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WORLD NEUROLOGY

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Epilepsy Care Rolls In by Rail in India

BY MAMTA BHUSHAN SINGH, M.D., D.M.

Epilepsy awareness and screening services are slowly but surely reaching the most remote Indian villages, with the help of a mobile "train hospital" known as the Lifeline Express. Ever heard of Piardoba, Dabra, or Gauriganj? They are small villages in the states of West Bengal, Madhya Pradesh, and Uttar Pradesh, respectively, and are among some of the stops I have made on the LLE in recent months.

Courtesy Dr. Mamta Bhushan Singh

At the Lifeline Express's epilepsy clinic, Dr. Mamta Bhushan Singh and her team screen patients for epilepsy, initiate treatment, and counsel them and their caregivers.

In addition to diagnosing and treating persons with epilepsy, our team collects data on epilepsy from each region, with a view to building a database of disease prevalence and distribution, patient demographics, and availability of services, which we plan to share with the government to raise its awareness of the patients' unmet needs and possibly influence policy decisions. In general, health-related data in India are sparse and large epidemiologic studies on active epilepsy are not available.

There is also a strong educative component to the project, through which we hope to build a network of caregivers comprising local doctors, nurses, elders, and family members in each region we visit and to mitigate the stigma associated with the disease.

About 8 -10 people out of 1,000 in India suffer from epilepsy. With the country's population now exceeding 1 billion, that means there are about 10 million persons with epilep-

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INSIDE

Stroke Risk Data Could Guide Preventions, Global Reduction

BY SHARON WORCESTER
Elsevier Global Medical News

Ten distinct risk factors account for about 90% of global stroke risk, according to findings from the first phase of the multinational, case-controlled INTERSTROKE study, which has enrolled 6,000 patients and controls thus far.

The findings suggest that the stroke burden could be substantially reduced by targeted interventions to address the identified risk factors.

Five of the risk factors found to be significantly associated with stroke risk accounted for about 80% of the population-attributable risk for all stroke. These were self-reported hypertension, current smoking, abdominal obesity (highest vs. lowest tertile of waist:hip ratio), diet (highest vs. lowest diet risk score), and regular physical activity. These comparisons yielded odds ratios of 2.64, 2.09, 1.65, 1.35, and 0.69, respectively.

The addition of another five significant risk factors identified in this study further increased the population-attributable risk for all stroke associated with these risk factors to 90%. These additional risk factors—diabetes mellitus, alcohol intake of more than 30 drinks a month or binge drinking, psychosocial stress/depression, cardiac causes, and highest versus lowest tertile of the ratio of apolipoproteins B to A-I—generally increased the odds of stroke by a smaller amount than did the other risk factors. The comparisons generated odds ratios of 1.36, 1.51, 1.30, 1.30/1.35, 2.38, and 1.89, respectively.

All the risk factors were significantly associated with ischemic stroke, whereas hypertension, smoking, waist:hip ratio, diet, and alcohol intake also were significantly associated with intracerebral hemorrhagic stroke, Dr. Martin J. O'Donnell of McMaster University, Hamilton, Ont., and his colleagues reported (Lancet 2010 June 18 [doi:10.1016/S0140-6736(10)

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New in This Issue of World Neurology

Neurological history and the importance of international relationships and exchange in the neurological community form the basis of a new column by the Dutch neurologist and medical historian, DR. PETER J. KOEHLER.

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EDITOR IN CHIEF'S COLUMN

History and Exchange: Creating A Global Neurological Village

BY MARK HALLETT, M.D.

We all know the famous quotation from George Santayana, "Those who cannot remember the past are condemned to repeat it" (*The Life of Reason,* Vol. 1, 1905). For researchers, it could be rephrased as "Those who don't know the literature might find that their new discovery has already been published"—the point being that history is useful, not only interesting.

In this issue of World Neurology, Dr. Peter J. Koehler reviews the new volume, *History of Neurology,* in the large series, *Handbook of Clinical Neurology* (p. 14), and writes the first of an occasional column on neurological history and in particular, the importance of international exchange within the specialty in the early 20th century (p. 4).

Such exchange has always been valuable and is likely more important than ever these days.

