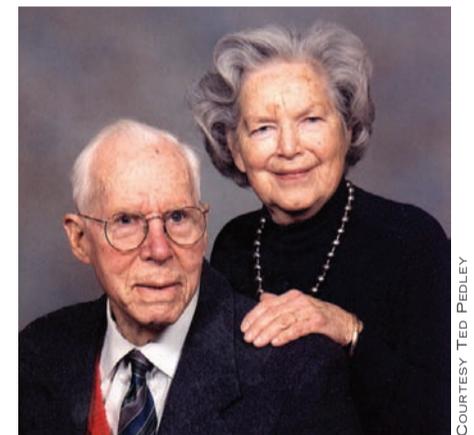
ty of Pennsylvania Medical School, and served residencies in neurology and psychiatry at Pennsylvania Hospital, interspersed by service in the Air Force during World War II. He then joined the faculty of the new Bowman Grey School of Medicine in Winston-Salem, N.C., U.S.A.

From 1959 to 1968 he was the director of the National Institute of Neurological Diseases and Blindness, and was part of the team that crafted the merit-based peer-review system that is the foundation of American medical research. He then became chair of the department of neurology at the College of Physicians and Surgeons of Columbia University in New York; in 1973, he became H. Houston Merritt Professor of Neurology, emeritus.

Dr. Masland mentored many of the most gifted research neurologists of two generations, including Carlton Gajdusek, Leonard Kurland, J. Kiffin Penry, and William F. Caveness.

He is best known for leading the National Collaborative Perinatal Project, a nationwide study of pregnancy and child development between 1959 and 1966. The study followed more than 50,000 women from the time of their pregnancies until their children reached the age of 8.

Dr. Masland was president of the American Epilepsy Society and the New York Neurological Society. He was pres-



COURTESY TED PEDLEY

ident of the WFN from 1981 to 1989, bringing to developing countries the battles against mental retardation, epilepsy, and head injury.

During his spare time, Dr. Masland built a 33-foot Herreshoff ketch. He launched the wooden sailboat in 1967 and vacationed on it between Cape Cod and the Chesapeake Bay for 30 years. Dr. Masland and his wife, Mary Wootton Masland, a speech and language pathologist, had four children.

The Richard L. and Mary Masland Lecture will be given by David Dodick, M.D., on Oct. 30 at 8:00 a.m. He is professor of neurology at the Mayo Clinic in Phoenix, Ariz., U.S.A. He is president-elect of the American Headache Society and editor in chief of Cephalalgia.

—DIANA M SCHNEIDER, PH.D., Public Relations Committee, WFN, and a Member of the Board of the World Neurology Foundation.

Smoking May Speed Progression of MS in Some

BY JEFF EVANS

Elsevier Global Medical News

The clinical course and disease status of multiple sclerosis patients appear to be worsened by current smoking, and in some cases, by the past amount of smoking in former users, according to a cross-sectional survey and longitudinal analysis of more than 1,400 patients at one center.

"Although causality remains to be proved, these findings suggest that patients with [multiple sclerosis] who quit smoking may ... delay the progression of MS," wrote Brian C. Healy, Ph.D., and his colleagues at Harvard Medical School, Boston.

Two previous studies that have examined whether cigarette smoking is associated with the progression of relapsing-remitting MS (RRMS) to secondary progressive MS (SPMS) or greater clinical disability arrived at opposing conclusions (*Brain* 2005;128:1461-5; *Neurology* 2007;69:1515-20). But the substantially larger sample size of the present study gives it "more statistical power to assess the relationship between smoking and MS progression," the investigators wrote (*Arch. Neurol.* 2009;66:858-64).

In the current study, 1,465 MS patients completed a questionnaire about their smoking history. Overall, 257 were current smokers, 428 were ex-smokers, and 780 were never smokers. The researchers used only smoking status at baseline in their analyses, but any bias introduced by this assumption "is likely small" because during follow-up few patients started smoking for the first time (7) or stopped smoking (57).

The results of analyses derived from baseline data showed that current smok-

ers had a significantly higher median Expanded Disability Status Scale (EDSS) score than did patients who never smoked. The score in never smokers significantly increased with the number of pack-years smoked. Current and ex-smokers were significantly more likely at baseline to have a primary progressive course of MS, rather than an initially relapsing course (such as RRMS or SPMS), than were never smokers. The odds ratio for a primary progressive course was 2.4 for current smokers and 1.9 for ex-smokers, both of which were adjusted for age, sex, and disease duration.

The researchers also evaluated markers of disease severity on MRI, which were not examined in previous reports. Current smokers had a significantly lower brain parenchymal fraction on MRI than did never smokers, although no difference could be seen in the volume of T2-weighted lesions between current smokers and never smokers. No difference could be detected in brain parenchymal fraction between ex-smokers and never smokers, but ex-smokers had a significantly greater T2-weighted lesion volume than did never smokers.

In a longitudinal analysis of 891 patients with median follow-up time of 3.3 years, Dr. Healy and his associates observed a conversion from RRMS to SPMS in 20 of 154 current smokers, 20 of 237 ex-smokers, and 32 of 500 never smokers.

The current smokers progressed significantly faster from RRMS to SPMS than never smokers. This risk did not change appreciably after controlling for baseline EDSS score. The rate of conversion from RRMS to SPMS, however, was similar between ex-smokers and never smokers.

This finding "provides evidence that the adverse effects of smoking may be at

least in part reversed by quitting," the researchers wrote.

At the end of 2 years and 5 years, the researchers found no association between smoking status and worsening of EDSS score, regardless of the type of MS at baseline, after adjusting the analyses for age at baseline, sex, disease duration, and treatment.

During follow-up on MRI, current smokers displayed significantly greater worsening of T2-weighted lesion volume and brain parenchymal fraction than did never smokers. However, no differences on these measures could be detected be-

tween ex-smokers or never smokers.

The authors cautioned that because they did not include healthy control subjects, they "could not determine the specific effect of smoking on MRI measures in patients with MS; some general consequences of smoking could have been mistakenly attributed to MS progression."

None of the researchers reported any financial disclosures. They received funding for the study from the Partners Multiple Sclerosis Center, the National Institute for Neurological Disorders and Stroke, and the National Institutes of Health. ■

Comment

Several recent studies, including two meta-analyses (*Curr. Opin. Neurol.* 2007;20:261-8; and *Ann. Neurol.* 2007;61:288-99 and 504-13) demonstrated adverse influences of smoking on incidence and disease progression in multiple sclerosis (either conversion from a first demyelinating event to clinically definite or from relapsing to chronic progressive MS). The current study by Dr. Healy and his associates adds to these observations.

Although negative effects of smoking on MS progression are generally moderate, they are of utmost importance because smoking is the only known modifiable MS risk factor. But why or how does smoking harm MS patients?

Speculations on direct neurotoxicity or immunostimulation of most tobacco components seem too simple. Concepts from autoimmune rheumatic diseases point to a possi-

bly important pathogenetic effect of posttranslational modification (e.g., hydroxylation, citrullination, deamidation, oxidation, methylation) of proteins/peptides that provoke immunity to neo-antigenicity by "self-alteration". Several inhaled noxious factors, including tobacco smoke, induce posttranslational modifications that trigger immune reactions to such modified autoantigens.

As with other environmental factors, such as infections, it is likely that such a vicious immunological cycle may depend on individual genetic susceptibility. The future scientific challenge will be to unravel the link between environmental factors (such as smoking) and (auto-) immunity.

—DR. THOMAS BERGER,
head of the Neuroimmunological and
Multiple Sclerosis Clinic & Research
Unit at the Innsbruck (Austria)
Medical University.

LETTERS

BoNT: Opinion vs. Evidence

We were under the impression that recommendations for treatment of neurologic disorders published in *WORLD NEUROLOGY* were evidence based. We were therefore amazed to find the article by Dr. Stephen D. Silberstein on the safety and efficacy of botulinum neurotoxin, which did not seem to adhere to that expectation ("BoNT for Headache: What You Need to Know," December 2008, p. 4).

The first quarter of the article addresses a 2008 evidence-based review by the therapeutics and technology assessment subcommittee of the American Academy of Neurology (*Neurology* 2008;70:1707-14).

The subcommittee recommended that BoNT injection probably is ineffective in the treatment of episodic migraine (EM), that there is insufficient evidence to support or refute a benefit of BoNT for the treatment of chronic daily headache (CDH), and that BoNT injections should not be considered in patients with EM and chronic tension-type headache (CTTH).

Dr. Silberstein then states that "basic science data and clinical experience sup-

port a beneficial effect of BoNT in the treatment of some types of headaches. However, data from clinical trials are inconclusive (for CDH) or negative (for EM and CTTH)."

He questions the reasons for this discrepancy and spends the rest of the article trying to explain it, citing study design and patient- and treatment-related factors.

The article ends with the comment, "my clinical experience shows that some headache patients benefit significantly from BoNT treatment," then he announces that BoNT is effective for chronic migraine in as yet unpublished phase III trials.

This is not evidence-based medicine and such personal statements should certainly be abandoned in general treatment recommendations. The author disregards the data from systematic reviews and presents his personal views and explanations. Despite the negative evidence, he advocates the use of BoNT for headache.

Such a paper in the official publication of the World Federation of Neurology will encourage the widespread use of

BoNT in migraine and headache despite evidence for its inefficacy.

Peer Tfelt-Hansen, M.D., Rigmor Jensen, M.D., and Jes Olesen, M.D.
Glostrup, Denmark

Dr. Silberstein replies:

The results of a large phase III clinical program evaluating botulinum neurotoxin A versus placebo as headache prophylaxis in 1,384 adults with chronic migraine were scheduled to be presented in September 2009 at the International Headache Congress in Philadelphia, U.S.A. (Cephalalgia, in press). These data provide level 1 evidence of the effectiveness for botulinum neurotoxin A for the prophylaxis of headaches in adults with chronic migraine.

