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# WORLD NEUROLOGY

THE OFFICIAL NEWSLETTER OF THE WORLD FEDERATION OF NEUROLOGY

# Neurological Care Under Scrutiny in Africa

BY SUSAN W. MARINO, PH.D.

Disorders of the nervous system produce a challenging and largely unmitigated disease burden in many countries in the sub-Saharan region, yet there is a severe shortage of people who are trained in the treatment of psychiatric and neurological conditions, and appropriate medications and equipment are in short supply, if available at all.

Last year, the Uganda National Academy of Sciences' Forum on Health and Nutrition and the US-based Institute of Medicine's Forum on Neuroscience and Neurological Disorders hosted a workshop in Kampala, Uganda, at which representatives from the medical, academic, and governmental communities of 16 countries met to address the quality of care for mental, neurological, and substance-use disorders (MNS) disorders in the region.

Much attention has been focused on infectious disease in developing countries since the issuance of the United Nations Millennium Development Goals in 2000, the establishment of the President's Emergency Plan for AIDS Relief (PEPFAR) program by George W. Bush in 2003, and growing support from nonprofit organizations such as the Gates Foundation. The organizers of the Kampala meeting hoped to emulate that effort for MNS disorders.

## Numbers Count

Good epidemiological data are needed for two purposes – to devise a strategy for improving quality of care and to convince government policy makers, who need to see evidence to act.

For the latter, data on the effectiveness of treatment and treatment delivery systems are needed in addition to accurate baseline information. The World Health Organization anticipates that the prevalence of MNS disorders will rise over the next 15 years, with changing contributory factors. It will be necessary to track these changes.

There was a consensus at the meeting that there is most likely an extreme underreporting of the burden of MNS disease in sub-Saharan Africa. Affected patients often are hidden by their families because of the stigma and superstition associated with mental disease and epilepsy, and are therefore not treated or their cases not reported. Those who are treated by traditional healers will not be reported. Even at clinics, the number of deaths, disabilities, and associated treatment needs related to HIV/AIDS, malaria, tuberculosis, and other infectious diseases are so great that MNS disorders are often misdiagnosed, overlooked, and underreported. This is exacerbated by the shortages of trained personnel and diagnostic equipment.


CATHERINE HARRELL/ELSEVIER GLOBAL MEDICAL NEWS

**Sound data on the nature and extent of mental, neurological, and substance-use disorders are needed, says Dr. Susan W. Marino.**

Analyzing epidemiological data is also complicated. For

*See* **MNS Disorders** • *page 8*

## INSIDE



# Alternate Cut-Off Might Boost Ultrasound Diagnostic Accuracy

BY KERRI WACHTER
*Elsevier Global Medical News*

BOSTON – Consensus criteria for the use of duplex ultrasound can be used accurately for the diagnosis of stenosis of the internal carotid artery that is 70% or greater, but diagnostic accuracy can be improved for 50%-69% stenosis by using other cut-off values, Dr. Ali F. Aburahma reported at the annual meeting of the Society for Vascular Surgery.

The conclusions are based on an analysis of the accuracy of the consensus criteria for carotid duplex ultrasound (CDUS), compared with angiography, of 376 arteries in 197 patients. The consensus criteria were developed by a multidisciplinary panel to simplify the ultrasound diagnosis of carotid artery disease (Radiology 2003;229:340-6).

The criteria's peak systolic velocity (PSV) cut-off (more than 230 cm/sec) for detecting stenosis of 70% and greater showed good sensitivity (99%) and specificity (86%). Positive predictive value (PPV) was 93%, the negative predictive value (NPV) was 98%, and the overall accuracy was 95%. Although other cut-off values offered comparable accuracy, none was more accurate than the consensus criteria for this level of stenosis, said Dr. Aburahma, professor of surgery at West Virginia University in Charleston. However, the NPV of the consensus criteria for 50%-69% stenosis (PSV, 125-230 cm/sec) was disappointing at 81%, he added.

Several classification systems have been used, offering different carotid velocity threshold numbers to define the severity of carotid stenosis. However, there had been no standardization until the consensus criteria in 2002. The consensus panel recommended that PSV should be the primary parameter.

In the study by Dr. Aburahma and his colleagues, arteries were

*See* **Ultrasound** • *page 4*

## Also in this issue of WORLD NEUROLOGY ...

**Efforts to contain the spread of Chagas disease in South and Central Amercia have paid off, but the disease is now an emerging problem in nonendemic countries because of migrations, writes Dr. Marco Oliveira Py.** See Page 12

## EDITOR IN CHIEF'S COLUMN

# The Burden of Neurological Disease

BY MARK HALLETT, M.D.

In the World Health Organization (WHO), Neurology is a footnote in the Noncommunicable Diseases and Mental Health Division. To a certain extent, the attention of the WHO is driven by consideration of the DALY, the Disability Adjusted Life Year. Disorders become important based on premature loss of life and disability.

In the grand scheme of things, infectious disease is still the biggest health problem worldwide. Lower respiratory infections are number 1, diarrheal diseases are number 2, HIV/AIDS is number 5, and neonatal infection, tuberculosis, and malaria are 10, 11, and 12, respectively.

Noncommunicable disease is of lesser importance. Cerebrovascular disease at number 6 is the only neurological condition in the top 20. It is anticipated, however, that in the coming years, infections will be better controlled, and noncommunicable diseases will become more important. Unipolar depression is predicted to be number 1 by 2030.

On page 1 of this issue of World Neurology, there is a report from the Uganda National Academy of Sciences' Forum on Health and Nutrition and the US-based Institute of Medicine's Forum on Neuroscience and Neurological Disorders about the quality of care for mental, neurological, and substance use (MNS) disorders in sub-Saharan Africa. The report makes it clear that there are important needs in that region for dealing with many noncommunicable neurological disorders. Epilepsy is one example of a substantial problem where more education as well as more therapy would be valuable.

Although neurological disorders are pegged as noncommunicable, there are many that are communicable. Two other articles in the current issue illustrate this point. Chagas disease (p. 12) is endemic in South America and should be suspected in patients with autonomic nervous system abnormalities or stroke.

Tetanus is still common in many developing countries, and this includes Ethiopia (p. 15). The acute onset of severe spasms and autonomic dysfunction is dramatic. As described in the articles, treatment for both these conditions is difficult, and the best approach is prevention. It is good to hear that progress is being made in public heath for Chagas disease and in vaccination for tetanus, though there is still a way to go. ■

# Calendar of International Events

## 2010

**Symposium on Neuroinflammation and Neuroinfection**
Nov. 2
Glasgow, Scotland
www.rcpsg.ac.uk/Education/Events/Physicians/Pages/ed_spMedicalSymposia.aspx

**7th International Congress on Mental Dysfunctions and Other Non-Motor Features in Parkinson's Disease and Related Disorders**
Dec. 9-12
Barcelona, Spain
www2.kenes.com/mdpd2010/pages/home.aspx

## 2011

**4th European Neurological Conference on Clinical Practices**
Jan. 28-30
Lisbon, Portugal
www.paragon-conventions.net/encp2011/

**10th International Conference on Alzheimer's & Parkinson's Diseases**
March 9-13
Barcelona, Spain
www.kenes.com/adpd

**3rd Asian and Oceanian Parkinson's Disease and Movement Disorders Congress**
March 25-27
Taipei, Taiwan
www.aopmc2011taiwan.com

**63rd Annual Meeting of the American Academy of Neurology**
April 9-16
Honolulu, Hawaii, USA
www.aan.com/go/am11

**21st Meeting of the European Neurological Society**
May 28-31
Lisbon, Portugal
www.congrex.ch/ens2011

**European Neuro-Ophthalmology Society Meeting**
June 18-21
Barcelona, Spain
www.eunos2011barcelona.com/

**World Congress on Huntington Disease**
Sep. 11-14
Melbourne, Australia
www.worldcongress-hd2011.org

**7th International Congress on Vascular Dementia**
Oct. 20-23
Riga, Latvia
www2.kenes.com/vascular2011/pages/home.aspx

**20th World Congress of Neurology**
Nov. 12-17
Marrakesh, Morocco
www2.kenes.com/wcn/Pages/Home.aspx



World Neurology

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PRESIDENT'S COLUMN

# Planned Change: An Antidote to Obsolescence

BY VLADIMIR HACHINSKI, M.D.

The new administration has committed itself to continuity and change. Our sound financial status despite the recession; our on-schedule planning for the World Congress of Neurology in Marrakesh, Morocco, (Nov. 12-17, 2011); and our successful publications, the *Journal of the Neurological Sciences* and WORLD NEUROLOGY, are evidence of that continuity.

The change I refer to was first mentioned in my candidate's statement for the World Federation of Neurology President (April 2009, p. 1) and it is what I continue to advocate in my bimonthly columns in this publication. It was also reflected in the outcomes of discussions at a planning retreat in London in June.

We began that meeting by exploring what makes the WFN unique. We are the voice of neurology worldwide. The Federation comprises 110 member societies, which represent most of the world's neurologists and through them, the hundreds of millions of current and future neurological patients.

Many new organizations have been formed in recent years in response to the proliferation of subspecialties, but the fact remains that most neurologists need to be general neurologists, and the WFN is one organization that aims to integrate, evaluate, prioritize, and apply general neurological knowledge. We are setting the standards for carrying out those aims and have created the Evaluation and Accreditation Task Force, chaired by Aksel Siva (Turkey) and cochaired by Sarosh Katrak (India) and Charles Warlow (UK), to evaluate teaching courses and congresses. The WFN's endorsement of a course or congress will mean that the activity has high quality and is practicable, identifying it as an activity of value.

### Reformulation of the Mission

Stephen Sergay (USA), chair of the WFN Education Committee, spoke at the retreat about the importance of planning for the future.

He noted that organizations generally progress by advancing along a series of steplike plateaux, but if an organization does not plan its ascent to the next level, changing circumstances will render it increasingly irrelevant. Planned change is the antidote to obsolescence, he asserted.