New information about the specialty is emerging and new methods of diagnosis and treatment are being developed in various places around the world, and it might well be useful for persons seeking that knowledge to visit the countries or institutions where it originated. In recent years, for example, many neurologists and neurosurgeons have visited Prof. Alim-Louis Benabid at Joseph Fourier University in Grenoble, France, to learn about deep brain stimulation as a therapy for Parkinson's disease. A disease can arise in one region and spread to others; HIV is an obvious example, as is West Nile virus. Or, patients might become infected with a disease while in one country, hop onto a plane, and come down with the disease in a different country.

Such scenarios underscore the importance of having a global view of disease as well as a global spread of neurological expertise, both of which can be promoted by education efforts in developing countries by experts from developed countries. The story on page 10 about the Honduras residency program is a great example of this.

Of course, the World Federation of Neurology (WFN) plays a pivotal role in international exchange, with its many programs, publications (including this newsletter), and biennial World Congresses. Some of its national and regional member societies are now also reaching out internationally, such as the American Academy of Neurology (p. 6) and the European Federation of Neurological Societies, which has worked with the Federation and other organizations on conducting teaching and continuing medical education courses in Africa (World Neurology, August 2009; and February and April 2010). The WFN plays a crucial role in coordinating these activities. ■

WFN Junior Travelling Fellowship Awards

BY KEITH NEWTON
Executive Director, WFN

For 18 years, the World Federation of Neurology has been supporting young neurologists from developing countries to attend international conferences through its annual Junior Travelling Fellowship program. Initially it did so with support from the pharmaceutical industry—GlaxoSmithKline PLC—and we gratefully took delivery of the first check for £10,000 from the company in June 1992. That helped 12 young doctors, from as far afield as Brazil and Peru in the West to India and Thailand in the East, to travel to meetings that year.

So began a program that over the next 2 decades has given exciting educational opportunities to literally hundreds of young neurologists from all over the world.

Regrettably, hundreds more have had to be disappointed, something that the WFN is eager to address in the future with further assistance; because these days, the Federation finances up to 20 awards annually from its own resources, each worth £1,000.

This year's winners represent an encouraging cross-section of the young talent to be found in our member nations, and the following list illustrates well the continuing importance of this longstanding and key part of the WFN's contribution to global neurological education.

12th European Conference on Epilepsy and Society, Aug. 25-27, Porto, Portugal: Dr. Birinus A. Ezeala-Adikaibe (Nigeria)

14th Congress of the European Federation of Neurological Societies, Sept. 25-28, Geneva: Dr. Ziad Adwan (Syria); Dr. Gayane Aghakhanyan (Armenia); Dr. Sunmono Taofiki Ajao (Nigeria); Dr. Suman S. Kushwaha (India); Dr. Maryam Mountassir (Morocco); Dr. Sopio Sopromadze (Georgia); Dr. Vinod Tiwari (India); Dr. Ashraf Valappil (India)

7th World Stroke Congress, Oct. 13-16, Seoul, Korea: Dr. Souhad Al Faqih (Syria); Dr. Akshay Anand (India); Dr. Bertha Ekeh (Nigeria); Dr. Kolawole W. Wahab (Nigeria); Dr. Edward Komolafe (Nigeria)

2nd European Headache and Migraine Trust International Congress, Oct. 28-31, Nice, France: Dr. Luis Rafael Moscote Salazar (Colombia); Dr. Delgermaa Tsagaankhuu (Mongolia)

4th World Congress on Controversies in Neurology, Oct. 28-31, Barcelona: Dr. Irma Khachidze (Georgia)

40th Annual Meeting of the Society of Neuroscience, Nov. 13-17, San Diego, Calif., USA: Dr. Anurag Kuhad (India) ■

World Neurology

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THE PRESIDENT'S COLUMN

A Focus on Partnering and Prioritizing

BY VLADIMIR HACHINSKI, M.D.

The World Federation of Neurology aspires to lead the battle against diseases of the brain, nerves, and muscles and to promote brain health globally. It is well positioned to achieve that goal, with its 110 member societies representing the majority of the world's neurologists and its recognizable name and good relationship with key organizations such as the International Brain Research Organization and the World Health Organization.

The relationship with the WHO is largely a result of the efforts of my predecessor, Prof. Johan A. Aarli, who played an important role in the publication of two influential WHO books, *Neurology Atlas 2004* and *Neurological Disorders: Public Health Challenges*.