Revisiting the Etiology of PMD

In his article "Individualize Psychogenic Movement Disorder [PMD] Diagnosis" (*August 2009*, p. 5), reporter Jeff Evans has misunderstood the message I was trying to get across about the way in which we think of PMD and communicate this to patients.

There are several ways of explaining these symptoms to patients, including a "psychological" explanation which em-

phasizes a psychogenic etiology, and a "functional" explanation in which the emphasis is on mechanism (reversible change in function of the nervous system) rather than etiology.

These options also reflect different ways of thinking about the problem. Research using functional imaging (*Brain* 2001;124:1077-90) and neurophysiology (*Ann. Neurol.* 2006;59:825-34) is challenging the purely psychogenic view of etiology that has dominated for over 100 years.

The article implies that a "functional" explanation is simply a useful device to keep a patient happy until they can accept a purely psychogenic explanation. Using a "functional" explanation in this way would be bordering on deception. The point I had intended to get across was that a functional explanation, as well as being easier for patients to understand, may actually be better theoretically as well.

Whilst psychological factors are undoubtedly important in these symptoms, the pure psychogenic etiological model may be wrong and in need of revision.

Jon Stone, Ph.D., FRCP
Edinburgh, Scotland



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NEUROLOGY IN PRACTICE

A Thriving Specialty in Krasnoyarsk Krai

Krasnoyarsk is the scientific center of Siberia, with Krasnoyarsk State Medical University, which is named after Prof. V.F. Vojno-Yasenetsky, forming the hub of research, academic training, and clinical practice in the Krasnoyarsk Krai.

The field of neurology is particularly dynamic here. Numerous projects that are important for the development of neurological science, practice, and care have flourished with help from the All-Russian Society of Neurologists (ARSN) and specialists from the Krasnoyarsk State Medical University, elsewhere in the country, and from overseas.

There are 501 neurologists in the region, with more than half of them based in the industrial cities of Krasnoyarsk, Norilsk, Achinsk, and Kansk and Minusinsk. The regional branch of the ARSN has a membership of 343 pediatric and adult neurologists, and the Krasnoyarsk Regional Society of Clinical Neurophysiologists has 61 members.

Annually, there are more than 10 training seminars for neurologists, several regional and interregional neurological conferences, and at least one ARSN conference in Krasnoyarsk. There are many conferences on rehabilitation and epilepsy as well as teleconferences with neurological centers in Germany, Switzerland, and other countries.

Training

Most of the region's neurologists train at the Institute of Postgraduate Education of Krasnoyarsk State Medical University in the departments of neurosurgery and neurology; neurology, which includes a course in traditional medicine; and medical genetics and clinical neurophysiology. They can also train at other institutes in Siberia, Moscow, St. Petersburg, and other cities.

Programs for continuous medical education (CME)



EEG training in Krasnoyarsk State Medical University's department of genetics and clinical neurophysiology.



A patient undergoes analysis of gait with simulation at the Krasnoyarsk Centre of Rehabilitation.

have been implemented through the World Federation of Neurology and the education committee of the ARSN. These programs are important as a means of delivering educational materials and information about new developments and advances in the specialty to all neurologists, especially those in remote areas. Online CME conferences, training seminars, and clinical analyses of difficult diagnostic cases in neurological practice are important for postgraduate education of our neurologists and are carried out regularly.

Pediatric and Adult Care

BY NATALIA A. SHNAYDER, M.D., PH.D.

Dr. Shnayder is head of the department of medical genetics and clinical neurophysiology at the Institute of Postgraduate Education at Krasnoyarsk State Medical University in the Russian Federation.



BY SEMEN V. PROKOPENKO, M.D., PH.D.

Dr. Prokopenko is head of the department of neurology, also at the Krasnoyarsk State Medical University.

As in other regions of Russia, there is a special system of pediatric neurology in Krasnoyarsk Krai focusing on diagnostics, prophylaxis, treatment, and rehabilitation in children and teenagers with the diseases of the nervous system. Generally, these neurologists are former pediatricians who have received special professional retraining or completed and internship in pediatric neurology and/or pediatric and adult neurology. They work in children's outpatient departments and hospitals.

In Krasnoyarsk, there are specialized pediatric neurological wards only in children's hospitals, with separate neurological departments for children aged 1-3 years and aged 3-18 years. There are 40-60 beds in these wards. Often, there is a demand for more beds, so they are added as needed—though never more than 10. On average, a neurologist working in the children's wards takes care of 20 patients a day.

The average length of a hospital stay for these children is about 2 weeks. In Krasnoyarsk Regional Children's Hospital and in children's hospitals of industrial cities, the specialized neurological help is provided in the wards for internal medicine (and, if needed, for infectious diseases). Neurologists in outpatient departments examine about 24 children a day.

Adult patients with neurological diseases are treated in the neurological wards in the hospitals and outpatient departments. Usually, they stay in the neurological departments for about 16 or 17 days.

Neurologists who work in outpatient departments and polyclinics for adults in the rural districts of Krasnoyarsk Krai see about 24-26 patients a day. Moreover, neurologists also visit patients with acute neurological pathology at home. Patients with brain trauma are treated in the departments of neurosurgery of big clinics or in the departments of surgery in central district hospitals.

From Isolation Centers to Telemedicine

Compared with hospitals in Krasnoyarsk, neurological care in more remote regions is of a lower quality as they have no modern diagnostic and laboratory equipment.

Historically, there are territorial isolation centers in the settlements of central and eastern Siberia, where there is a prevalence of hereditary disorders. So in an effort to improve diagnostics, care, and education in neurology, the department of medical genetics and clinical neurophysiology and the Centre for Medical Genetics were founded in 2006 as part of the Institute of Postgraduate Education at Krasnoyarsk State Medical University.

In Krasnoyarsk and Norilsk, the departments and wards are equipped with modern diagnostic techniques

comparable with those in Moscow polyclinics and other big industrial cities in Russia. But these methods are available only in big hospitals. Krasnoyarsk is a vast region, and patients in its remote rural areas are treated in their local hospitals by specialists from the Krasnoyarsk Regional Clinical Hospital who travel to the areas on an air medical service.

If necessary, seriously ill patients are transferred to neurological departments or the intensive care unit of Krasnoyarsk Regional Clinical Hospital by air medical service or emergency ambulance. The most difficult situation with emergency neurological care is in distant northern districts, because the connection with settlements in winter is possible only by aviation and in summer, by river transport.

In the last 3 years, specialists at larger hospitals in the region have begun using telemedicine in their consultations for difficult-to-treat neurological patients and those in remote areas. In 2009, the region's

ministry of health care introduced teleconsultations and teleconferences both in health care institutions and in remote rural hospitals. Key specialists from the Krasnoyarsk Regional Clinical Hospital, Krasnoyarsk State Medical University, and specialized diagnostic centers in Krasnoyarsk participate in this form of care.

Subspecialty Focus

Neurological science and practice in Krasnoyarsk focus on neurorehabilitation, epileptology, and neurogenetics. Krasnoyarsk is one of eight territories selected to pilot a federal program aimed at improving stroke care. The Centre of Neurology and Neurorehabilitation, with its modern methods of rehabilitation, is one of those venues. Three hospitals—Krasnoyarsk Regional Clinical Hospital No. 1, Urban Hospital of Krasnoyarsk, and the Central Regional Hospital in Minusinsk—are part of the program. A stroke-care register has been started at Clinical Hospital No. 51 in Zheleznogorsk.

At the beginning of this year, the Centre of Epileptology, Neurogenetics, and Brain Research was established at the University Clinic at Krasnoyarsk State Medical University. Data on the epidemiology of epilepsy are being collected with guidance from specialists at Russian State Medical University in Moscow. This effort is seen as an important component in efforts to improve care for patients with this disease. ■

About the Region

Krasnoyarsk Krai—"krai" means region or area—is a federal subject of Russia. It is the second largest territory of Russian Federation after the Sakha Republic, occupying an area of 903,400 square miles.

Krasnoyarsk Krai lies in the middle of Siberia and belongs to Siberian Federal District, stretching from the Sayan Mountains to the south along the Yenisei River to Taymyr Peninsula in the north. The administrative center of the region is the city of Krasnoyarsk.

The most recent data (2002) put the population 3,023,525. Most of the population is Russian, with the indigenous Siberian peoples making up no more than 1% of the population.

Krasnoyarsk Krai is an important industrial region that includes the cities Krasnoyarsk, Norilsk, Achinsk, Kansk, Zheleznogorsk, and Minusinsk.

Sleeping Sickness: Africa's 'Neglected Disease'

Every aspect of the disease—diagnosis, staging, therapy, follow-up—presents a unique challenge.

Human African trypanosomiasis, which is also known as sleeping sickness, is a major killer disease in 36 countries in sub-Saharan Africa, where 60 million people are at risk for the disease and up to 50,000 people die annually from the infection.

Human African trypanosomiasis (HAT) is caused by protozoan parasites of the genus *Trypanosoma brucei*, and is transmitted by the bite of the blood-sucking tsetse fly of the genus *Glossina*.

Although HAT was almost brought under control mainly as a result of effective surveillance measures in the 1950s, there have been several resurgencies and epidemics since then, with a steady increase in the number of cases, largely due to disruption of social and surveillance infrastructure, especially during successive wars in affected regions. However, there is good evidence that the number of new cases is decreasing again because of improved patient surveillance.

Despite the fact that HAT is associated with a very significant morbidity and mortality, it is one of the world's "neglected diseases." Drug treatment for HAT is outdated and highly toxic, and this highly unsatisfactory situation reflects the chronic lack of financial investment from the developed world into new drug development for both stages of the disease. If untreated, or inadequately treated, the disease is invariably fatal.