His comments sparked an animated discussion that led to a reformulation of the **WFN's mission: "To foster quality neurology and brain health worldwide."**

### Web Site and Communications

An essential step in fulfilling the WFN mission will be to upgrade and enhance our Web site. It represents our public face and can serve as a medium for education, communication, and interaction among our Committees, Task Forces, and Applied Research Groups.

A Web Site and Communications Task Force chaired by Werner Hacke (Germany), Wolfgang Grisold (Austria), and Pete Engel (USA) brought proposals for improving the Web site at the WFN Council of Delegates meeting that took place during the European Federation of Neurological Societies in Geneva in September. The Web site will mark a new beginning for the way in which we interact as a global community. It will be designed and managed by a professional company, and will be interactive, flexible, modular, and highly user friendly and accessible.

Communication between the Committee and Task Force members will be enhanced by having conference calls set up through the WFN Central Office (laura@wfneurology.org). Each Committee or Task Force will be required to appoint a member to keep detailed minutes of the conversations and the steps and actions arising from them. The WFN expects to receive brief trimonthly reports of the activities of all Committees and Task Forces.

### Education

Dr. Sergay and his Education Committee cochair, Dr. Grisold, presented a comprehensive plan for developing a coherent accreditation of programs and certification of individuals and fellowships, and the possible facilitation of departmental exchange programs. They noted that the plans will need support from an office structure, a Web master, and an annual budget based on its priorities.

### Applied Research

Donna Bergen, chair of the Applied Research Committee, reported on her ongoing discussions with the WFN's Research Groups. Currently, 28 are listed, although 2 groups – Cerebrospinal Fluid and Neurorehabilitation – no longer exist. The entities are referred to as research groups, which is a reflection of their origin, but their main activities seemed to be more focused on education.

The participation of the Research Groups in determining the scientific and educational programs of the biennial World Congress of Neurology is a priority, and most have shown an interest in being more involved. The Applied Research Committee was one of those that met last month in Geneva to establish a template of new mutually beneficial relationships between the Applied Research Groups and the Committee. There will be a report back on that meeting in the December issue of WORLD NEUROLOGY.

Findings from numerous studies have shown that continuous medical education has little impact on patient care unless it is linked to an audit, incentives, or both. To implement what we know, we need to do research. If we measure something we do, implement a change, and measure the result, then we have done research. Not all the results will be worthy of a journal article, but all results are worth writing up and sharing.

"Research" has acquired the unfortunate connotation of an elitist activity carried out in laboratories. The important questions in medicine are those that matter to patients. In its broadest sense, research is a method of finding answers, whether in fundamental biology or in patient care. Philip Gorelick (USA), cochair of the Applied Research Committee, has been charged with exploring how the WFN can encourage the application and evaluation of available knowledge.

### Membership

There was an exploratory discussion at the retreat about our current system of "one society, one vote" and its effect on issues such as the election of Officers and Trustees and the selection of sites for the World Congresses.

Some argue the impact of individual members of societies with thousands of members is devalued, compared with the impact of a single neurologist of a five-member society. The counterargument is that the WFN is a federation of societies and not an organization of individual neurologists.

Several other international societies have a balanced model, whereby the largest society cannot have more than an upper limit – say, 4 votes – compared with the smallest society with 1 vote. This complex issue, with practical and symbolic implications, is being addressed by the Membership Committee, chaired by William Carroll (Australia) for consideration by the Council of Delegates.

### The Africa Initiative

Alfred Njamnshi (Cameroon), chair of the Africa Initiative, and Amadou Gallo Diop (Senegal), presented a thoughtful, systematic approach and plan. Their priority is the accreditation of training programs on the continent. Some of these programs have been in place for half a century, in part because of the efforts of pioneers such as Michel Dumas working with our African colleagues.

Dr. Njamnshi highlighted the importance of financing priority activities on a continuous basis. The Africa Initiative also met in Geneva last month.

Our colleagues in Cairo and elsewhere have offered to train neurologists for sub-Saharan Africa. Secretary-Treasurer General Raad Shakir will go to Egypt to sign a memorandum of understanding on behalf of the WFN.

Gustavo Roman (USA) reported on the success of the 3rd Regional Teaching Course in Africa that was held in Abidjan, Ivory Coast. He had represented the WFN at the course, which was held jointly with the European Federation of Neurological Sciences and the International Brain Research Organization. The event drew participants from 14 sub-Saharan countries – and resulted in our Ivory Coast colleagues joining the WFN.

### The Asia Initiative

Ryuji Kaji (Japan), chair of this initiative, reported (via Skype) on his investigation of opportunities to improve and expand neurological care in Asia, where most – about 60% – of the world's neurological patients live. He presented a list of possible members of Asia Initiative Executive.

### The Latin America Initiative

Dr. Roman, chair of the Latin American Initiative, reported on the distinguished history of neurology in Latin America, the long and strong presence of the Latin American branch in the WFN Neuroepidemiology Research Group, and the upcoming neuroepidemiology congress in Punta del Este, Uruguay (Nov. 29-Dec. 3, 2011). He said there were numerous opportunities for collaboration with other societies. He also reported on plans for next year's Panamerican Congress of Neurology in La Paz, Bolivia (March 5-8). Our Latin American colleagues are to explore the desirability of forming a Panamerican Federation of Neurology.

### Reports on Neurological Diseases

Dr. Diop presented highlights of his detailed and impressive World Health Organization report on stroke and epilepsy in Africa. He is planning to publish a similar document on neurology in general in Africa under the auspices of the WFN and the Africa Initiative.

Dr. Shakir presented data on neurology in Arab countries from a forthcoming article with a coauthor. The attendees also discussed whether the WFN should produce comprehensive reports on neurology for all regions of the world.

### Criteria for Evaluation

Dr. Grisold presented a proposal for evaluating projects for funding. He emphasized the need to implement a classic project management approach that would include prioritization, initiation, planning and design, execution, control and monitoring, and closure and evaluation.

### Financial Report

Dr. Shakir presented the financial report. Although the Federation's operating costs are modest and last year's World Congress in Bangkok fared well financially, it is facing increasing costs in the planned investment in the Web site and in supporting the new initiatives. This reinforces our need to focus our efforts in seeking partners and to begin fundraising for our projects.

The London retreat and last month's meeting in Geneva were important because they signaled the beginning of a number of new initiatives and a new era for the WFN. ■

NEUROLOGICAL HISTORY

# Foot Eponyms Leave Their Mark

BY PETER J. KOEHLER, M.D., PH.D.

At the turn of the 19th century, the neurological examination as we know it today could already be recognized. However, physicians worldwide continued searching for more signs to differentiate between weakness resulting from structural lesions of the central nervous system and that caused by hysteria. For example, Joseph Babinski, who had described his Babinski-extensor sign in 1896, went on to describe several more signs, including the trunk-thigh sign in 1897.

In the first decade of the 20th century, two physicians, one working in Japan and the other in the United States, tried to find variant signs on the foot. In 1906, Kisaku Yoshimura described the external malleolus sign (*Igaku Chuo Zasshi* 1906;4:533-49; 824-41; 939-55). He published (in Tokyo and Vienna) on another reflex, the Mendel dorsal foot reflex. But a 56-page article on the lateral foot reflex was published in 1906 only in Japanese, which is probably why it remained largely unnoticed until his compatriot, Kunio Tashiro, published it in English (*Arch. Neurol.* 1986;43:1179-80).

PHOTOS COURTESY DR. PETER J. KOEHLER

**Charles Gilbert Chaddock (left) described the malleolar sign in 1911, unaware that Kishaku Yoshimura had published on the same sign in a Japanese journal in 1906.**

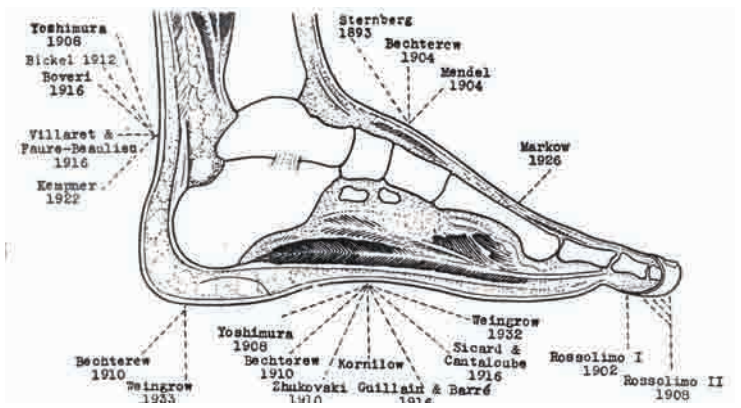
The American physician working on the same sign was Charles Gilbert Chaddock, professor of nervous and mental diseases at Marion-Sims College of Medicine – later the school of medicine at St. Louis (Mo., USA) University. He had worked with Babinski in Paris between 1897 and 1899 and had introduced the Babinski sign in the United States on his return.

Chaddock translated numerous works and was author of *Outlines of Psychiatry* (St. Louis: Commercial Printing Company, 1904). However, after 1898, he published mainly on neurological subjects, including three papers in 1911 on the malleolar sign, of which he wrote, "I have found in extension of one or more, or all, of the toes, with or without fanning of them, when the external inframalleolar skin area is irritated, in cases of organic disease of the spino-cortical reflex paths. I shall call it the external malleolar sign."

Chaddock was not aware of Yoshimura's work. He believed his sign had advantages over Babinski's plantar reflex because dorsiflexion of the foot as withdrawal reaction to painful stimuli occurred less often. He published on several other differences between his and Babinski's signs and sent the papers to Babinski for comments. Babinski's brother Henri (author of *Gastronomie Pratique* under the pseudonym Ali-Bab), acting as his secretary, wrote to Chaddock: "My brother ... has confirmed your observations on the reflexes. He thinks your work is very interesting."