That close relationship with the WHO continues through our Secretary-Treasurer General, Dr. Raad Shakir, chair of the organization's Expert Committee advising on the revision of the International Classification of Diseases 10. Dr. Shakir and Dr. Shekhar Saxena, head of mental health and substance abuse at the WHO, will convene a session on the revision process at the 20th World Neurology Congress in Marrakesh, Morocco, next year (Nov. 12-17).

The Congress, whose theme is "With Africa, for Africa," will be the first in our cycle of every 2 rather than 4 years, and is part of our effort to support regional and national societies and provide members with more frequent opportunities for learning and interacting in places that are more easily accessible and affordable for some of our members.

The WFN's greatest asset is the large number of neurologists who are willing to do international work, exchange ideas, and contribute to the common cause of preventing, delaying, or vanquishing diseases of the nervous system in our patients. Neurologists from different countries have much to learn from each other.

Knowledge accrues in pieces, but it is understood in patterns. The WFN has the opportunity to develop integrated approaches from the proliferating fragments of subspecialization and to begin evaluating and prioritizing knowledge that can be applied with the greatest efficacy.

Neurologists with a special interest are well served by their subspecialty societies, but they need a broader understanding of neurology to be able to perform at a high level. Our Congresses offer members a wonderful opportunity to update their knowledge of general neurology. We have programs for undergraduates, programs for residents, continuing medical education, and neurology for nonneurologists and other health professionals.

In addition, we offer Junior Travelling Fellowships to young neurologists and we are looking at the possibility of clinical fellowships, faculty exchanges, and helping with the creation of training centers. The WFN Research Groups also continue to sponsor important international conferences, organize educational programs in developing countries, and promote the sharing of new ideas and projects among neurologists around the world.

The WFN has been very active in education and it is partnering with the American Academy of Neurology in offering *Continuum: Lifelong Learning in Neurology,* a self-study continuing medical education publication, to neurologists from developing countries, and with the International Brain Research Organization and the European Federation of Neurological Societies (EFNS) in organizing teaching courses.

Our progress in partnering has been steady and smooth, creating a perfect time to review our achievements and set out priorities for the years ahead. Consequently, the WFN is undergoing an internal review of its activities, which may be supplemented by an external review. The questions that are being asked regarding each activity are:

- ► What is its value?
- ► What is its viability? (This question points to the importance of partnering from the beginning of an activity, because we are able to offer expertise and modest resources but do not have the capacity for long-term commitments, particularly in delivery of services.)
- ► How will it be evaluated? (Each initiative will have specific aims and a timetable.)
- ► Does it fit within the WFN goal?

We are also reviewing our publications, upgrading our Web site, and looking at ways of facilitating communications among committee and task force members. A planning and priority retreat was held in London in July to compile recommendations for the WFN Council of Delegates' meeting at the EFNS congress in Geneva (Sept. 25-28).

Our agenda is ambitious, but we have great assets in our members' talent and commitment . The greatest risk is not that we will fail, but that we will fail to try. ■

Half of TBI Patients Develop Major Depressive Disorder

BY MARY ANN MOON
Elsevier Global Medical News

Major depressive disorder is markedly prevalent in patients with traumatic brain injury, which developed in half of patients during the year after their injury in a single-center study.

This rate is nearly 8 times higher than that in the general population, and considerably higher than the rates of 12%-42% reported in previous high-quality studies that seem to have underestimated the problem, reported Charles H. Bombardier, Ph.D., and his associates at the University of Washington and Harborview Medical Center, Seattle, USA.

Aggressive efforts are needed to educate clinicians about the importance of major depressive disorder (MDD) in this population, they noted. Moreover, it would be advisable to integrate mental health services into standard TBI care and rehabilitation programs.

The investigators studied the issue because psychological impairments after TBI are significant causes of disability, yet the rates of MDD in this setting remain uncertain. More definitive studies could galvanize efforts to improve recognition and treatment of this important secondary condition, they said.

The study enrolled consecutive patients admitted with complicated mild to severe TBI to a level 1 trauma center during 2001-2005. Most of the participants were men who had been injured in vehicular crashes and had sustained complicated mild injuries. They were assessed using the Patient Health Questionnaire (PHQ) depression and anxiety modules at baseline, monthly for 6 months, and bimonthly thereafter for 1 year. At 12 months, the participants were assessed using the European Quality of Life measure.