There are two forms of the disease: East African HAT caused by *Trypanosoma brucei rhodesiense* (*T.b. rhodesiense*), and the West African variant caused by *T.b. gambiense*, which accounts for about 95% of cases of HAT. The disease caused by *rhodesiense* has a faster tempo than *gambiense* disease and leads to death if untreated in several weeks to a few months, whereas the course of *gambiense* disease may last many months to years.

There are two stages of HAT, the early (stage 1), or hemolymphatic stage, which occurs 1-3 weeks after the initial insect bite, and then the late (stage 2), or encephalitic stage, when the parasites cross the blood-brain barrier to enter the CNS (Ann. Neurol. 2008;64:116-26). In the early stage, the parasites spread in the bloodstream, lymph nodes, and systemic organs causing a variety of nonspecific symptoms, including malaise, headache, arthralgia, headache, and fatigue. Involvement of the heart, liver, spleen, skin, eyes, and endocrine system may also occur. Lymphadenopathy is typical of *gambiense* disease.

Two Stages and a Range of Symptoms

There are two stages of HAT, the early (stage 1), or hemolymphatic stage, which occurs 1-3 weeks after the initial insect bite, and then the late (stage 2), or encephalitic stage, when the parasites cross the blood-brain barrier to enter the CNS (Ann. Neurol. 2008;64:116-26). In the early stage, the parasites spread in the bloodstream, lymph nodes, and systemic organs causing a variety of nonspecific symptoms, including malaise, headache, arthralgia, headache, and fatigue. Involvement of the heart, liver, spleen, skin, eyes, and endocrine system may also occur. Lymphadenopathy is typical of *gambiense* disease.

The range of symptoms and signs during the late stage is very wide. In most cases, there is a characteristic sleep distur-

bance with alteration of the normal sleep/wake cycle with a constant urge to sleep, and polysomnography demonstrates sleep structure abnormalities. There may also be motor disturbances, such as pyramidal weakness, extrapyramidal features, cerebellar ataxia, myelopathy, peripheral motor neuropathy, muscle fasciculation, and also frontal lobe features such as pout and palmarmental reflexes.

Sensory disturbances can also occur, as may a variety of neuropsychiatric symptoms. Various types of visual involvement have also been described. Untreated or un-

BY PETER G.E. KENNEDY M.D., PH.D., D.SC.

Dr. Kennedy is the Burton Chair of Neurology and head of the Division of Clinical Neurosciences at the University of Glasgow, Scotland, and an honorary consultant neurologist at the Institute of Neurological Sciences, Southern General Hospital in Glasgow.



successfully treated patients will rapidly deteriorate with seizures, cerebral edema, incontinence, and death. Typical autopsy findings in such patients will show a widespread meningoencephalitis, an extensive infiltration of cerebral white matter with inflammatory cells and pathognomic Mott cells, which are plasma cells containing immunoglobulin M eosinophilic inclusions. Extensive data from both patients and a mouse model of the disease have implicated the key roles of pro- and counterinflammatory cytokines, astrocyte activation, and trypanosome-induced immune responses in causing the brain damage (J. Clin. Invest. 2004;113:496-504).

No General Criteria to Aid Diagnosis

Sleeping sickness is diagnosed by identifying parasites in the peripheral blood or lymph node aspirates in the case of *rhodesiense* disease, and by serological means using the Card agglutination trypanosomiasis test (CATT) in the case of *gambiense* disease because in the latter case, there are usually few detectable parasites in the blood.

There are no clinical suspicion criteria that can reliably distinguish the two disease stages, which may appear to merge into each other. All patients with proven HAT therefore require a lumbar puncture to examine the cerebrospinal fluid (CSF) as that is the only current method of diagnosing CNS involvement. Accurate staging of HAT is absolutely crucial because the drugs used for treating CNS disease are so toxic. If drug treatment is mistakenly withheld from a patient who has CNS disease then the patient will die, but giving highly toxic CNS drug therapy for early-stage disease carries the high risk of severe drug toxicity. This is one of the key dilemmas in managing patients with sleeping sickness.

Unfortunately, there is no general consensus as to what criteria best define late-stage disease, and this is one of the most

problematic issues in HAT. The WHO criteria for late-stage disease are the identification of trypanosomes in the CSF or a CSF white blood cell count (WBC) of greater than 5/mcL. But not everyone accepts this definition, and in West Africa a cutoff point of 20 CSF WBC/mcL is often used. Others have suggested a compromise figure of 10 WBC/mcL, but the actual presence of CSF trypanosomes is unequivocal proof that the CNS has been invaded.

Although both CT and MRI scan abnormalities have been shown in the few patients who have been studied in Western hospitals, such facilities are not available in field conditions and are therefore primarily of value in investigating patients who have recently returned from Africa. There are about 50 cases a year of HAT diagnosed outside Africa, mainly in Western travellers returning from vacations to East African game reserves.

Toxic Drugs Hamper Treatment

Drug treatment of HAT is highly unsatisfactory and essentially relies on the use of four drugs, none of which can be given orally and which are so toxic that it is unlikely that they would have passed currently rigorous safety standards had they been introduced in recent years.

Early-stage *rhodesiense* disease is treated with intravenous suramin, and early-stage *gambiense* disease is treated with intramuscular pentamidine. For late-stage *rhodesiense* disease, the only effective drug at present is intravenous melarsoprol (Mel B), a highly toxic arsenical drug that was first used in 1949. It is given either as 2-4 courses of three times weekly injections or, more recently, as a 10-day course of injections. Although melarsoprol is generally effective treatment for late-stage HAT, in about 10% of patients, it is followed by a severe posttreatment reactive encephalopathy (PTRE), 50% of whom will die. Melarsoprol treatment has an overall fatality rate of 5%, which is remarkable.

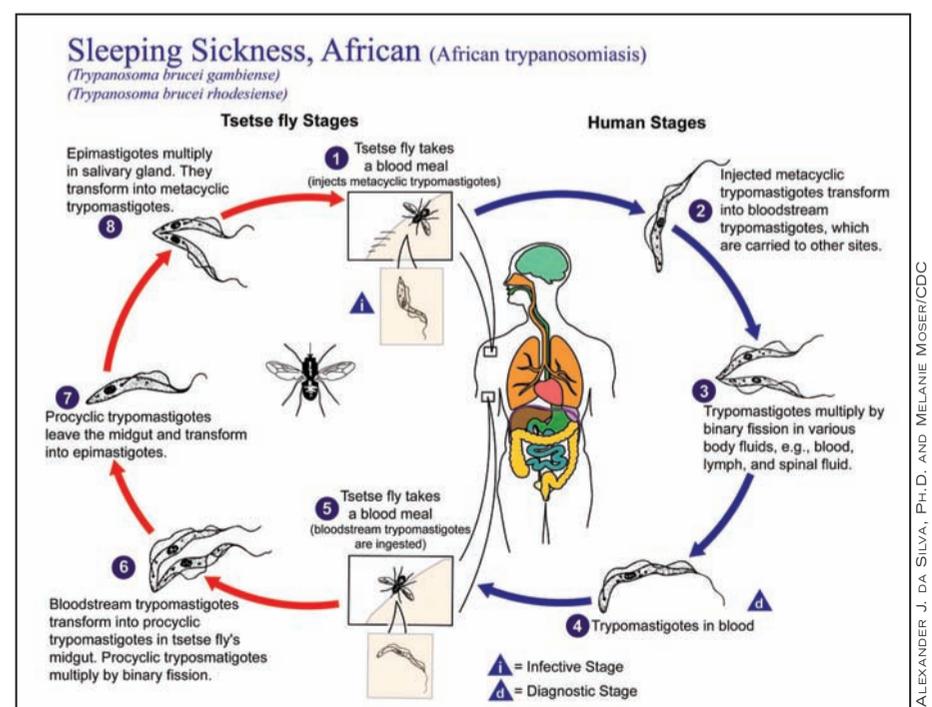
The role of prophylactic corticosteroids

in preventing the PTRE is controversial, although I personally would prescribe them. An alternative drug for late-stage *gambiense* disease is eflornithine (DFMO), which was first shown to be effective in 1981 but then became an "orphan drug." Because of efforts by Médecin Sans Frontières, working closely with the World Health Organization and the pharmaceutical industry, DFMO, which is expensive, was again made available for treatment of HAT. Eflornithine is less toxic than melarsoprol, but needs to be given intravenously over 14 days, which is not always practical in field hospitals. It is not without side effects and completely ineffective for treating *rhodesiense* infection. It has recently been suggested that a combination of eflornithine and nifurtimox is probably the optimum drug treatment for *gambiense* disease. After effective treatment, all patients with HAT require regular follow-up, but this can be neither easy nor feasible.

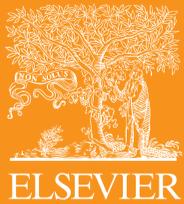
What are the prospects for better diagnosis and treatment of sleeping sickness? Despite many decades of underinvestment in HAT, there is now an increasing awareness of the importance and seriousness of the problem with increasing financial input from the developed world including from the Bill and Melinda Gates Foundation, WHO, the U.S. National Institutes of Health, and the Wellcome Trust.

Looking Toward an Ideal Solution

For better diagnosis, a rapid, user-friendly, inexpensive, reliable, and preferably noninvasive method of staging for both types of HAT is urgently needed. There are no new treatment drugs on the horizon and a promising oral drug for early-stage disease, DB 289, has been withdrawn near the end of a phase III clinical trial because of unexpected liver and renal toxicity. What is required, ideally, is a safe, inexpensive, oral drug that is effective for both early- and late-stage HAT. Such an advance would obviate the current dilemmas associated with CSF diagnosis of late-stage disease. ■



There have been several resurgencies in HAT since the 1950s, largely due to disruption of social and surveillance infrastructure, especially in war-torn regions.