Yoshimura and Chaddock's signs were among some of the many reflexes and signs that are recognized in a figure on the plantar muscle reflex in Robert Wartenberg's *The Examination of Reflexes. A Simplification* (Chicago: Year Book Publishers, 1945; first published as papers in *Archives of Neurology and Psychiatry* in 1944).

Wartenberg had fled the Nazis in 1935 and settled in San Francisco, where he tried to order, interpret, and simplify the plethora of signs that had been published. The names of neurologists from many different countries now distinguish the signs and reflexes associated with the foot: Bechterew and Rossolimo (Russia); Guillain, Barré, Sicard, and Cantaloube (France); Sternberg and Mendel (Germany); Markov (Poland), and Weingrow (USA). Obviously, the description of these reflexes and signs had been an international occupation. ■




**Yoshimura and Chaddock's signs were among the many depicted in Robert Wartenberg's *Examination of the Reflexes. A Simplification.***

©EXAMINATION OF THE REFLEXES, WARTENBERG, THE YEAR BOOK PUBLISHERS, INC., 176

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# Criteria Okay for 70% Stenosis

**Ultrasound** • *from page 1*

evaluated with both CDUS and angiography within a 30-day period. The percentage of stenosis was measured in accordance with the NASCET (North American Symptomatic Carotid Endarterectomy Trial) method. Peak systolic velocity and end-diastolic velocity of the internal carotid artery were both measured during CDUS.

Patients were excluded if they had undergone carotid artery endarterectomy or carotid artery stenting, or had a carotid artery dissection, flow-mediated dilation, or significant brachiocephalic stenosis.

The patients had a mean age of 68 years and 47% were men. Of these, 11% had normal carotid arteries, 30% had less than 50% stenosis, 23% had 50%-69% stenosis, 26% had 70%-99% stenosis, and 10% had total occlusion. Patients were also fairly evenly divided between symptomatic (53%) and asymptomatic.

In terms of Pearson correlation between the consensus criteria and angiography, the overall correlation was quite good for PSV cut-offs at 0.81 – better than the correlation for EDV or systolic or diastolic ratios.

The researchers compared several PSV cut-offs for diagnosing stenosis no greater than 50% and found the most accurate value was 137 cm/sec, with an overall accuracy of 93% compared with 89% for the consensus cut-off of 125 cm/sec.

The standard values used up until the consensus criteria were developed were a PSV of at least 120 cm/sec for less than 50% stenosis, PSV of at least 140 cm/sec for at least 50% stenosis, and a PSV of at least 150 cm/sec and an EDV of at least 90 cm/sec for at least 70% stenosis.

Using these cut-offs, the overall accuracy was 92% for stenosis of 50%-69%.

"Consensus criteria can be used accurately for the diagnosis of greater than or equal to 70% stenosis, but the accuracy can be improved in detecting 50%-69% stenosis if the [internal carotid artery] PSV is changed to 140 cm/sec to less than 230 cm/sec," Dr. Aburahma concluded.

**Disclosures:** Dr. Aburahma reported that he had no relevant disclosures. ■

COMMENTARY

Dr. Aburahma and his colleagues proposed an alternative duplex ultrasound (DUS) peak systolic velocity (PSV) cut-off for a 50%-69% stenosis that resulted in a significantly higher diagnostic accuracy. An important question is how the newly proposed cut-off for a 50%-69% stenosis performs in other patient populations. In the past, other groups have also suggested different PSV cut-offs for various degrees of stenosis, such as 220 cm/sec for ipsilateral arteries and 290 cm/sec for contralateral arteries for 70%-99% stenosis (Stroke 2005;36:2105-9), illustrating the wide variability in DUS criteria. Factors such as location- and operator-dependency of DUS testing may in part explain this variability.

Moreover, an earlier meta-analysis reported a low diagnostic accuracy for DUS in general and for detecting a 50%-69% of stenosis in particular (Lancet 2006;367:1503-12).

Therefore, the results of the study by Dr. Aburahma and his coworkers raise the important question of whether or not DUS as a single test is sufficient to estimate carotid artery stenosis reliably. In clinical practice, DUS may be a valuable first tool in screening patients suspected of having carotid artery stenosis. If treatment is considered however, in my opinion, a second noninvasive test should be added, such as CT or MR angiography, to estimate the degree of stenosis reliably.

PAUL J. NEDERKOORN, M.D., *is a neurologist and clinical epidemiologist at Academic Medical Center, Amsterdam. He has no relevant disclosures.*

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RESEARCH GROUP REPORT: MOTOR NEURON DISEASES

# Seeking Common Ground Across Spectra

**BY ALBERT LUDOLPH, M.D.,**
*Chair, WFN Motor Neuron Diseases Research Group*
**ORLA HARDIMAN, MB BCH**
*Secretary*

*Dr. Ludolph (left) is professor of neurology and chair in the neurology department, University of Ulm, Germany. Dr. Hardiman is professor of neurology in the neurology department at Beaumont Hospital and Trinity College Dublin, Ireland.*

Recent research has shown that amyotrophic lateral sclerosis and frontal temporal dementias partially form a spectrum of diseases and share etiological, pathogenetic, and clinical features. In light of this, the World Federation of Neurology's Motor Neuron Diseases and Aphasia and Cognitive Disorders research groups have decided to combine their respective interests.

This approach is timely, given the established relationship between the two spectra. We plan to collaborate with the frontal temporal dementias (FTD) group by organizing educational programs to facilitate genetic studies of amyotrophic lateral sclerosis (ALS) in FTD – in particular, in developing countries. The research groups also intend to organize a symposium during next year's World Congress of Neurology in Marrakesh, Morocco.

### Guidelines for Biologic Samples

In our field, we have learned that standardized and systematic preprocessing of biological samples for modern techniques such as proteomics, transcriptomics, and metabolomics is essential. Under the auspices of our group, Prof. Markus Otto of the University of Ulm, Germany, has convened a group of neurochemists, CSF specialists, and geneticists out of the FTD and ALS/motor neuron diseases (MND) fields to compile guidelines for preprocessing of samples.

These guidelines will be published in *Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders*, the journal of the ALS/MND research group, which is edited by Prof. Orla Hardiman. We plan to organize a symposium during this year's international symposium on ALS/MND in Orlando, Fla., USA (Dec. 11-13), at which we shall discuss the clinical applications of these guidelines. We shall also discuss the implementation of biomarkers into clinical trials in the ALS/MND field; this is necessary because most clinical trials of ALS/MND have been unsuccessful.

### A Global Perspective on Epidemiology

We intend to work on the worldwide epidemiology of ALS/MND. We recognize that ALS/MND has been carefully described in the Western and industrialized world, but the epidemiological features of these diseases in developing countries are less known. According to the established studies in some developing countries (Guadeloupe, New Guinea, and Guam), there may be a much closer link among ALS, atypical parkinsonism, and frontal dementias than is the case in Europe and North America. Conversely, the frequency of ALS in genetically admixed countries such as Cuba seems to be considerably lower. We are planning an initiative that will systematically study the epidemiology, clinical features, and natural history of ALS, ALS/FTD, and ALS/Parkinson's in developing countries.

### Redefining Through Education

As a first step to redefine the clinical spectrum of ALS/MND with regard to the relation to atypical parkinsonism/frontal dementias, we will attempt to establish teaching seminars with respected and noted colleagues from developing countries. This teaching will include epidemiological features as well as the new findings on the molecular relations of ALS/MND to atypical parkinsonism and frontal dementias.

We are establishing a group of colleagues comprised of epidemiologists, dementia specialists, Parkinson specialists, and motoneuron specialists from China, India, Africa, and South America. We plan to discuss procedures with these colleagues during our symposium in December.

### Scrutinizing the El Escorial Criteria

The WFN's El Escorial Criteria for the diagnosis of ALS have served us well, but their practical use is sometimes confusing for general practitioners and laypersons. Therefore, we have started working on making these criteria more practical and useful. We organized an initial meeting of European experts in Frankfurt in November 2009 to define the problems. The participants included the authors, along with Wim Robberecht (Belgium); Leonard van den Berg (the Netherlands); Mamede de Carvalho (Portugal); Reinhard Dengler (Germany), and Adriano Chio and Vincenzo Silani (Italy). Our American colleagues have been informed of the initiative and we will further discuss the developments in late 2010.

### Support for the ALS Journal

*Amyotrophic Lateral Sclerosis and Other Motor Neuron Disorders,* the ALS/MND research group's journal, is currently in a niche. In an effort to bolster the journal, we plan to team up with the Aphasia and Cognitive Disorders research group to include articles on frontal temporal dementia whenever possible. ■

# Plasma Beta-Amyloid Fluctuations Flag Cognitive Decline

BY MARY ANN MOON
*Elsevier Global Medical News*

When plasma levels of beta-amyloid rise above normal and then decrease or stabilize in healthy elderly patients, it signals the onset of a rapid decline in several cognitive domains, according to Stephanie A. Cosentino, Ph.D., of the Taub Institute for Research in Alzheimer's Disease and the Aging Brain, New York.

In most patients, that decline takes the form of Alzheimer's disease. In the minority of patients who don't develop full-blown dementia, there is a marked cognitive decline that primarily affects memory rather than language or visuospatial domains, the authors wrote (Arch. Neurol. 2010 Aug. 9 [doi:10.1001/archneurol.2010.189]).

Some studies have shown a correlation between elevated plasma beta-amyloid (Abeta) levels and development of mild amnestic cognitive impairment or frank Alzheimer's disease (AD) within a few years; others have found that decreasing levels correlate with these cognitive declines.

The findings the current study suggest that the timing of the plasma sampling and of the subjects' disease stage might account for these discrepant results.

The investigators used data from a population-based study of aging to examine the link between plasma levels of the soluble oligomers Abeta-40 and -42 and cognitive changes. A total of 880 nondemented participants provided one blood sample at baseline in 1999 and a second sample about 4.5 years later. They also underwent a battery of neuropsychological tests at about 18-month intervals.