A total of 297 patients (53%) met criteria for MDD at some time during that interval, compared with 7% in the general population. In addition, the sample was characterized by high rates of depression-related risk factors such as alcohol dependence and other preinjury mental health diagnoses, including posttraumatic stress disorder, the authors wrote (JAMA 2010;303:1938-45).

The median duration of depression was 4 months. There was no difference in the rate of depression between patients with mild TBI and those with severe TBI.

About half of the patients who developed depression did so within 3 months of their injury, which challenges the idea that poor awareness of impairment precludes depressive reactions during the first 6 months after injury.

MDD was associated with greater difficulty with mobility, usual activities, pain or discomfort, and role functioning. It was a significant predictor of comorbid anxiety, poor self-reported health, and lower quality of life.

About 16% of the participants were depressed at the time they sustained the traumatic injury, and another 27% had a history of depression but were not depressed when injured.

The authors cited several study limitations. They said the presence or absence of MDD was based on telephone interviews using the PHQ-9, rather than more traditional diagnostic interviews such as the Structured Clinical Interview for DSM-IV Disorders (SCID-IV). They noted that the results might not be generalizable because the study was conducted at a single level I trauma center in a region where many of the patients were Medicaid recipients, and their ethnic/racial diversity was somewhat limited.

The US-based National Center for Medical Rehabilitation Research and the National Institutes of Health supported the study. Dr. Bombardier reported owning stock in Pfizer Inc. ■

MY TAKE

This is the largest prospective study on the frequency and predictors of MDD after traumatic brain injury published to date. It showed a strong association of post-injury MDD with a history of pre-injury psychiatric disorder as well as a high rate of novel cases (41%). There was also a high comorbidity of MDD with anxiety, which raises the question about the rates of other psychiatric disorders before and after TBI. A key next step will be to document the full range of pre- and post-injury psychiatric disorders prospectively with comprehensive studies using the SCID-IV.

The findings highlight the need for routine screening and efforts to treat these disorders. But evidence on treatment efficacy for MDD after TBI is sparse. The study was conducted in the context of a trial of pharmacological treatment with sertraline. Other recent trials have shown limited success of pharmacological interventions in TBI. Moreover, the impact of psychological therapies might be reduced by cognitive impairments. There should be further testing of psychological therapies that have been adapted for the unique needs of this population.

JENNIE PONSFORD, PH.D., *is professor of neuropsychology at Monash University and director of the Monash-Epworth Rehabilitation Research Centre at Epworth Hospital, both in Melbourne, Australia. She has no relevant disclosures.*

INTERNATIONAL RELATIONSHIPS IN THE NEUROSCIENCES

A Dutch Lecturer in the United States

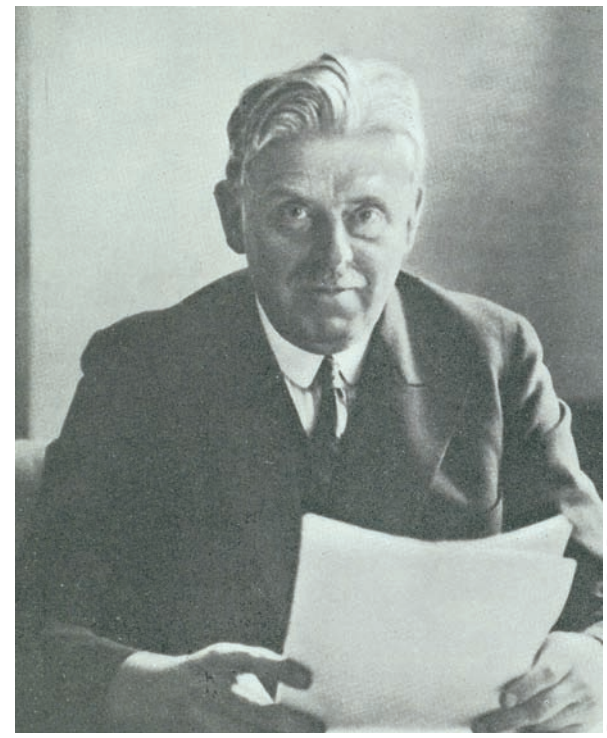
International relationships have long played a role in medicine. As early as the 16th and 17th centuries, medical students would travel across Europe to important university cities such as Paris, Montpellier, and Padua to study medicine. Two well-known examples of these young peregrinati are the anatomist-physicians Andreas Vesalius and William Harvey.