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World Stroke Day: What You Can Do

BY JEYARAJ D. PANDIAN, M.D.

The incidence of stroke is a global health problem. It is the leading cause of adult disability and the second leading cause of mortality worldwide.

A recent review of stroke incidence and case fatality from 21 days to 1 month post stroke showed a divergent, statistically significant trend in stroke incidence rates over the past 4 decades, with a 42% decrease in stroke incidence in high-income countries and a greater than 100% increase in stroke incidence in low- to middle-income countries.

During 2000-2008, the overall stroke incidence rates in low- to middle-income countries have, for the first time, exceeded the level of stroke incidence in high-income countries by 20% (Lancet Neurol. 2009;8:355-69). In developing countries, stroke affects individuals in the most productive part of their lives where the average age of stroke patients is 15 years younger than that in high-income countries.

Stroke treatment has shown rapid advances. Proven therapies include management of acute stroke patients in a stroke unit, intravenous thrombolysis with recombinant tissue-type plasminogen activator (rTPA), use of aspirin within 48 hours and decompressive surgery for malignant middle-cerebral artery infarction. Effective measures for

secondary prevention are the use of antiplatelets, warfarin in atrial fibrillation, endarterectomy for carotid stenosis, and cholesterol reduction.

Among the various strategies, rapid diagnosis, implementation of early preventive treatment, early recognition of complications and mobilization improve the overall outcome of these patients. Management of these patients in acute stroke care units has a greater impact at community level than do other treatments such as aspirin and rTPA (Lancet 2008;371:1612-23).

Stroke care services are not uniformly developed across the world. Even in developed countries, a small proportion of patients receive thrombolysis. In developing countries, well-organized stroke and emergency transport services are lacking, many treatments are unaffordable, and sociocultural factors may influence access to care. Moreover, public awareness of stroke is lacking in both developed and developing countries.

The World Stroke Day proclamation was issued 2004 at the World Stroke Conference in Vancouver. It was relaunched in 2006 at the Stroke Conference in Cape Town when the International Stroke Society and the World Stroke Federation merged to form a single organization, the World Stroke Organisation (WSO). Since then, World Stroke Day is held each year on October 29—on the “birthday” of the WSO

(Stroke 2008;39:2407-20).

The WSO promotes World Stroke Day to raise awareness of stroke—a preventable and treatable catastrophe. The theme this year “Stroke—What Can I Do?” This question implies that everyone can do something about stroke. Individuals can learn their risk for stroke and do something about it; they can learn the symptoms of stroke and what to do about them; and they can help advance the stroke cause in many other roles: as physician, nurse, health care professional, patient, caregiver, donor, business person, citizen, volunteer, policy maker, or member of government. The theme has been developed to prompt action against stroke at the personal, family, or group level.

This year, we are encouraging people to run World Stroke Day events. The WSO will be delivering tools, such as lists of ideas for activities and media releases. There will also be awards for the best, most innovative activities to recognize efforts that heighten stroke awareness. To register your interest in running a World Stroke Day event, send an e-mail to admin@world-stroke.org or visit www.world-stroke.org. ■

DR. PANDIAN is professor of neurology and head of research at the Betty Cowan Research and Innovation Centre at Christian Medical College in Ludhiana, India.

Foundation's Quest for Global MS Awareness

The Multiple Sclerosis International Foundation aims to stimulate and facilitate international collaboration in research to better understand the nature of MS, develop better treatment and rehabilitation of people with MS, and inform relevant communication and advocacy initiatives.

Through the International Medical and Scientific Board, the MSIF focuses on a number of research programs and activities to achieve this aim.

We offer several awards for research in MS. In 2007, we launched the McDonald Fellowships, which enabled five young researchers from developing countries to carry out a 2-year research project at an MS center of excellence. Another three fellowships were awarded in 2008. Also last year, we awarded seven Du Pré Grants for researchers to learn new skills through collaborative research projects, we launched the International Research Meeting Grants (www.msif.org/en/research/msif_research_awards/index.html) and we supported the 9th Gordon Conference on “Development and Diseases of Myelin” in Lucca, Italy.

From 2005 to 2007, MSIF collaborated with the World Health Organization to gather data from 112 countries on the epidemiology of MS and the availability and accessibility of resources to diagnose, inform, treat, support, and rehabilitate people with MS. The Atlas of MS publication and new Web site were

launched in September last year at the World Congress on Treatment and Research in MS in Montreal. It raises awareness and encourages exploration of the validity and robustness of data on epi-



BY ALAN THOMPSON, M.D.

Dr. Thompson is chair of the MSIF International Medical and Scientific Board. He is director of the Institute of Neurology at the University College London.

demology and services for people with MS (www.atlasofms.org/index.aspx).

We have also commissioned a report into the global economic impact of MS, containing data on the personal, social, and economic costs of MS for use in raising awareness of the impact of MS and argue for the allocation of scarce resources for the benefit of individuals, communities, and society as a whole.

The MSIF Research Alumni Programme was launched in April 2008 to foster a lifelong relationship between research alumni and MSIF, and promote scientific communication and formation of a global MS research network. We have 36 alumni (www.msif.org/en/research/msif_research_alumni/index.html).

In 2008, we developed a Member So-

ciety Research funding database with data on annual MS research funding by our member societies to help us and our member societies determine global funding trends and patterns, inform fu-

ture research funding decisions, and develop international collaborative initiatives. This past summer, we organized an MS Research Coordination meeting that brought together key players in the global MS medical and scientific community to review global MS research

spending and anticipate and prepare for future challenges and opportunities.

Issue 13 of MS in Focus, on tremor and ataxia in MS, came out in March. Most issues of this biannual publication are available free in English, German, and Spanish (www.msif.org/msinfocus). We also published an online update of MS: The Guide to Treatment and Management, which now includes a new chapter on unconventional therapies.

We coordinate work of the International Pediatric Multiple Sclerosis Study Group (IPMSSG) and facilitated and part-funded the first research symposium of this group in Toronto, Canada, in April this year (www.ipmssg.org).

Finally, we were instrumental in setting up and coordinating global activities of the first World MS Day on May 27. ■

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MEETING UPDATE

AOAN Elects President At Delhi Congress

The 12th Asian and Oceanian Congress of Neurology and the Asian and Oceanian Association of Neurology meeting were held in October 2008 in New Delhi, India.

At that meeting, I was elected the 13th president of the Asian and Oceanian Association of Neurology (AOAN). I would like to thank everyone for their participation and support during the



BY CHING-PIAO TSAI, M.D.

Dr. Tsai is professor and section chief at the Neurological Institute at the Taipei Veterans General Hospital and National Yang-Ming University in Taipei, Taiwan.

meeting. I look forward to serving the association during my tenure. I hope to keep members connected by sending out regular newsletter updates, and I encourage you to visit our new Web site at <http://www.aoan-neuro.org/>.

Also at the meeting, Dr. William Carroll of Australia was elected vice-president and Dr. Man Mohan Mehndiratta (India) secretary treasurer. The committees will be headed up by Dr. Lawrence Wong of Hong Kong (education); Dr. Mohammad Wasay, Pakistan (research); and Dr. Mehndiratta (membership). The regional director for the World Federation of Neurology is Dr. Amado San Luis of the Philippines.

The AOAN was founded almost 50 years ago after Dr. Charles M. Posner, a WFN representative, toured the region and suggested neurologists form an association to foster the advancement and exchange of neuroscientific information within the region. Dr. Shigeo Okina

naka invited neurologists to a planning meeting in Tokyo, Japan, and the association was established on June 26, 1961.

The statutes stipulate that the Asian and Oceanian Congress of Neurology (AOCN) be held every 4 years.

On Sept. 14, 1962, the association's board was chosen, and it included representatives from Australia, Hong Kong, India, Japan, Korea, New Zealand, Philippines, the Republic of China (Taiwan), and Thailand. The AOCN inaugural was held in October 1962 in Tokyo, under the leadership of Dr. Okinaka.

Membership has increased over the years from the initial 9 member countries to the current 18. Current members are Australia, Hong Kong, India, Japan, South Korea, New Zealand, Philippines, Malaysia, Pakistan, Saudi Arabia, Israel, Indonesia, Singapore, Sri Lanka, Taiwan, Thailand, and Mongolia—with Vietnam recently becoming the 18th.

The founding AOAN mission statement, as proposed by Dr. Carroll, is to:

- ▶ Promote development of clinical neurology and neurological science in the Asian and Oceanian region;
- ▶ Assist, as required, in the development of training programs and research efforts in member and potential member nations of the region;
- ▶ Facilitate cooperative exchange programs for trainee and qualified neurologists and neuroscientists;
- ▶ Participate with activities promoted by the WFN;
- ▶ Respect the aims and aspirations of member organizations in providing support and advice; and
- ▶ Promote friendship among regional neurologists and neuroscientists. ■

FROM THE LANCET NEUROLOGY

In Some, DBS Improves Dystonia-Choreoathetosis CP

Bilateral pallidal deep brain stimulation may hold promise as a treatment for some patients with dystonia-choreoathetosis cerebral palsy, according to results of a small pilot study reported by Marie Vidailhet, Ph.D., of Groupe Hospitalier Pitié-Salpêtrière, Paris, France, and her colleagues in the French SPIDY-2 Study Group.

Dystonia-choreoathetosis cerebral palsy (CP) is a form of CP characterized by severe disabling movement disorders with little or no spasticity and little or no cognitive impairment.