During follow-up, 481 remained cognitively healthy, 329 developed cognitive or functional impairment but no dementia, and 70 developed AD. The cohort involved nearly equal percentages of Hispanics (37%), whites (31%), and African Americans (31%).

"Overall, high initial levels of plasma Abeta-40 and Abeta-42, and stable or decreasing Abeta-42 at follow-up, were associated with faster global cognitive decline regardless of dementia status," the investigators wrote.

Subjects whose initial Abeta-40 and Abeta-42 levels were in the top three quartiles had significantly faster cognitive decline than did those in the lowest quartile. Those with either decreasing or stable Abeta-42 levels at the second measurement had significantly faster cognitive decline than other subjects.

An elevated level of Abeta-42 at baseline predicted cognitive decline in memory, language, and visuospatial domains, with subjects in the highest quartile of beta-amyloid level consistently declining significantly faster than subjects in the lowest quartile.

However, in the subgroup of subjects who remained cognitively unimpaired, those with high baseline levels of Abeta-42 showed declines only in the memory domain.

The authors suggested that these subjects may be in the early stages of AD but have not yet shown sufficient decline in nonmemory domains to meet the criteria for dementia. Alternatively, they may remain free of dementia due to biological factors such as the ability to clear high levels of beta-amyloid or psychosocial factors such as the presence of cognitive reserve.

**Disclosures:** The study was funded by grants from the National Institutes of Health, Bethesda, Md., USA. The investigators had no relevant disclosures to report. ■

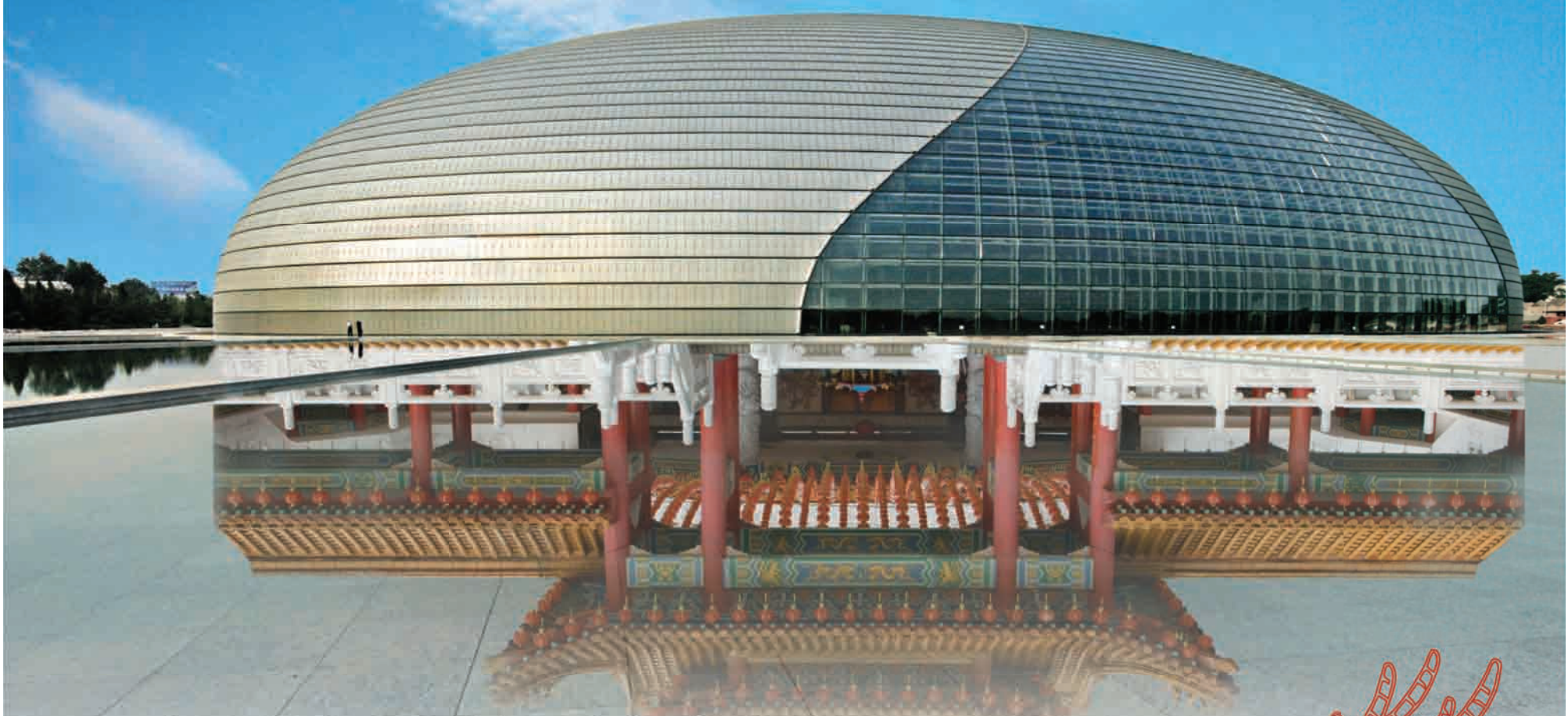
**COMMENTARY**

It is too early to recommend the measurement of plasma Abeta for diagnosis of AD or its prediction in normal individuals. Multiple measurements of plasma Abeta over time, starting in the cognitively normal state, are necessary to determine the true longitudinal course of this protein. These measurements should arguably begin in middle age because the pathogenic processes in AD are likely to begin decades before symptoms become manifest. If and when certain limitations are overcome, serial plasma measurements might provide an important window to the longitudinal course of the molecular mechanisms underlying AD. It could help address why some individuals with high plasma levels of Abeta do not develop dementia, and whether Abeta has a role in normal aging. It could suggest the age at which intervention to reduce the production of Abeta-42 is likely to prevent AD.

PERMINDER SACHDEV, M.D., PH.D., *is a professor of neuropsychiatry at the University of New South Wales, Sydney. He has no disclosures.*

BEIJING 2010

# From Ancient to Modern Pain Medicine



## The 14th World Pain Clinic Congress & The 1st Asian Congress on Pain

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MEETING ROUND-UP

# WFN Holds Movement Disorders Course in Ukraine

BY YURIY MATVIYENKO, M.D., PH.D.

About 100 neurologists and neurology residents from across Ukraine attended a day-long course in movement disorders organized by physicians from the Lviv Regional Clinical Hospital, Lviv National Medical University, and the World Federation of Neurology's Parkinsonism and Related Disorders Research Group. The gathering marked the first time the Federation has organized a meeting in Ukraine.

The incidence of Parkinson's disease (PD) in Ukraine is high. There are 1,800 persons in the database for the Lviv region alone, which has a total population of 2.5 million people; and incidence is about 85-95 patients per 100,000 persons of the general population of the country, based on data from noncontrolled epidemiologic investigations. However, there is almost no special training in movement disorders for general neurologists, except for a certified course organized twice a year in Lviv by the regional center of extrapyramidal disorders.

Courtesy Dr. Yuriy Matviyenko

**Among the faculty of experts in parkinsonism and related disorders who participated in the movement disorders course were (from left) Lyudmyla Fedoryshyn, Yanush Sanotsky, Zbigniew K. Wszolek, Tetiana Slobodin, Erik Ch. Wolters, Andrzej Friedman, and Erwin van Wegen.**

For these reasons, the event was important for the attendees who had the opportunity to be updated on current diagnostic and therapeutic trends in parkinsonology by world experts in the field – Dr. Zbigniew K. Wszolek from the United States; Prof. Dr. Erik Ch. Wolters and Dr. Erwin van Wegen (the Netherlands); and Dr. Andrzej Friedman (Poland) – as well as four local lecturers, Dr. Yanush Sanotsky, Dr. Iryna Karaban, Dr. Tetiana Slobodin, and Dr. Sergiey Moskovko. The topics they covered included cueing and autonomic dysfunction in PD, the etiopathophysiology of idiopathic PD, genetics of PD, and current therapies, among others.

Many of the attendees said they had found the course informative and useful for their clinical practice. They each received a copy of the textbook *Parkinsonism Disease & Related Disorders* by Erik Wolters, Teus Van Laar, and Henk Berendse (Amsterdam: VU University Press, 2008).

For my part, I was honored to be a member of the organizing committee for this event and I sincerely hope that the WFN Parkinsonism and Related Disorders Research Group continues to support such courses in Ukraine. ■

Dr. Matviyenko *is an assistant professor in the department of neurology at the Lviv National Medical University, Ukraine.*

# Integrated Approach Is Best

**MNS Disorders** • *from page 1*

example, while we were in Uganda, we met a few children who will be included in a study of pediatric neurological disorders to be funded by the US-based National Institutes of Health (NIH) and National Institute of Neurological Disorders and Stroke (NINDS). It was striking that the etiology in two out of five cases seemed to be a high fever from a previous unidentified infection, while a third disorder was present at birth.

This underscores Dr. Donald Silberberg's observation that in sub-Saharan Africa, the burden of neurological disorders is related to the higher incidence of birth defects; mental retardation; cerebral palsy; bacterial, viral, and parasitic infections; epilepsy; and head and spinal cord trauma from traffic accidents than in more developed countries (Soc. Psychiatry Psychiatr. Epidemiol. 2010;45:487-95).

Furthermore, in instances in which the neurological consequences of HIV/AIDS, malaria, and tuberculosis are diagnosed, treatment can still be complicated. Dr. Angela Kakooza-Mwesige, a neurologist from Makerere University School of Medicine, Kampala, explained that standard antiepileptic medications interact badly with antiretrovirals. This presents a dire challenge given that in some regions of Africa more than 20% of the population is infected with HIV. Terminology and language differences, and problems with record-keeping also contribute to uncertainty in the data.

## Trickle-Down Training

Participants at the meeting noted that we know how to treat the common MNS disorders, as overwhelming as that might be, but that the root of the problem lies with the severe shortage of trained personnel and lack of resources.