These international relationships became even more common and widespread during colonialism. Transatlantic exchange for medical education prevailed in the 19th and 20th centuries, when, between 1870 and 1914, thousands of American students and physicians traveled to Europe, particularly Vienna and Berlin, to take medical courses and improve their scientific skills. However, between the two world wars, the direction of exchange for purposes of medical education gradually reversed, as increasing numbers of European physicians and students traveled to the United States.

The following essay—the first of an occasional series about these international exchanges—focuses on an early European-American exchange.

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

Dr. Koehler is a neurologist in the department of neurology at the Atrium Medical Centre, Heerlen, the Netherlands. Visit his Web site at www.neurohistory.nl.



Photos courtesy Dr. Peter J. Koehler

Bernard Brouwer visited university clinics in the United States in 1926 and 1933.

After years of neuroanatomical work at the Central Institute for Brain Research in Amsterdam, the Dutch physician Bernard Brouwer (1881-1949) was invited to deliver lectures at university clinics in the United States—first in 1926 and again in 1933.

Brouwer, who had been appointed chair of neurology at the University of Amsterdam in 1923, had studied the projection of the retinal fibers to the lateral geniculate body and occipital cortex in primates and the spinal sensory pathways, both of which were the subjects of his lectures.

On his first visit to the United States, Brouwer delivered the 17th annual Herter Lectures at the Johns Hopkins University in Baltimore. He was offered a research chair in the institution's department of neurology but declined it, choosing to stay in Amsterdam.

He also visited several other cities in the United States, including Washington; Philadelphia, where he met Charles K. Mills; Chicago, where he met Charles Judson Herrick, who, like him, also worked on comparative anatomy; and New York, where he delivered the Harvey Lecture and met Smith Ely Jelliffe, Frederick Tilney, Bernard Sachs, Robert Foster Kennedy, and Charles L. Dana.

In San Francisco on the same tour, Brouwer delivered a lecture at the 55th annual session of the California Medical Association, where he famously criticized Henry Head's theory of distinct pathways for protopathic and epicritic sensibility; and in St. Louis, he was struck by the fact that women were not allowed to study at St. Louis University, in contrast to Washington University.

His final stop on the tour was Rochester, Minn., where he was impressed by the large numbers of patients. He was surprised to learn that American neurologists' chief source of income was from private practice, because universities either did not pay a salary at all or provided only a small amount of money. He speculated that this source of income might have been the reason it was almost impossible for neurologists to perform meaningful studies in a systematic way.

However, he was impressed by the results of the brain tumor surgery performed by the pioneering neurosurgeon Harvey Cushing, and after his return to Amsterdam, he sent the Dutch surgeon Ignaz Oljenick to train under Cushing.

In 1929, a new 120-bed neurological clinic was opened in Amsterdam, which included a neurosurgical ward directed by Brouwer.

In his correspondence with the Swiss neurologist Constantin von Monakow, with whom Brouwer had worked a decade earlier, he wrote that he had found a vivid interest in neurological science everywhere he visited in the United States, and that the Americans were very competent and diligently engaged in pathological and experimental-anatomical studies.

Brouwer had the opportunity to visit the United States again in 1933, at the invitation of the Association for Research in Nervous and Mental Disease in New York. There, he was impressed by Charles Elsberg's achievements in brain tumor surgery and listened to Wilder Penfield's presentation on unilateral lobotomies.

Brouwer also visited the experimental neurologist John Fulton, whom he had met previously at the first International Neurology Congress in Berne, Switzerland, at Fulton's laboratory at Yale University in New Haven, Conn.

Brouwer and Fulton continued corresponding for many years and exchanged postgraduate students.

Margaret Kennard, an American who would become a pioneer in the experimental study of sparing and recovery of brain function, was one of Fulton's students who spent several months at Brouwer's neurological institute in Amsterdam.