"This is the first demonstration that BP-DBS [bilateral pallidal deep brain stimulation] can improve patients with this type of CP. So far, no drug or therapy has proven to be effective. The modest improvement in this pilot study is the beginning of a new era for patients with CP," said senior author Dr. Pierre Pollak of Joseph Fourier University Hospital in Grenoble, France (*Lancet Neurol.* 2009;8:709-17).

BP-DBS is effective for patients with primary dystonia, which encouraged the investigators to study the procedure in dystonia-choreoathetosis CP. The multicenter prospective pilot study enrolled 13 adults with dystonia-choreoathetosis CP with no cognitive impairment, little spasticity, and only slight abnormalities of the basal ganglia on magnetic resonance imaging. Patients were treated with neurostimulation of the internal part of the globus pallidus for 1 year and then evaluated for improvement in movement, functional disability, pain, and mental health-related quality of life.

The mean improvement on the Burke-Fahn-Marsden dystonia rating scale was 24%, which is about half of the magnitude of mean improvement achieved by DBS in primary dystonia (about 52%). Patients also showed improvements in body pain ($P = .04$), emotional role ($P = .06$), and mental health ($P = .05$), with no deterioration in cognition or mood.

One-year outcomes on the Burke-Fahn-Marsden dystonia rating scale were variable in the 13 patients, with 3 showing no improvement, 5 showing some improvement (2 in the same range as in primary dystonia—greater than 50% improvement), and 5 only mildly improved (less than 50% on the rating scale). The investigators sought to determine characteristics associated with improved outcome, but Dr. Pollak said that is difficult with such a small number of patients. "Placement of the electrodes is very im-

portant. The two patients who did the best had optimal placement and stimulation of the globus pallidus internus, whereas the results were poorer in patients whose electrodes were implanted suboptimally—2 or 3 mm outside the globus pallidus internus—spreading the electrical current beyond the target site," he explained.

Another factor for success seemed to be patient selection. Those with mobile dystonia seemed to do better than those with static dystonia, though that observation needs to be validated by further study, he noted. Future steps are to reimplant the electrodes in four of the five patients with poor outcomes and suboptimal placement of electrodes. "If they improve, then this will be a strong argument that placement of electrodes is a critical factor for success."

The investigators plan to continue to study the 13 patients using formal scales and to implant more CP patients outside of a trial setting. "It may be possible to extend BP-DBS to patients with some intellectual impairment and abnormal movement. We have operated on one patient with an intellectual deficit and some abnormal movements. This procedure is safe for cognition but won't improve it, so we can propose stimulation of the globus pallidus internus for patients with severe dystonia and some intellectual impairment," Dr. Pollak said.

In an accompanying editorial, Dr. Stefan Berweck of Children's Hospital, University of Munich, Germany, wrote that the "pilot study on BP-DBS is encouraging, but it remains a challenge to advise an individual patient with dystonia-choreoathetosis CP about whether to undergo this treatment."

"BP-DBS was tested in a highly selected subgroup of patients with CP. We do not know in how many patients within the spectrum of CP this approach significantly improves health status. We have to be careful not to raise unrealistic hopes in patients and families," he said (*Lancet Neurol.* 2009;8:692-3).

Dr. Berweck also noted that patients should be counseled that the after-care will take several visits within the first year after implantation to optimize therapeutic effects through adjustment of stimulation parameters. The decision to have this procedure should be made between the physician and the patient, he wrote.

— Alice Goodman

Ms. Goodman is a freelance writer for *The Lancet Neurology*.

Focus on Disease Classification

ICD-10 • from page 1

neurology specialists, and researchers.

For the first time, the revision process will be fully transparent. A beta draft is expected in 2011, and it will be field tested at various sites around the world for feasibility, reliability, clinical utility, and validity. Committee members will be seeking and choosing these sites over the next half year. The penultimate draft will be posted on the WHO Web site, and interested parties and the public will be invited to respond. It is hoped that the final version will be submitted to the World Health Assembly in 2014.

Advances in neurogenetics, molecular biology, neuroimmunology, and other fields have prompted dramatic changes in disease classifications. Categories of disorders once classified by clinical phe-

notype, for example, have been reshuffled to reflect their specific genetic causes, new disorders have been discovered, and some diagnostic categories have been redefined to reflect new understanding of their causes and risk factors. Many hope computerized health data management will facilitate more frequent remodeling of the ICD-11 codes to keep up with the growth of neuroscientific and clinical knowledge. The absolute need to track epidemiological disease data over time requires each modification of the ICD to be "mappable" onto the previous version, a function simple for computers but highly complex for those devising each new classification. (See <http://who.int/classifications/icd/en.>) ■



DR. VIDAILHET



DR. POLLAK

Comment



YHU-CHERING
HUANG, M.D., PH.D.

Influenza A and B viruses are known to cause encephalitis or encephalopathy, but they are rare complications. It is assumed that influenza virus causes neurological symptoms in two main ways: first, by direct invasion of nervous tissue, usually presenting with neurological manifestations within 4 days of onset—classified as encephalitis—or second, by an immune reaction affecting nervous tissue that usually presents with neurological manifestations

5 days after the onset of the infection—classified as encephalopathy. However, virological evidence is rarely documented in the CSF.

The neurological manifestations vary from mild cases of transient cortical dysfunction, such as excessive sleep, stupor, hallucination, inappropriate behavior, and seizure (with or without fever) to severe cases of necrotizing encephalitis with neurological sequelae or even death. Clinicians

caring for children should remain vigilant for this complication of influenza virus infection. Influenza virus-associated CNS dysfunction may be more common than previously recognized, but the prognosis is not always grave.

—DR. YHU-CHERING HUANG,
division of pediatric infectious diseases at
Chang Gung Children's Hospital and Chang
Gung Memorial Hospital, Kweishan, Taiwan.

Antiviral Timing May Be Key

H1N1 • from page 1

seizure and subsequent postictal mental state. While he was hospitalized, he had a 30- to 40-minute partial complex seizure. Brain magnetic resonance imaging was consistent with encephalopathy.

A third child, a 7-year-old white male with a history of febrile seizures, presented to the emergency room following a seizure, 2 days of cough, nasal congestion, and fatigue. A brain MRI showed nonspecific white matter abnormalities, and localized cerebral dysfunction was evident on electroencephalography.

The fourth patient, a black male aged 11 years with a history of asthma, had fever, fatigue, headache, abdominal pain, and vomiting. Neurological examination of this patient revealed ataxia. He also had a seizure after hospital admission and later experienced visual hallucinations. He had difficulty responding to questions and required supplemental oxygen. An electroencephalograph was consistent with encephalopathy, but a CT scan was normal.

Antiviral therapy included oseltamivir in all four patients and rimantadine in all but the 11-year-old. All four children recovered fully, with no neurological sequelae at discharge.

This is the first report of patients with neurological complications of the H1N1 influenza virus infections. The severity of the complications in these four patients was less than described in two previous studies of neurological complications associated with seasonal influenza, which have included reports of severe static encephalopathy and death.

The frequency of neurological complications with pandemic flu is not known, but it is likely that additional cases in children will be reported as the pandemic continues, especially because children appear to be infected with the H1N1 virus more often than adults, the CDC noted.

The center also added that antiviral treatment should be initiated as soon as possible for any patient who is hospitalized with neurological symptoms and suspected influenza infection of any type. ■

Jeff Evans contributed to this report.

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Is There a Universal Theme Underlying the Challenges to Medicine?

A synopsis of the American Academy of Neurology president's address in Seattle, U.S.A., April 2009.

The World Federation of Neurology's mission is to advance research and the standard of neurological practice. The dawning of our information age and our escalating ease of travel have reconfirmed with unambiguous clarity, that national boundaries are irrelevant to science and disease and that sharing experience and knowledge can add value to all.

From the beginning of time, the House of Medicine in every region of the world has existed in an unstable equilibrium with the scientific, religious, social, political, and economic concerns of the day. We do not differ from our predecessors in having to embrace these challenges, and in doing so, we merely define one component of the work to which we have dedicated our lives. This commitment to the greater good, a conspicuous necessity for doctors in the past and at present, will undoubtedly continue to be required of every future generation.

Similarities Amid Challenges

A life in medicine has always been meaningful and captivating, summoning from its devotees the most noble of human qualities, and it is neither self-serving nor arrogant to believe that this has never been more engrossing. Yet these challenges continue, and despite vast and specific regional and national differences, many similarities exist.

For example, economic circumstances affect each of us differently. Local opportunities for physician research and training and the manner in which we are able to administer to patients vary for many additional reasons, including the disparities in the ratio of physicians to population size.

Is there a universal theme enmeshed in these challenges? Is there a soft underbelly of health care delivery, research, and education? What is the breaking point? And if there is, will defining and understanding it empower physicians and strengthen our entry into health care debates around the world?

I believe that all of these threats imperil the behavioral attributes of the doctor and are felt most on our character, which has been developed over centuries giving birth to the philosophy or ethos of doctoring. Our ethos is the universal, its application, of course, varying from country to country and from time to time. It is our responsibility alone to inform our policy makers of this.

The physician's charter is considered by many to be the basis of medicine's contract with society, and it requires our

commitment to competence, respect, education, and collaboration and that we promote access to care ("Medical Professionalism in the New Millennium: A Physician Charter" [Ann. Intern. Med. 2002;136:243-6]). Yet this is not enough; the charter is about our behavior and not



BY STEPHEN M. SERGAY, M.B. B.CH.

Dr. Sergay is immediate past-president American Academy of Neurology and immediate past-North American Regional Director of the WFN. He is a general neurologist practicing in Tampa, Florida, U.S.A.

the most significant component of our professionalism and the principal influence on our motivation and behavior, our ethos.