The MNS terminology reflects integration of neurological disciplines but, given the interconnectedness of MNS disorders with other diseases and trauma, it makes sense for treatment, patient education, and referrals to be integrated with primary care as well. Not only would that kind of coordination leverage trained personnel and resources, but it would also better serve the majority of people, who mostly live in villages and must walk long distances to clinics.

Several participants proposed training more community health workers to carry out specific neurological tests with appropriate long-term supervision. This would require that professional neurologists and psychiatrists reduce their practices and become public health leaders instead, and that there be task-shifting to health care workers who are trained for shorter periods of time in specific skills at all levels. It is in the area of workforce management that governmental policies could be helpful – in formalizing the structure and providing remuneration for community health workers, resources, and career paths for professionals.

## The Community as a Resource

Dr. Paul Farmer, a medical anthropologist and physician, has noted that there are advantages to community-based health care. In the sub-Saharan setting, these would include an opportunity to address the social causes of MNS disorders, the mutual reinforcement of treatment and prevention, and improved adherence to treatment regimens.

The meeting participants were divided on the involvement of traditional healers, as distinct from trained community health workers, in the delivery of treatment. In support of their involvement, some participants said that traditional healers know the village where they practice, they are accessible and accepted, and they have time to spend with patients and engage the whole family. There were examples of traditional healers who had learned to complement Western forms of treatment and to refer particular conditions to hospitals. We were even told about a Ugandan chemotherapeutic laboratory that is analyzing the active ingredients of traditional remedies while preserving intellectual property for the healers. However, others pointed out that there is no standard of care among healers and that respectful handling of the relationship can be challenging, particularly when the traditional treatments are harmful.

## Tapping In to Technology

Mobile phone technology already is widely used in Africa for banking and might also be useful as a tool for both providers and patients. Radio, television, and CDs allow for one-way education efforts, but mobile phone technology would allow for a one-to-one interaction between health workers in the field who need to use diagnostic or treatment algorithms and a centralized expert or system. The technology could be used for reminding or informing patients about treatment follow-ups, test results, medication availability, clinic hours, or to allow them to ask questions relating to their records. More broadly, it could also provide epidemiological data in real time.

Development of these systems is underway. For example, a Ghana-based nonprofit, with support from pharmaceutical companies, has established a mobile phone–based system called mPedigree that consumers in West Africa can use to verify whether a drug is genuine or counterfeit by texting a code to a central registry.

A joint Uganda National Academy of Sciences-IOM report, entitled "Mental, Neurological, and Substance Use Disorders in Sub-Saharan Africa: Reducing the Treatment Gap, Improving Quality of Care," will soon be available from the NAS. The NINDS has been funding research grants in Africa under the trans-NIH Brain Disorders in the Developing World program in Uganda, Zambia, Malawi, and Tunisia. The institute will also cofund a hypertension and stroke project in Zimbabwe through the Medical Education Partnership Initiative, which built on the PEPFAR effort. ■

Dr. Marino *is a scientific information analyst and special assistant to the director at the National Institute of Neurological Disorders and Stroke in Bethesda, Md., USA.*

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# Ruling Puts US Embryonic Stem Cell Research in Limbo

*Researchers stress the importance of having access to all possibilities to help advance their work.*

BY MARY ELLEN SCHNEIDER
*Elsevier Global Medical News*

Some researchers studying human embryonic stem cells in the United States are surprised, disappointed, and even angry about the legal back-and-forth over the federal government policy on funding research using the cells (see Box, top right).

Last year, President Obama greatly expanded opportunities to receive federal funding for embryonic stem cell research when he issued an executive order that eliminated many of the restrictions placed on funding during the George W. Bush administration. The US National Institutes of Health in Bethesda, Md., followed with guidelines that allowed research to be conducted on embryonic stem cells derived from embryos created through in vitro fertilization and donated for research.

But with the current uncertainty, some researchers worry that the development of therapies that use embryonic stem cells will be set back and that the loss of federal funding will have a chilling effect on newly minted researchers who are considering whether to enter the field.

The US-based Coalition for the Advancement of Medical Research, which advocates for stem cell funding, called the original injunction a "blow to the hopes of millions of patients and their families suffering from fatal and chronic diseases and disorders."

Evangelos Kiskinis, Ph.D., of the Harvard Stem Cell Institute, said that it was important to remember that many of the recent advances in stem cell research were a direct result of researchers having access to embryonic stem cells. "Milestone advances such as the generation of induced pluripotent stem [iPS] cells, a promising, novel technology to 'make' embryonic stem-like cells, would never have been achieved without knowing what we do about the properties of embryonic stem cells [and] they are also continuously relying on research with embryonic stem cells for improvement and eventual clinical application," he said.

Even institutions with deep pockets are concerned that private funding alone is not enough. "It's a blow to us," said B.D. Colen, a spokesman for the Harvard Stem Cell Institute. "It's a blow to the field."

Dr. D. Eugene Redmond, Jr., professor of psychiatry and neurosurgery and director of neural transplantation and repair, Yale (Conn.) University School of Medicine, USA, commented that his human embryonic stem cell research "is funded by the forward-looking state of Connecticut and therefore not subject to this federal funding decision. But it is important that this ruling is overturned.

"Stem cells, of all types should be studied to see which type is the best, within the strict ethical guidelines set forth by the National Academy of Sciences. Using all of the possibilities, scientists will be able to learn about development and disease and as well as repair damage from trauma, aging, and disease," Dr. Redmond asserted.

There is also concern about privately funded labs becoming isolated.

"Although certain labs are increasingly relying on private funding for embryonic stem cell research and therefore are less affected than those that are mainly NIH funded, major advances in the field are more likely if [there are] more labs. One or two isolated, privately funded labs are never going to [be able to answer] major questions such as 'what causes neurodegeneration in ALS?' These are issues that the research community has to be able to pursue unaffected as a whole," said Dr. Kiskinis.

Another source of concern for researchers has to do with the legal issues involved in the case. An earlier lawsuit challenging the Obama stem cell guidelines had been dismissed after the court ruled that the plaintiffs had no standing to challenge it.

However, the recent injunction came about after the court decided that two researchers who work with adult stem cells could challenge the guidelines because funding of embryonic stem cell research was harming their chances for receiving federal funds for adult stem cells.

This move was not well received by those involved in research. "This judge opens the door for every scientist who ever has a grant request rejected on the merits to sue the federal government," the American Society for Reproductive Medicine said in a statement condemning the court decision.

Dr. Redmond added that the argument for standing for the two scientists was a "terrible" precedent and that it "shows the judge's lack of understanding of the funding process."

In granting the temporary injunction, Judge Royce C. Lamberth, the chief judge in the US District Court for the District of Columbia, said the NIH guidelines violated the intent of Congress to bar the use of federal funds for research in which human embryos are destroyed.

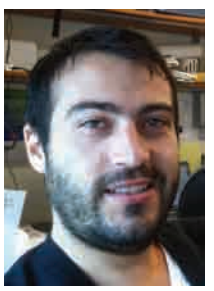
He said that the rules violated the Dickey-Wicker amendment, a rider generally attached to health spending bills each year. It prohibits the use of federal funds for the creation of a human embryo or embryos for research purposes or research in which a human embryo or embryos are destroyed or discarded.

However, the Obama administration has argued that the amendment doesn't apply because federal funds are used for research on the embryonic stem cell lines, not in the destruction of the embryos.

Judge Lamberth did not find the argument persuasive. "[Embryonic stem cell] research is clearly research in which an embryo is destroyed," he wrote in the order. "Despite defendants' attempt to separate the derivation of [embryonic stem cells] from research on the [embryonic stem cells], the two cannot be separate." ■

**Eligible and ineligible activities will need to be isolated to ensure NIH funds don't support nonsanctioned research.**
DR. KRIEGSTEIN

**The argument for the two scientists 'shows the judge's lack of understanding of the funding process.'**
DR. REDMOND



**Researchers couldn't have generated iPS cells if they hadn't known about embryonic stem cells.**
DR. KISKINIS

## Judicial Ping-Pong

► **Aug. 23.** A US federal judge hands down a ruling that bars the use of federal funds for any research involving human embryonic stem cells.

As a result of the temporary injunction, the US NIH stops accepting submissions of information on human embryonic stem cell lines for review and suspends all review of embryonic stem cell lines.

► **Aug. 31.** The US Justice Department asks for a stay of the lower court's injunction.

► **Sep. 9.** The Justice Department is granted a temporary administrative stay by the US Court of Appeals for the District of Columbia Circuit.

► **Sept. 20.** The date by which both parties to the suit had to present information to the court.

COMMENTARY

Stem cell science has had to navigate a complex ethical and political landscape ever since human embryonic stem cells were first created in the lab. Over the past 9 years, and over two administrations, federal funding was available for this research subject to specific restrictions based on ethical considerations. Within this awkward framework, the science has advanced, but the recent injunction would countermand all the previous policies and put a full stop to federal support for human embryonic stem cell research.

The impact on the field of stem cell research is enormous and profoundly discouraging, not only to scientists and students, but most of all to patients who have staked their hopes on the promise of stem cell research. At [my institution], we are partially shielded from the immediate effects of the injunction because relatively few of the human embryonic stem cell projects here are NIH funded. Most of [us] are funded by the California Institute of Regenerative Medicine (CIRM) for the work we do using human embryonic stem cells. We have newly constructed stem cell laboratories that were paid for by philanthropic donations and CIRM grants, where stem cell research, including work with human embryonic stem cells, can proceed regardless of the twists and turns of NIH policy.

A bigger impact will be the burden of isolating our eligible and ineligible activities to ensure that NIH funds for allowable research do not spill over to support nonsanctioned research. We may also need to scrutinize all our multi-investigator NIH grants including our training grants to ensure that inclusion of investigators working with embryonic stem cells does not jeopardize continued funding.