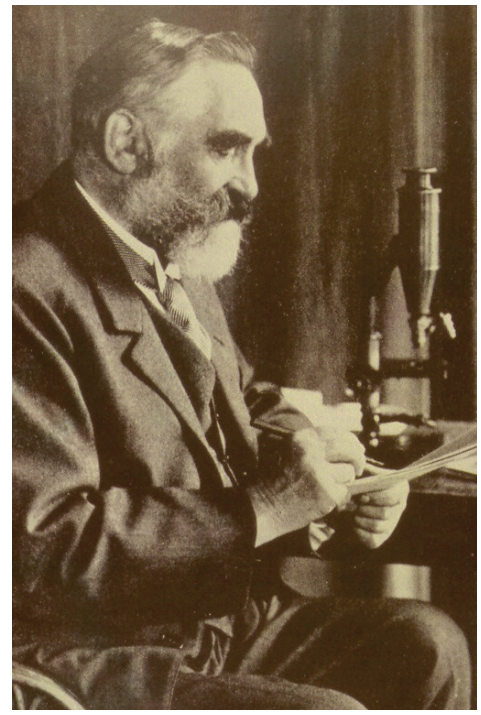
In a 1934 letter to Fulton, Kennard wrote the following about her experiences at Brouwer's Amsterdam institute: "I continue to be amazed and delighted by the clinic here. … I've never seen any organization where clinic and research were used so well for mutual benefit as here. I think it's due, as Prof. Brouwer himself says, to the fact that he completely controls both."

In addition, she wrote, "I'm impressed with the unity in time here, as well as in organization. It is quite something to follow a patient thirty years and then spend a year on the pathology as they do here."

The last city that Brouwer visited on his second trip was Montreal, where he met Wilder Penfield and discussed the building of a new neurological and neurosurgical institute that would open in 1934.

Brouwer's visits to the United States and the exchange of students serve as examples of shifts in international neuroscience exchange whereby the traditional German influence in Dutch neurological circles was gradually replaced by American influences. ■

John Fulton of Yale University sent students to do research at Brouwer's institute in Amsterdam.



Constantin von Monakow was a Swiss neurologist who worked with Brouwer.

Share your thoughts and comments on this topic by writing to us at worldneurology@.com.

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Calendar of International Events

2010

7th World Stroke Congress
Oct. 13-16
Seoul, Korea
www2.kenes.com/Stroke/Pages/Home.aspx

2nd European Headache and Migraine Trust International Congress
Oct. 28-31
Nice, France
www2.kenes.com/ehmtic/Pages/Home.aspx

14th World Pain Clinic Congress & the 1st Asian Congress on Pain
Oct. 29-Nov. 1
Beijing
www.ccwspc.org

4th World Congress on Controversies in Neurology
Oct. 28-31
Barcelona
www.comtecmed.com/cony/2010/

7th International Congress on Mental Dysfunctions & Other Non-Motor Features in Parkinson's Disease
Dec. 9-12
Barcelona
www2.kenes.com/mdpd2010/Pages/Home.aspx

2011

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

World Congress on Huntington's Disease
Sept. 11-14
Melbourne
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

AAN Extends Benefits Worldwide

BY HANNS LOCHMÜLLER, M.D.

The American Academy of Neurology is committed to providing its members—in the United States and internationally—with access to benefits that contribute to improving the care of patients with neurological diseases and to promoting professional, scientific, and educational excellence. Its board of directors recently reviewed the AAN's international policy to facilitate its global training and education efforts, especially in regard to developing nations, and it routinely reviews the ways in which the academy can assist its international members in taking advantage of its numerous benefits and offers.

One outgrowth of this commitment has been the International Attendee Summit, which is held each year at the academy's annual meeting. This year, Dr. Hanns Lochmüller, the chair of the AAN's international subcommittee, hosted the summit at the Toronto annual meeting. AAN leaders were present to provide an overview of what the academy has to offer its international members and nonmembers and to participate in the question-and-answer session.

As in the previous 2 years, the summit was well attended by representatives from many countries, including Argentina, Australia, Bangladesh, Brazil, Canada, China, India, Nigeria, Serbia, South Africa, and the United Kingdom.

The following benefits are available to the AAN's international members:

- A reduced dues structure for members living outside the United States and Canada in countries rated as low or low-middle income by the World Bank.
- The official peer-reviewed journal, *Neurology*, which publishes news about professionals in the international neurological community and includes the *Neurology International Newsletter* and some translated articles (www.neurology.org).
- Membership in the AAN listserv, which allows for those with an interest in international neurology to communicate—e-mail Lynee Koester (lkoester@aan.com) for information about joining.
- The International Scholarship Award, which provides eligible international candidates the opportunity to attend the AAN's annual meeting. It is not necessary to be a member to apply. Up to 10 scholarships have been awarded annually to applicants demonstrating financial need and interest in attending the meetings (www.aan.com/science/awards/?fuseaction=home.info&id=33).
- The integrated neuroscience sessions at AAN annual meetings. These have enjoyed excellent attendance and positive feedback. Ten sessions were available in 2009, for example, with some focusing solely on global neurological disorders.
- Training under the Palatucci Advocacy Leadership Forum, which has trained 239 advocacy leaders since its inception in 2003. The leaders form a network of neurology advocates throughout the United States and 15 other countries and work on issues that are critical to the future of neurology and patients with neurological disease (www.aan.com/go/advocacy/active/palf).
- Involvement in the AAN's social networking sites, such as Facebook, Twitter, LinkedIn, and YouTube.
- Participation in the AAN's communities, where you can connect with your colleagues in your subspecialty or area of interest. Each community is supported through forums whereby members can discuss topics important to them, access relevant articles, and contribute to community-generated resources. ■

DR. LOCHMÜLLER *is professor of experimental myology in the Institute of Human Genetics, Newcastle University, England.*

Protein Linked to Brain Atrophy, AD Progression

BY MARY ANN MOON
Elsevier Global Medical News

Elevated plasma levels of the protein clusterin seem to correlate with the degree of brain atrophy, the severity of symptoms, and the speed of the clinical progression of Alzheimer's disease.

Moreover, clusterin levels seem to rise well before symptom onset or amyloid-beta deposition is noted in the seemingly normal brains of older patients who go on to develop Alzheimer's disease (AD), said Dr. Madhav Thambisetty, who was at the King's College Institute of Psychiatry, London, when he conducted the study with his associates.

They reported that raised plasma clusterin concentrations were seen 10 years before amyloid-beta deposition, suggesting that clusterin plays an etiopathological role, and is not simply a reaction to other pathology in AD. The findings do not endorse plasma clusterin level as a stand-alone biomarker for AD, they noted, and there may be "other proteins in plasma related to the disease process," as suggested in previous studies (Arch. Gen. Psychiatry 2010;67:739-48).

The researchers used plasma proteomics and neuroimaging to identify possible AD-associated proteins. They identified 13 spots on gel electrophoresis that correlated with hippocampal atrophy in a sample of 44 patients who had mild cognitive impairment or mild to moderate AD, then performed the same analysis in a separate sample of 51 AD patients who had either slow-progressing or fast-progressing AD. Only one protein—clusterin—was common to both groups in this discovery-phase study.

The clusterin-AD link was then confirmed in a validation cohort of 689 patients from two European studies: 464 with AD, 115 with mild cognitive impairment, and 110 normal controls. This time, they correlated clusterin levels with MR imaging showing atrophy of the entorhinal cortex, a component of the medial temporal lobe showing early pathological changes in AD. Plasma clusterin also negatively correlated with cognitive scores on the Mini-Mental State Examination in a subset of 576 patients, indicating a correlation between rising clusterin and declining cognition.

RAISED PLASMA CLUSTERIN LEVELS WERE SEEN 10 YEARS BEFORE AMYLOID-BETA DEPOSITION, SUGGESTING THAT THE PROTEIN HAS AN ETIOPATHOLOGICAL ROLE.

Higher clusterin levels were also noted in patients with rapid AD progression than in those with slower progression. The association was observed in 344 patients who had shown accelerated cognitive decline before blood samples were obtained, and in 237 whose cognitive decline accelerated after blood samples were obtained. Thus, the association was evident retrospectively and prospectively, relative to the time of blood sampling.

The researchers used data from a US longitudinal study of aging to test the hypothesis that plasma clusterin level is a marker of future AD pathology in apparently normal older adults. They found high clusterin levels predicted AD-associated changes on PET imaging as long as 10 years before changes were evident.

"This suggests that increased plasma concentrations of clusterin, even in nondemented older individuals, predicts a greater extent of fibrillar amyloid burden in the entorhinal cortex, the same region where we have also demonstrated robust association with atrophy in subjects with mild cognitive impairment and AD," Dr. Thambisetty, who is now at the National Institute of Aging, Bethesda, Md., USA, and his colleagues wrote. "These results have wider implications for the identification of other amyloid chaperone proteins in plasma, both as putative AD biomarkers as well as drug targets of disease-modifying treatments."