The philosophy of doctoring closely resembles the Greek concept of eudaimonism, first discussed by Socrates. This has led to the development of contentment theory and the concept of the opportunity for human flourishing. Human flourishing is not a consequence of honor, wealth, or power; rather, it flows from rational activity in a complete or meaningful life, filled with virtues of character, such as honesty, integrity, personal responsibility, intellect, and rational judgment. Many consider this search for contentment inherent in humans as social animals after satisfying our basic survival drives. Contentment theory is now a component of economic and social planning in many countries, and the validity of incorporating this thinking has been confirmed by economists, philosophers, psychologists, and more recently, biologists.

A Larger Humanistic Whole

Medical care quality is jeopardized when contentment theory is not a component of health policy decisions, and the impact of its absence is borne predominantly by our ethos. In defending our ethos, we as biologists and neurologists in particular, are strengthened by emerging concepts in neuroscience research, which provide a window to our behavior and confirm that doctrinaire economic and social planning, when not part of a larger humanistic whole, is suboptimal.

This necessity for concurrent economic and social planning is suggested by human capability on a preconceptual cellular level to recognize expectations, intentions, and motivation (Rizzolatti, G., Sinigaglia, C., Anderson, F., "Mirrors in the Brain," New York: Oxford University Press, 2008) and also, value, utility, and numerosity (Nature, 1999;400:233-8). We also understand that meaningful planning can lead to new

long-term memory formation and thus lasting behavior modification. Eric Kandel defined both the molecular basis of long-term memory formation by the synthesis of a new mRNA and protein, and its epigenetic impact on our genome ("In Search of Mind," New York: W.W. Norton & Co., 2006). Our understanding of epigenesis, reflecting in part the consequences and the causes of our social evolution, confirms our inescapable duty and responsibility to our larger genetic future, vastly different from eugenics. Because of this, it is necessary for us to inform planners of their responsibility to consider the deeper consequences of their actions.

Defining Our Ethos

But our ethos has not been fully defined, and it needs to be. It is not an abstraction but rather a set of behavioral principles that determine how we respond to the sick. It is our character, behavioral characteristics, internal motivators, physician-patient relationship requirements, the ethics of our professionalism, and our guardianship of appropriate autonomy for physicians and patients. Our ethos has not been, nor will it be, forever impenetrable, and therefore our definition must incorporate integrity to counter human weaknesses such as envy,

greed, and power. Preeminently, our definition must include personal responsibility, because if we do not accept responsibility, we will surrender our responsibility to others.

Societal complexity requires more than one method of dialogue in health care policy debates. It is our responsibility to speak for the House of Medicine. We must sit at the negotiating table, not as agents of the government, politicians, economists, or managers of the problems created by uninformed policy. We will be most effective when, conversant with the details of our medical philosophy, we become the voice of our ethos, and educate our politicians and economists in advance of their decision making, of the potential impact of their planning on those who deliver medical services and those whom we serve, our patients. We must work to encourage policies that strengthen and not those that weaken our ethos, because of our belief, that by so doing, the health care we plan for will have a greater chance of spawning better quality research, education, and care delivery, all performed most cost effectively. ■

Adapted from Neurology, Sergay S.M., "Doctoring 2009: Embracing the Challenge. Neurology" (in press).

AAN Presents Award for Neuroepidemiology

Dr. Edgard B. Ngougou from Libreville, Gabon, received the 2009 Bruce S. Schoenberg International Award in Neuroepidemiology from Dr. Joseph Zunt of the University of Washington, Seattle, at the annual meeting of the American Academy of Neurology in Seattle, U.S.A.

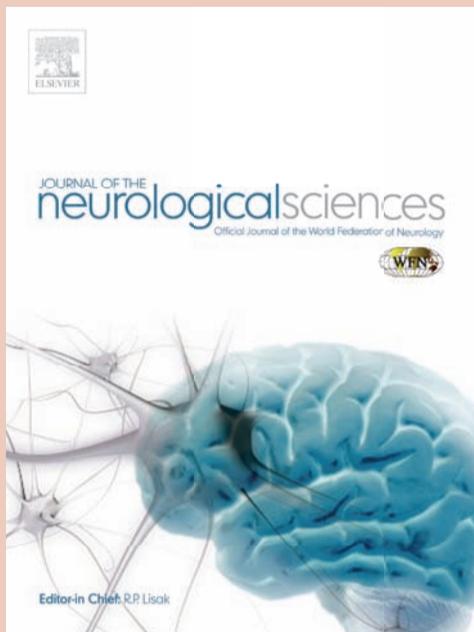
He presented the results of an epidemiologic study on the role of malaria infection in causing epilepsy in Africa. The study was conducted

with the cooperation of the Institute of Neuroepidemiology and Tropical Neurology in Limoges, France.

During the past 25 years, the WFN's Research Group on Neuroepidemiology has held a 1-day annual meeting concurrently with the AAN meeting. Beginning in 1984, the abstracts of the invited lectures, papers, and posters presented at the annual meeting have been published in the journal, Neuroepidemiology.



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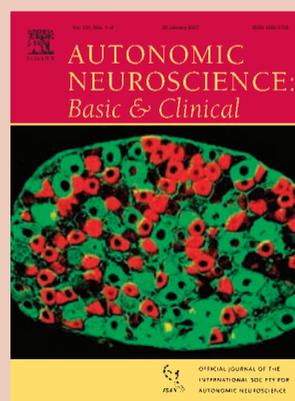
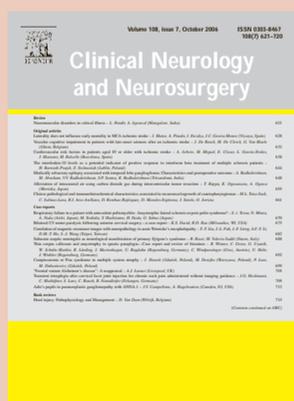
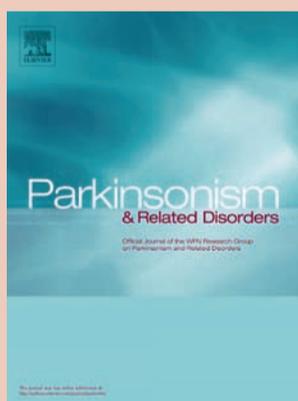
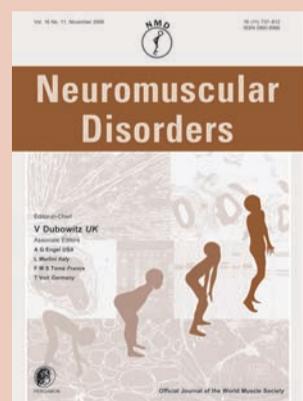
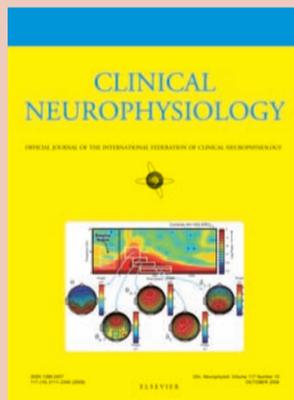
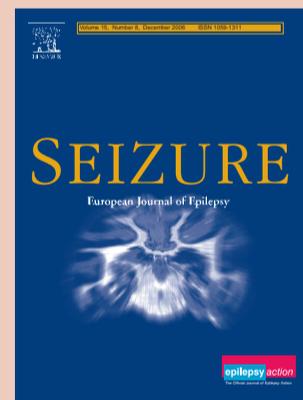
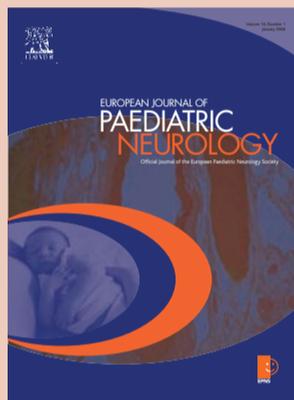
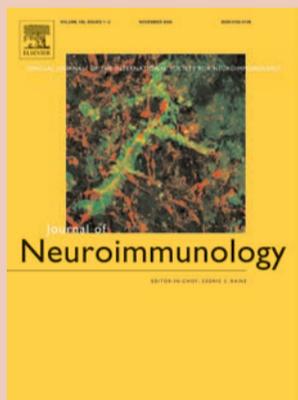
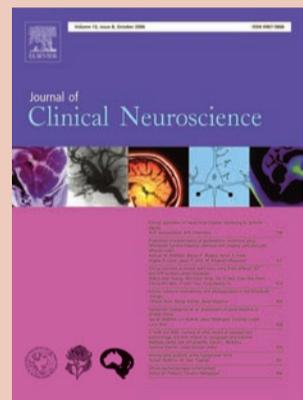


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OBITUARY

John Alexander Simpson (1922-2009)

BY PETER O. BEHAN, M.D.

Felix, qui potuit rerum cognoscere causas.
Virgil, The Georgics, Book II

John A. Simpson, professor of neurology at the University of Glasgow from 1964 to 1987, died in May at the Royal Infirmary in Glasgow, Scotland, from a relatively acute illness. He was the esteemed international authority on myasthenia gravis and played a major role in the modern development of neurosciences in Scotland, particularly in Glasgow.

Iain, as he was known, came from a long Scottish lineage that includes the 18th century political cartoonist James Gillray.

He is a good example of serendipity and major advances in science. In 1960, while he held a Medical Research Council traveling fellowship at the National Hospital for Nervous Diseases at Queen's Square, London, he observed the increased association

of myasthenia gravis with other diseases, thought at that time to be autoimmune in etiology. He published his hypothesis in the *Scottish Medical Journal*, and that paper is regarded as the seminal paper that directed research into the immunological etiology of myasthenia gravis. It was logical, therefore, that Iain should pursue his interest in neurology and head up the University of Glasgow's department of neurology, where the main research interest was muscle diseases.



Dr. John Simpson, renowned clinician and researcher and valued colleague.