Research progress in science is unpredictable. But progress most certainly cannot be made without a policy that ensures sustained funding. The US Congress should act to clarify its real intent concerning the pursuit of human embryonic stem cell research, rather than let policy be held hostage by the whim of an individual judge.

Arnold R. Kriegstein, M.D., Ph.D., *is the John G. Bowes Distinguished Professor in Stem Cell and Tissue Biology and director of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at the University of California–San Francisco.*

*To share your comments on this ruling on stem cells, write to us at worldneurology@elsevier.com. If you are in a country outside of the United States, are there similar rulings on or debates around the use of human embryonic stem cells in research? If not, how do your policies differ from those in the United States, and what are the implications for researchers?*

# Study Backs Alteplase Within 4.5 Hours of Stroke

BY DIANA MAHONEY
*Elsevier Global Medical News*

Extending the time window for giving the recombinant tissue plasminogen activator alteplase to ischemic stroke patients has increased the percentage of patients who are eligible to receive the thrombolytic therapy without causing treatment delays, according to an analysis of two databases.

Until recently, the use of alteplase, which has been shown to decrease the incidence of stroke-related disability, was recommended for use within 3 hours of the onset of acute ischemic stroke symptoms. In the fall of 2008, however, the European Stroke Organization, the American Heart Association, and the American Stroke Association began recommending that the alteplase treatment time window be expanded to within 4.5 hours after stroke onset. The recommendation was based on findings from the European Acute Stroke Study III (ECASS III) and the International Stroke Thrombolysis Registry (SITS-ISTR), which both demonstrated the safety and efficacy of the broader treatment parameter, wrote Dr. Nils Wahlgren of Karolinska University Hospital in Stockholm, Sweden, and colleagues (Lancet Neurol. 2010;9:866-74).

**THE EXTENDED TIME WINDOW DID NOT RESULT IN A RISE IN ADMISSION-TO-TREATMENT TIME, BUT REMAINED AT THE PRE-2008 LEVEL OF 65 MINUTES.**

The researchers conducted a follow-up safety analysis using data from SITS-ISTR. They sought to confirm or refute whether patients receiving late alteplase treatment (between 3 and 4.5 hours) had an increased risk of intracerebral hemorrhage and death within 3 months – a possibility that was reported in the initial SITS-ISTR study.

Of 23,942 patients included in SITS-ISTR between December 2002 and February 2010, 2,376 were treated with alteplase between 3 and 4.5 hours after symptom onset.

"The proportion of patients treated in the 3-4.5 hour time window was twice as high in the last quarter of 2008 and three times higher during the last quarter of 2009, compared with the first three-quarters in 2008. The number of patients treated within 3 hours also increased," the authors wrote. "Therefore, not only did the publications seem to encourage participating SITS physicians to offer treatment to patients beyond the 3-hour window, but also they might have encouraged treatment with intravenous alteplase within the already accepted treatment criteria."

The support for the extended time window by the various stroke associations might also have contributed to its rapid acceptance, they noted.

The extended time window was not associated with an increase in admission-to-treatment time. For patients registered both before and after 2008, the median admission-to-treatment time was 65 minutes, suggesting "the widening of the time window has not resulted in delayed treatment of patients," the authors wrote.

As was the case in the earlier SITS-ISTR observational study, symptomatic intracerebral hemorrhage and mortality within 3 months in the current investigation occurred at significantly higher rates in patients treated within 3-4.5 hours than in those treated within the shorter time window. Functional outcomes at 3 months after adjustment for confounding variables also were worse in those who received alteplase during the additional 1.5 hours of time. But Dr. Wahlgren and his colleagues wrote that "the overall proportion of these outcomes was still low in the cohort treated within 3-4.5 hours and the statistical significance can probably be explained by the large sample size" and that the risks of these outcomes were outweighed by the benefits of the treatment.

**Disclosures:** Some of the authors disclosed receiving grants or financial compensation from Boehringer Ingelheim, Ferrer, Thrombogenics, Sanofi-Aventis, Novo Nordisk, Paion, and Lilly. ■

# Chagas Disease Presents Long-Term Challenges

American trypanosomiasis, or Chagas disease, was first described in Brazilian rural areas in 1909 by Carlos Chagas, who noticed the relationship between occurrence of the disease and the prevalence the barber beetle (or kissing bug), an insect in the Reduviidae family.

**BY MARCO OLIVEIRA PY, M.D., PH.D.**

*Dr. Py is the coordinator of the neuro-ICU of the University Hospital of the Federal University of Rio de Janeiro, Brazil.*

Chagas isolated the responsible parasite (*Trypanosoma cruzi*) from a Reduviidae insect bowel. Then, working with Oswaldo Cruz, he isolated the same parasite from the blood of a child with the disease and of a cat from the same house as the child, and was thus able to describe the entire cycle of that new disease.

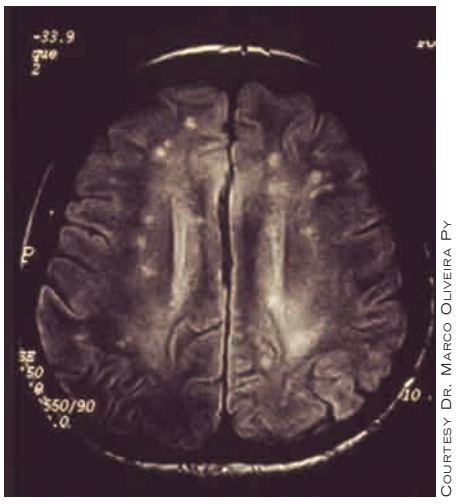
The Reduviidae insects live in the cracked walls of houses where living conditions are poor. They suck victims' blood, and at the same time eliminate feces that contain the parasite, which in turn penetrates broken human skin and enters the blood vessels (Mem. Inst. Oswaldo Cruz 1909;1:159-218).

Few patients present with the acute form of the disease in the first 10-60 days after infestation. This acute form is characterized by fever, eyelid and face edema, conjunctivitis, and in some cases lymphadenomegaly, hepatosplenomegaly, and anasarca. Most patients (66%-99%) remain asymptomatic during this period, but a severe and often fatal form of the disease that includes acute myocarditis or encephalitis might occur in about 10% of symptomatic patients, mostly in infants or immunosuppressed individuals (Rev. Inst. Med. Trop. São Paulo 1993;35:111-6).

A chronic asymptomatic but serologically positive phase usually follows. This phase lasts 10-30 years until cardiac or digestive symptoms arise in 20%-40% of infected subjects. Although the physiopathology of this late symptomatic phase is not entirely clear, an autoimmune mechanism is most probable (Brain Pathol. 1997;7:599-611).

Chagas disease is endemic to Central and South America, where the World Health Organization estimates 16 to 18 million people are infected. Vectorial transmission is the leading cause of the disease, though blood-product transfusion and mother-to-baby transmission is possible. Oral transmission is rare.

Since the 1980s, the incidence of Chagas disease has been declining in Brazil, Chile, and Uruguay. In 2003, Brazil was considered free of new cases of the disease (World Health Organ. Tech. Rep. Ser. 2002;905:1-109), but there are still some cases of oral transmission. Transmission through blood transfusion is rare in South American countries because of mandatory testing for the disease. However, Central and South America will have Chagas disease patients for at least a few more decades because of the disease's long latent period.



COURTESY DR. MARCO OLIVEIRA PY

**A brain MRI in a patient diagnosed with chronic Chagas disease shows white matter hyperintense lesions.**

## Lingering Symptoms

► **Neurological disorders.** These occur from the early phase of Chagas disease. Complex cardiac arrhythmias may be verified by 24-hour Holter and ergometric tests and get worse with progression of the disease (Rev. Soc. Bras. Med. Trop. 2004;37:376-83). There have been reports of sympathetic and parasympathetic cell destruction, although a direct vagus nerve lesion could not be demonstrated (Trans. R. Soc. Trop. Med. Hyg. 2000;94:405-8). Autonomic disturbances may cause these arrhythmias and cardiomyopathy. Apart from autonomic fibers, the peripheral nervous system can also be affected, although that is rare and is generally characterized as a mild sensitive-motor polyneuropathy.

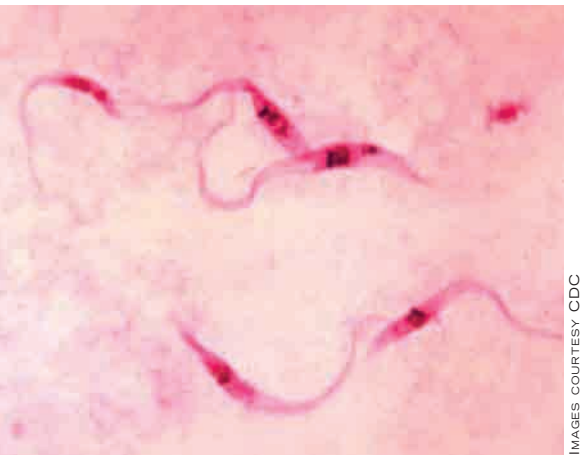
Alencar described cerebral and cerebellar atrophy without any inflammation in the central nervous system (J. Bras. Neurol. 1982;18:7-12). Although some still dispute the existence of direct central nervous system lesions, Chagas disease is strongly associated with cardioembolic strokes (Arq. Neuropsiquiatr. 1984;42:105-15) and other stroke mechanisms (J. Neurol. Neurosurg. Psychiatry 2003;74:516-8), with some authors suggesting an association between trypanosome infection and stroke even in the absence of cardiomyopathy or cardiac arrhythmias (Stroke 2005;36:2015-7).

► **Cognitive function.** Data on cognitive function in Chagas disease are scarce. Some authors have reported worse results in the Mini-Mental State Examination, Wechsler Memory Scale, and Wechsler Adult Intelligent Scale in Chagas disease patients, compared with controls (Arq. Neuropsiquiatr. 1994;52:200-3). Others have reported neurophysiological dysfunction as revealed by the EEG (P300 potential) in these patients, which could indirectly be related to cognitive impairment (Arq. Neuropsiquiatr. 2000;58:262-71).

► **Parasympathetic disorders.** My colleagues and I have shown that Chagas disease patients – even in the early stages and without cardiac dysfunction – present signs of a parasympathetic disorder that correlates significantly with brain subcortical white matter abnormalities. This was shown by an inverse and significant correlation between reduced cardiac frequency variability (evaluated by the respiratory sinus arrhythmia test) and the presence and number of hyperintense lesions in brain white matter seen in MRI.

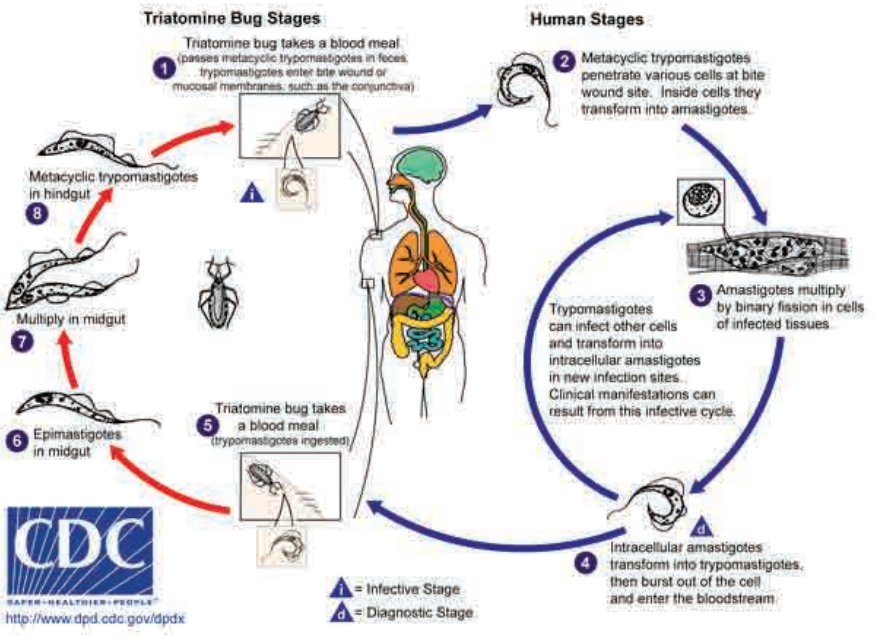
In all, 52% of our patients showed hyperintensities in MRI, compared with about 13% in the general population. But there was no correlation with cerebral hemodynamics or cognitive domains. (Low educational levels hampered interpretation of the neuropsychological tests.) We suggested parasympathetic dysfunction in chronic chagasic patients is associated with brain white matter lesions. We speculated that even in early stages, the disease could promote an imbalance between sympathetic and parasympathetic systems, resulting in an unstable cardiac rhythm (J. Neuroimaging 2009;19:332-6).

In another study, we found no correlation between the presence of serum functional circulating antibodies with beta-adrenergic or muscarinic activity and the autonomic system function or the presence of white matter hyperintense lesions (seen in MRI) in chronic chagasic patients (Arq. Neuropsiquiatr. 2009;67:633-8). The mechanism of the pathobiology of the genesis of hyperintense lesions is still unresolved, although apparently related to parasympathetic dysfunction.



IMAGES COURTESY CDC

**The barber beetle or kissing bug (left), is a vector for Chagas disease. It sucks blood from humans and eliminates feces containing the *Trypanosoma cruzi* parasite (right), which penetrates broken skin and enters the blood vessels.**

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## The Clinical and Public Health Route

The practitioner neurologist should always be aware of the possibility of Chagas disease in a patient with unexplained strokes and/or autonomic nervous system dysfunction, especially if the patient has returned from an endemic area or has received blood products, even decades ago. The disease is diagnosed through sensitive, specific serological testing using immunofluorescence and hemagglutination.

Specific treatment for Chagas disease is underused because of the delay in the diagnosis most of the time. Use of trypanocidal drugs, such as benznidazole, in the disease's acute phase can be reasonably safe and effective, although more effective drugs for Chagas disease are scarce. For most patients diagnosed in the chronic phase, the only treatment is the control of the consequences of the disease, such as treating cardiac arrhythmias and heart failure to prevent embolic strokes.

Prevention is the best management for Chagas disease. Eradication of the vector, better living conditions in rural areas, and mandatory testing of donor blood have been effective. But the disease is now an emerging problem in nonendemic countries because of migrations. Rigid control of blood donors could be useful in those countries as well, where serological tests for the disease should be mandatory. ■

# Tetanus Weighs on Neurological Burden in Ethiopia

BY YOHANNES W. WOLDEAMANUEL, M.D., AND ANHAR HASSAN, MB BCH

*Dr. Woldeamanuel (left) is in the department of neurology at Addis Ababa University Medical Faculty in Ethiopia.*

*Dr. Hassan (right) is in the department of neurology at the Mayo Clinic in Rochester, Minn., USA.*

## Background

The burden of neurological disease is high in Ethiopian hospitals (1). Neurological admissions account for a significant proportion of medical admissions – up to 18% in one study. Findings have shown that both infectious and noninfectious etiologies are responsible (2). Among the neuroinfectious diseases seen, vaccine-preventable neurological disorders include rabies, poliomyelitis, and tetanus, all of which are associated with high morbidity and mortality.

Tetanus cases are rarely seen in developed countries. In the United States, the annual incidence rate of tetanus has dropped from 600 in the 1940s to less than 100 in 2005. The average annual incidence was 0.15 per million between 1997 and 2001. This decline is a result of widespread tetanus immunization (3,4).

In contrast, the annual incidence of tetanus worldwide is about 1 million, with the disease occurring mostly in developing countries. One study in a Nigerian hospital showed that tetanus is the second most common reason for neurological admission (5,6,7). A report in 1981 showed the mortality rate from tetanus to be 28 per 100,000 in Africa, compared with less than 0.1 per 100,000 in North America (8).

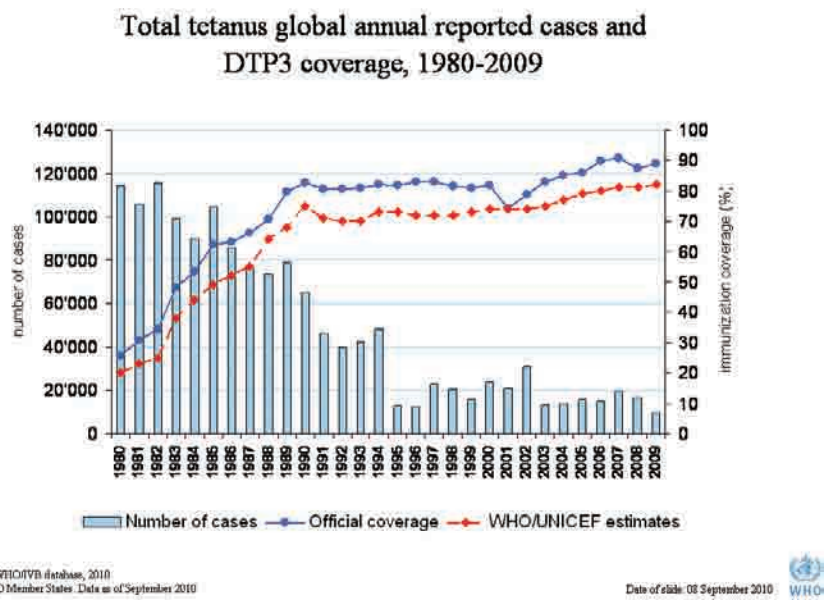
Because of the low vaccination rates and home deliveries that take place in unsanitary conditions, Ethiopia has one of the highest neonatal tetanus morbidity and mortality rates in the world (9). A study in southern Ethiopia revealed the missed opportunity for tetanus immunization in pregnant women during antenatal care to be 11.6% (10).

In this article, we report on recent observations of patients admitted with tetanus, and highlight the preventable aspects of this disease.

## Methods

We reviewed the number of patients with tetanus admitted to the intensive care unit (ICU) at Addis Ababa University's Tikur Anbessa Hospital during February and March 2010.

Four patients with tetanus (three men and a teenaged girl) were admitted during that time (see table). All of them had had severe generalized tetanus. Their mean age was 22.8 years (range 13-30 years), mean incubation period was 8.3 days (2-18 days), and average onset time was 21.1 days (12-24 days). The patients' mean ICU stay was 19.5 days (2-41 days).




Courtesy World Health Organization

**Ethiopia has not seen the significant decline in the incidence of tetanus that comes with improved DTP3 coverage, as shown in this graph based on global data.**

All of the patients were treated with tetanus antitoxin, intravenous antibiotics (ceftriaxone 1 g IV b.i.d., metronidazole 500 mg IV t.i.d.), antispasmodics (chlorpromazine 12.5 mg IV q.i.d., diazepam 5 mg IV p.r.n.), adrenergic blockers (propranolol 10 mg PO b.i.d.), and general supportive measures.

Two of the patients showed progressive improvement, were transferred to the general ward, and were discharged 2 weeks later. The other two patients died, with sudden cardiac death secondary to severe dysautonomia. The survivors received tetanus toxoid before discharge.

## Discussion

Diagnosis of tetanus is largely clinical, and is made by exclusion of other spasm-causing diseases such as strychnine poisoning, acute dystonic reactions, seizures, tetany, and stiff-person syndrome (11). The possible factors that predisposed our patients to tetanus were not being vaccinated, a recent penetrating tetanus-prone wound, and failure to present for initial first aid. Short incubation period and onset time, with complications of dysautonomia in an underserviced ICU, likely result in higher mortality at an earlier period of admission.

Tetanus cases have high morbidity and mortality. A study of generalized tetanus cases from six hospitals in Addis Ababa showed that none of the patients were immunized. The study included 55 patients (39 men, 16 women) with a mean age of 30 years. The mean incubation period was 11.9 days (range 1-90 days), and the mean onset time was 38 hours (1-9 hours).