He was appointed the James Watson Lecturer of the Royal Faculty of Physicians and Surgeons of Glasgow, a Honeyman Gillespie Lecturer at Edinburgh, an Abbott Lecturer at Newcastle, and later a fellow of the Royal Society at Edinburgh. Other appointments included that of honorary consultant neurologist to the army, to the civil service commission, chairman of the Scottish Council for the Neurological Services and of the Scottish Epilepsy Association, and a member of the Research Committee of the Muscular Dystrophy Group of Great Britain.

At the time he became head of the Glasgow department, there had been enormous changes in the structure of neuroscience in Scotland—with the Institute of Neurological Sciences being established at the Southern General Hospital in Glasgow, where Dr. Bryan Jennett, professor of neurosurgery, and Dr. J. Hume Adams, professor of neuropathology, were among the main contributors.

Iain had come to Glasgow from the University of Edinburgh, where he had been chief of neurology and had built up an active department with a sound reputation. He was ideally equipped to develop neurology in Glasgow, and his department there became a showpiece in 1967 for the International Congress of Electromyography, a subject he excelled in and contributed to. This was the beginning of many occasions when Iain and his wife, Elizabeth, would generously entertain visiting neurologists and neuroscientists. Indeed, Iain's kindness to obscure authors often had grateful individuals plan their

journey to include a visit to Glasgow and the Simpsons.

Iain was a good general physician, and wrote and studied not only on myasthenia gravis but the chorea related to hypothyroidism, the dermatological alterations and hypocalcaemia, and several findings related to abnormal nerve conduction velocities. He was among the first who noted the neurophysiological abnormalities of the Eaton Lambert Syndrome.

He was in demand to give many guest lectures, accepted invitations to visit neurology departments throughout Australia, India, Europe, and Japan, and contributed to now classic textbooks of muscle and neurological disease. He also peer-reviewed several journals and had more than 94 original papers on neuromuscular neurological diseases published.

He clearly was of the "old school" and looked after his patients well. They became part of his family to the extent that he could recount their marriages and achievements. He was a kind, caring, decent fellow of whom it was an honor to be considered one of his friends. He delighted in making a solid and sound diagnosis of extremely rare diseases, and he imparted this knowledge so that his students were, like Byron's hero, wax to receive and marvel to retain. Patients with myasthenia gravis could expect to see him at any time of the day or night taking as he did a personal interest in their treatment.

No account of Iain would be complete without describing his addiction to and pleasure in sailing and Scottish fiddle music. He once told me that for him, the greatest pleasures was drinking hot soup followed by a large quantity of malt whisky after a successful sail.

Iain left behind a department in excellent health, and his advice and warm friendship will be sadly missed. ■

DR. BEHAN is professor emeritus of neurology at the University of Glasgow.

FROM THE JOURNAL OF THE NEUROLOGICAL SCIENCES

Tracking Dementia Risk in Atomic Bomb Survivors

BY ALEX TSELIS, M.D., PH.D.

The effects of radiation on the brain are well recognized from the experience with radiation therapy to the brain in cancer patients. Not much is known about these effects, but the basics are clear: Ionizing radiation breaks DNA molecules, fragments RNA, generates free radicals, denatures proteins, and thus damages or kills cells.

Things become more complicated at the multicellular level. Different cells have different susceptibilities to radiation damage, they may be affected by or affect neighboring cells, they may acquire neoplastic properties, and/or their loss or dysfunction may or may not strongly affect the organ (thus loss of neurons is more significant than that of hepatocytes).

Clinically, radiation damage to the brain comprises several well-described syndromes in patients who are treated with radiation therapy. Acute, early-delayed, and late-delayed encephalopathies are all well-defined, if not completely understood. The late effects are of particular interest because they can tell us about

the basic mechanisms of neurodegenerative diseases and generate epidemiologic hypotheses.

Radiation necrosis can occur several months or even years after radiation therapy. Postradiation brain atrophy can be accompanied by disabling cognitive deficits. The radiation doses in these patients are in the range of hundreds to thousands of centigrays, often given in a sequence of fractions to minimize toxicity. What happens at lower radiation doses—can such syndromes arise years later with a slowed tempo? Can other relevant tissues be damaged with very late effects?

An important example would be radiation vasculopathy. Most often, this is extracranial large-vessel disease, a form of accelerated atherosclerosis usually involving a carotid artery and resulting in cerebrovascular disease. Does radiation predispose to the development of dementia—vascular or Alzheimer's?

In an interesting paper, Dr. Michiko

Yamada and her colleagues described a study in which they examined the risk of dementia in survivors of the atomic bombings of Hiroshima and Nagasaki in 1945. The researchers are based at the Radiation Effects Research Foundation Adult Health Study (RERF), a joint

Japan-United States research organization with laboratories in the two cities.

They estimated the radiation doses the subjects were exposed to depended on the distance from the explosion and shielding by the terrain. The subjects were then divided into three tertiles of radiation dose with about 500-800 subjects in each group, serially evaluated for

cognitive problems, then assigned a diagnosis of dementia classified as vascular or Alzheimer's type. The radiation doses were in the range of milligrays, roughly a tenth of the doses used for radiation therapy (*J. Neurol. Sci.* 2009;281:11-4).

The findings showed no increase in the risk of either dementia type with radia-

tion dosage, in the dose range to which the subjects had been exposed. The authors noted that the findings might have been subject to certain biases but that its strengths included its prospective, population-based nature. The findings were in line with results in other populations.

Dr. Yamada, a physician and epidemiologist, has been in charge since 1983 of the analysis of the RERF study to investigate the long-term effects of exposure to radiation from the atomic bomb blasts. The study is one of the largest and longest-running cohort studies in the world. Another study based on these data has shown no increase in the incidence and prevalence of Parkinson's disease in this population. An attempt to examine a similar hypothesis for amyotrophic lateral sclerosis was unsuccessful because of the small number of subjects with the disease. ■

DR. TSELIS is an associate professor of neurology at Wayne State University in Detroit, U.S.A. He is the book review editor for the *Journal of the Neurological Sciences*.



DR. MICHIKO YAMADA

MOVIE REVIEWS

Lyme Documentary Misleading, Perhaps Irresponsible

“Under Our Skin,” directed by Andy Abrahams Wilson

Why, you may ask, is there a movie review in WORLD NEUROLOGY? A reasonable question.

“Under Our Skin” is a documentary-style film about chronic Lyme disease and the debate surrounding it. With lovely cinematography and sobering music, it depicts a number of clearly suffering patients and the “Lyme-literate physicians” who have treated them.

The treating physicians are seen talking to their patients with great empathy as they explain the rationale for their approach. We even see a pathologist who, mad scientist-like, applies molecular biologic techniques in a laboratory in his home basement, studying a well-worn 1940s volume on syphilology. He reasons that “just as general paresis of the insane is indistinguishable from Alzheimer’s disease,” Lyme disease can be responsible for multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), Parkinson’s, and Alzheimer’s disease.

Of course, there are excerpted authoritative quotations and interviews—carefully edited—to support the filmmakers’ premise. (Though the plot also requires villains, and unfortunately, I make a cameo appearance in what resembles an array of wanted posters.)

Several experts were interviewed to provide “balance.” For example, an internationally respected infectious disease expert states that few of the patients referred to him for chronic Lyme disease have anything to suggest they ever had the infection; his 30-second excerpt is juxtaposed with a Simpson’s clip. Other expert comments are rebutted—in one instance, by a psychiatrist who has given up the practice of psychiatry to treat “chronic Lyme patients” with antibiotics, and in another by the office manager of a “Lyme-literate physician.”

Finally, the authors who wrote the Infectious Disease Society of America (IDSA) Lyme disease treatment guidelines are repeatedly accused of being tainted by conflicts of interest. This position is bolstered by focusing on the Connecticut attorney general’s lawsuit that alleged that the IDSA violated antitrust law in promulgating its guidelines. Not mentioned is the fact that that lawsuit was settled with no finding



BY JOHN J. HALPERIN, M.D.

Dr. Halperin is the medical director of the Atlantic Neuroscience Institute and chair of the department of neurosciences at the Overlook Hospital, both in Summit, New Jersey, U.S.A., and professor of neurology at Mount Sinai School of Medicine in New York.

of either an antitrust violation or of any meaningful conflicts of interest.

The movie continues with scenes of multiple legal proceedings in which the medical establishment and the IDSA authors are portrayed as persecuting the “Lyme-literate physicians”—apparently either because all medical experts want to help the health insurance industry save money or because these supposedly conflicted physicians stand to make windfall profits from patents they hold related to this disease [sic].

It would be easy to dismiss this film as artfully crafted propaganda; however that would ignore its important lessons. As Dr. Bernard Raxlen (the antibiotic-wielding psychiatrist) says in the film, “Something funny is going on here.”

So what is it exactly?

As the film makes obvious, there is a significant population of patients who are not satisfied with the diagnoses and treatment provided by conventional medicine. As they have sought a sympathetic ear, they have helped sustain a group of physicians who are apparently convinced they have unearthed both an unprecedented

illness and a conspiracy to conceal it.

Of importance to the neurology community, is that these physicians—none of whom has any neurological expertise—have focused on what they perceive (incorrectly, in most instances) to be neurological manifestations of their patients’ symptoms. This is terrifying for the patients, who often become convinced that they have a progressive nervous system-destroying illness, which can only be cured with these physicians’ unique ministrations.

These physicians and their supporters argue that the IDSA guidelines ignored a “vast worldwide literature” in support of “chronic Lyme disease.” Curiously though, when they published their own “evidence-based guidelines,” they included no references to anything except Class IV anecdotal evidence substantiating the existence of this entity, or validating prolonged antibiotic treatment. In a contrast that epitomizes the tension between evidence-based medicine and anecdotal observation, a physician leader of this group has defined evidence-based medicine as “a treatment approach that allows physicians to take into account their own values, clinical expertise, and patient values in addition to published research from level 1 studies.”