The patients in the study were treated with TAT, antibiotics, and sedatives, and only three of them received tetanus toxoid before discharge. Death occurred in 27% of the patients, and was correlated with shorter incubation and invasion periods, as well as with abdominal rigidity, tachycardia, sweating, and fluctuating blood pressure, the researchers reported (12). Another hospital chart review from Gondar, Ethiopia, showed a higher mortality rate of 41.4% (13).

The World Health Organization has reported that the age-standardized disability-adjusted life year (DALY) rate for tetanus per 100,000 inhabitants in Ethiopia and the rest of sub-Saharan Africa is 200-750, compared with rates of less than 10 in North America (14). Thus, tetanus continues to contribute a significant neurological burden to Ethiopia, even though it is vaccine preventable.

## Conclusion

Tetanus is a vaccine-preventable disease. Completing vaccination schedules and increasing awareness of the importance of seeking medical care for tetanus-prone wounds are important in decreasing the high incidence, morbidity, and mortality of this disease. ■

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## Characteristics of Four ICU Patients With Severe Generalized Tetanus

| Case | Age (yrs.)/ sex | Injury type/ location | Vaccination | Incubation (days) | Onset time | ICU (days) | Complications | Outcome |
|---|---|---|---|---|---|---|---|---|
| 1 | 13/F | Thorn/left calf | None | 2 | 1 day | 32 | Aspiration pneumonia, dysautonomia, deep venous thrombosis | Improved |
| 2 | 20/M | Fall/right knee | Unknown | 18 | 1 day | 41 | Aspiration pneumonia, dysautonomia | Improved |
| 3 | 30/M | Nail/right sole | Unknown | 4 | 12 hours | 2 | Dysautonomia, cardiac arrest | Died |
| 4 | 28/M | Nail/right sole | Unknown | 9 | 1 day | 3 | Dysautonomia | Died |

Source: Dr. Woldeamanuel

Elsevier Global Medical News

# LETTER TO THE EDITOR

### Misleading Information

An article on trabedersen for treating malignant glioma contained misleading information on the efficacy of this drug ("Trabedersen Bests Standard Chemotherapy for High-Grade Gliomas," WORLD NEUROLOGY, June 2010, p. 3).

Trabedersen is an antisense oligonucleotide to TGF-beta$_2$ that is being examined for safety and efficacy in malignant glioma. The above-mentioned article suggested to report positive results of the previous trials or new information about the compound. Neither is correct.

Data from the phase IIb trial AP 12009-G004 in recurrent or refractory high-grade glioma (anaplastic astrocytoma/glioblastoma multiforme) have been repeatedly presented at meetings but await full publication.

Looking into the available data, the trial was negative for the primary end point, that is, tumor response in the cohort of 145 patients in comparison with standard chemotherapy – temozolomide (TMZ) or procarbazine/lomustine [or CCNU]/ vincristine (PCV); not vincristine alone as stated in the article. The lead investigators reported a promising signal in the subgroup of 39 anaplastic astrocytoma patients (27 of which were treated with the study compound and 12 with chemotherapy) for tumor control (complete or partial response or stable disease according to the McDonald criteria) at 14 months and also the secondary end point, overall survival.

Progression-free survival at 14 months is a novel and not a prespecified end point. It was never disclosed how the decision matured to look at this end point. The survival data are likely influenced by salvage therapies that need to be carefully analyzed.

The article provided no new data and implied efficacy that awaits confirmation. In addition, the reference to the subgroup of younger glioblastoma patients is difficult to appreciate because none of the data have undergone peer review. Moreover, the ongoing trial is not further pursuing this subgroup, but focusing on anaplastic astrocytoma only. Why?

Part peer-reviewed publications on the clinical efficacy data include a review (Expert. Rev. Anticancer Ther. 2009;9:1663-74) and some very preliminary efficacy evaluations from the phase I trial (Oligonucleotides 2007; 17:201-12). TGF-beta$_2$ is undoubtedly a promising target for malignant gliomas. However, more care and prudence are advisable when reporting on new agents in diseases with a prognosis as dismal as glioblastoma.

*Wolfgang Wick, M.D.*
*University Clinic, Heidelberg, Germany,*
*and Michael Weller, M.D.*
*University Hospital Zurich*

***Dr. Piotr Jachimczak replies:***

A report on the phase IIb study AP 12009-G004 has been accepted for publication in the peer-reviewed journal *Neuro-Oncology*. The Dr. Wick and Dr. Weller are correct in stating that the control group was treated with TMZ or PCV. However, they are incorrect on two essential points.

First, the primary end point of the trial was "tumor control rate at 6 months" and not "tumor response;" and second, we presented at the American Association of Cancer Research "tumor progression rate at 14 months" and not "progression-free survival."

The tumor progression rate at 14 months was 16.7% for patients treated with trabedersen and 58.3% for patients treated with chemotherapy ($P = .0032$). In addition, tumor progression rate was a prespecified secondary end point of the trial.

The phase IIb trial was mainly conducted to elaborate on the most effective dose of trabedersen – one of the common tasks of phase II trials. The integration of a control group should lead to a valid clinical trend. Significant efficacy data are then required from phase III trials for regulatory approval.

The phase IIb results clearly showed that patients with anaplastic astrocytoma and glioblastoma multiforme have a different prognosis. Therefore, we decided to investigate the efficacy of trabedersen in two different trials.

A phase III trial in anaplastic astrocytoma patients has started. A separate study to proof efficacy of trabedersen in glioblastoma patients is currently planned.

The sponsor of these studies, Antisense Pharma, is a small, solely venture-capital–financed company, and the development of trabedersen has to be realized step by step. ■

DR. JACHIMCZAK *is senior scientific adviser at Antisense Pharma.*

## TALK BACK

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# B Vitamins Fail to Cut Vascular Events

Daily supplementation with B vitamins was no better than was placebo in preventing recurrent stroke and other major vascular events in patients who sustained recent stroke or transient ischemic attacks.

Investigators in the first placebo-controlled trial of B vitamins in this population reported that major vascular events occurred in 15% of patients assigned to daily B vitamin supplementation, compared with 17% of those assigned to placebo. "These results do not support the use of B vitamins to prevent recurrent stroke," they wrote (Lancet Neurol. 2010;9:855-65).

**B VITAMIN SUPPLEMENTATION SIGNIFICANTLY REDUCED TOTAL HOMOCYSTEINE, BUT DIDN'T TRANSLATE INTO PREVENTION OF VASCULAR EVENTS.**

However, Prof. Graeme Hankey, from the Royal Perth Hospital in Australia and principal investigator of the VITATOPS (Vitamins to Prevent Stroke) study, qualified this statement in an e-mail interview.

"It is possible that we have reported a false-negative result, and that the [trial] was underpowered statistically to reliably identify a clinically important treatment effect, such as the one observed [that is, 9% relative risk reduction and 1.56% absolute risk reduction over a median of 3.4 years of follow-up]," he said. "If such a treatment effect is confirmed in ongoing trials, then B vitamins would present a widely accessible, affordable, safe, and effective addition to the current armamentarium of secondary prevention strategies for patients with transient ischemic attack and stroke."

The investigators wanted to test the hypothesis that daily B vitamin supplementation would lower total homocysteine levels and thereby reduce the combined incidence of nonfatal stroke, nonfatal myocardial infarction, and death attributable to vascular causes as secondary prevention in patients with a recent stroke or transient ischemic attack.

The randomized, double-blind, placebo-controlled trial assigned 8,164 patients in 20 countries between Nov. 19, 1998, and Dec. 13, 2008, to daily supplementation with B vitamins (2 mg folic acid, 25 mg vitamin $B_6$, and 0.5 mg vitamin $B_{12}$) or matching placebo. All of the patients had experienced a stroke or transient ischemic event in the previous 7 months.

### Strong on Safety, Weak on Benefits

Baseline demographic and disease characteristics were similar between the groups. Of the total, 42% of patients were white; 24%, east or southeast Asian; 26%, south Asian, and 7% were listed as "other" (numbers rounded). At the time of randomization, 76% of patients were functionally independent.

Although daily B vitamin supplementation was safe, it provided no benefit over placebo for the composite primary end point of nonfatal stroke, nonfatal myocardial infarction, and death attributable to vascular causes (15% and 17%, respectively). Looking at those end points separately, B vitamin supplementation did not achieve a significant reduction in the risk of nonfatal or fatal stroke, nonfatal or fatal myocardial infarction, or death from any cause; however, it was associated with a significant reduction in death from vascular causes ($P = .04$).

According to results of a fasting blood test at the end of follow-up in 1,164 patients, B vitamin supplementation achieved a significant reduction in total homocysteine, compared with placebo (difference, 3.8 micromol/L; $P$ less than .0001), but this did not seem to translate into prevention of major vascular events.

The authors noted that the study had several limitations, including incomplete adherence to trial design and incomplete follow-up. The median duration of adherence to treatment was 2.8 years and the median duration of follow-up was 3.4 years, which might not have been long enough to identify or exclude any long-term effects of B vitamin supplementation.

Results of a planned meta-analysis of individual data from previous trials of B vitamins as well as results of three ongoing, randomized, controlled trials of B vitamins might shed more light on the long-term effects of B vitamins as prevention of stroke and other major vascular events among the patient population studied in VITATOPS, they said.

**Disclosures:** The study was funded by health and medical research councils in Australia, the United Kingdom, and Singapore, the Australia National Heart Foundation, Royal Perth Hospital Medical Research Foundation, and Health Department of Western Australia. Dr. Hankey disclosed that he has received payments for serving on committees or as an adviser from drug companies that are conducting trials on stroke prevention drugs, including Boehringer Ingelheim, Johnson & Johnson, Pfizer Australia, Sanofi-Aventis, and Schering-Plough.

**—Alice Goodman**

*Ms. Goodman is a freelance writer for* LANCET NEUROLOGY.

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