At a time when many physicians feel their traditional autonomy is rapidly vanishing, is it surprising that some view it as their right to treat however they see fit, particularly when reinforced daily by devoted patients who are willing to pay out of pocket for their treatment? This mutually reinforcing alliance of physicians and patients has been tremendously politically skillful. Their supporters include numerous politicians who have even enacted legislation legitimizing their unorthodox treatment and who instituted the unprecedented antitrust suit against the IDSA.

How can we resolve this dilemma? Guidelines adopted by the 8,000-member IDSA and the 21,000-member American Academy of Neurology have only served to bolster the sense of solidarity in persecution of the “Lyme-literate community.” The IDSA agreed to have its guidelines reviewed to determine if it will need updating. Since the “Lyme-literate physicians” all derive substantial income from treating patients with “chronic Lyme disease” the overseeing ethicist felt this constituted an undue conflict of interest and excluded them from the new review panel. Needless to say, they are already protesting that the review will be unfair.

Does this case have implications beyond Lyme disease? For those physicians who participate in guideline development, volunteering innumerable hours reviewing articles, weighing evidence, debating conclusions while trying to do this in as fair and rational a way as possible, this movie is like being the guest of honor at a Salem witch trial. The intrusion of this irrational debate into politics—with legislatures and state attorneys general inserting themselves into the substance of medical decision making—could have a profoundly chilling effect on future guideline development.

Equally important, at a time when American health care is rightly criticized for spending too much on tests and treatment with limited, if any, impact on health outcomes, it is remarkable that this “controversy” has resulted in legislatures legitimizing treatment that is both costly and demonstrably of no meaningful benefit. As the United States debates changes in health care, is this helpful?

This movie makes good theater but it is far removed from reality. Sadly, it serves to perpetuate unfortunate medical care that subjects patients to unnecessary and significant risk, and reflects a process that is clearly detrimental to the ideal of providing patients with effective, safe, and appropriate care. And that is why there is a movie review in WORLD NEUROLOGY. ■

Artful and Entertaining—Despite the Tic-less Tourette

“Phoebe in Wonderland,” written and directed by Daniel Barnz, featuring Elle Fanning, Patricia Clarkson, and Felicity Huffman

Artistic license, commercial exaggeration, or simple ignorance in movie scriptwriting often generate an inaccurate view of medical conditions. However, sometimes art succeeds where documentaries fail in giving us empathy for disease sufferers.

The movie “Phoebe in Wonderland,” while inaccurate diagnostically, succeeds in this way. The plot centers around a sensitive girl, Phoebe (Fanning), who wishes to land the leading role in the school play, “Alice in Wonderland,” and her ensuing struggles with try-



BY DONALD L. GILBERT, M.D.

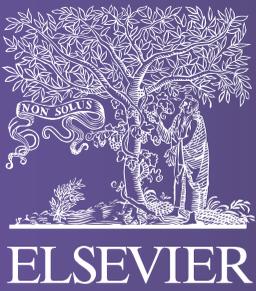
Dr. Gilbert is the director of the Movement Disorders and Tourette Clinics at the Cincinnati Children’s Hospital Medical Center in Ohio, U.S.A.

outs, rehearsals, and performance. The idiosyncratic school drama teacher (Clarkson) recognizes Phoebe’s ability to connect with the character of Alice. Unfortunately, Phoebe’s traits become magnified as tryouts and then rehearsals progress, resulting in severe anxiety and compulsions.

Ultimately, a psychiatrist diagnoses her with “Gilles de la Tourette syndrome,” an epiphany for the family but a surprise to me, since I observed lots of obsessive compulsive behaviors and not tics in the film. Still, the film does capture some essence of the irrepressible imps in Tourette, a view confirmed to me by several parents of children with the syndrome.

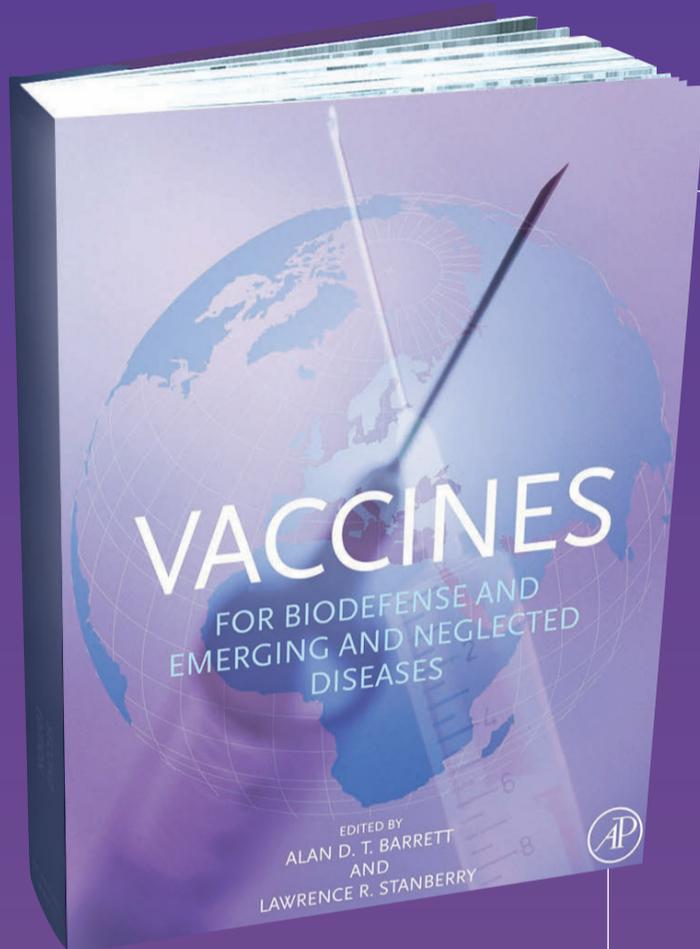
The plot’s juxtaposition of Phoebe’s tensions in balancing external school rules and her internal obsessive compulsive disorder rules and of Alice’s frustration at Wonderland rules works well as a scaffold for the exploration of Phoebe’s character and the effects of her symptoms on her family and classmates. Her situational social disinhibition, such as when she spits at a peer or shouts “Fat, you’re fat; you’re fat,” at a stout neighbor, depicts the impulsiveness and social impairments we see in some children and adults with Tourette. The anguish of her mother (Huffman) and the stressed parental dialogue around Phoebe’s symptoms worked particularly well.

So, while the film risks misinforming viewers that compulsions equal tics, I recommend suspending your DSM-IV and enjoying the writing, acting, and cinematography in “Phoebe in Wonderland.” In the process, you gain some insight into the imps in Tourette syndrome. ■



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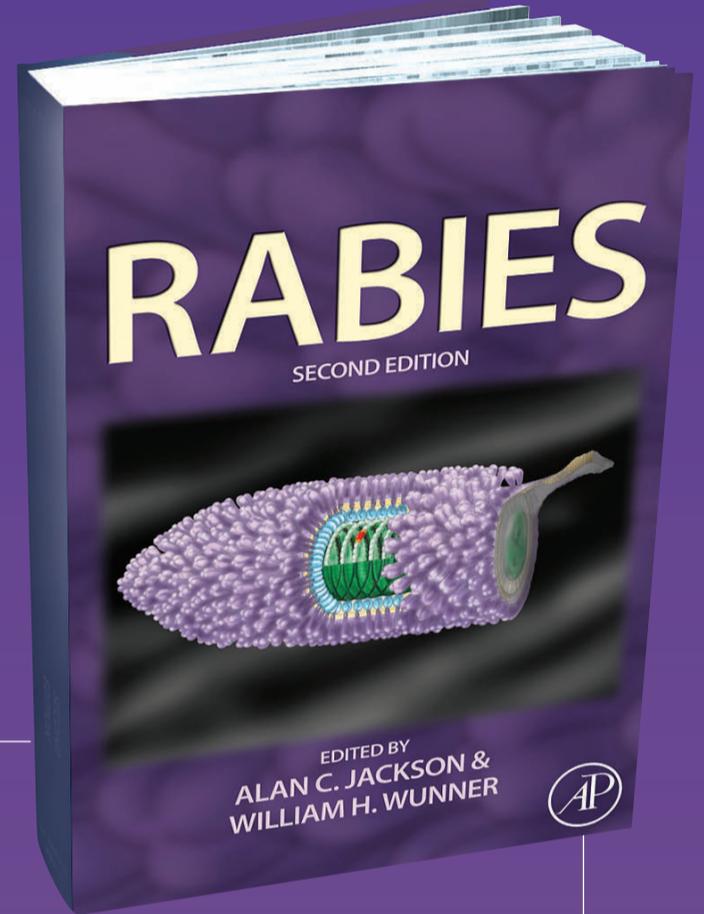


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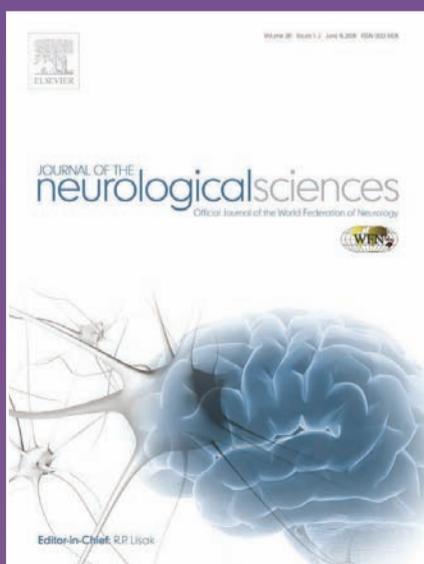


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