The study was funded by numerous nonprofit and government organizations in the United States, England, and Europe. Intellectual property has been registered on the use of plasma proteins, including clusterin, for use as biomarkers for AD by by King's College London and Proteome Sciences, with Dr. Thambisetty and an associate named as coinventors. One of the researchers is supported by the US National Institutes of Health and numerous companies involved in Alzheimer's disease research. ■

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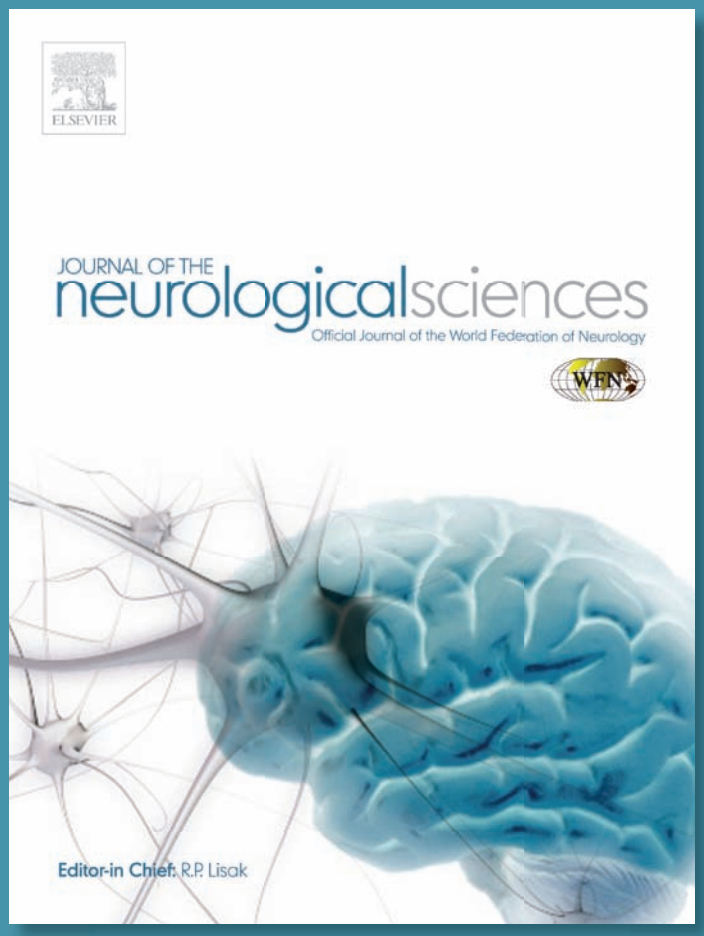

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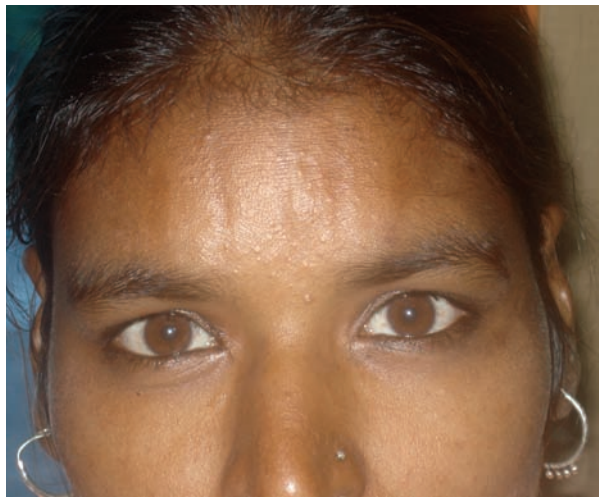
Rural Areas Are Targeted

Epilepsy • *from page 1*

sy (PWE), of whom a dismal 20%-30% at best receive adequate treatment. Put another way, the treatment gap for epilepsy in India is about 70%-80%, meaning 7-8 million PWE are not being treated.

There are several reasons for such a wide treatment gap. Two very important factors are the lack of awareness about epilepsy and the various societal stigmas associated with it. Another factor is a lack of easy, affordable access to care—about 70% of the population in India is rural.



Some faith healers apply a scarring plant juice in vertical lines on the forehead as a form of treatment.

Charms, such as those around this girl's neck, might also be used by faith healers for 'treating' epilepsy.

In addition, there are only about 1,000 neurologists in India serving a population of 1.1 billion people. About a third of them practice in six metropolitan cities: Delhi, Hyderabad, Bengaluru, Chennai, Kolkata, and Mumbai. Small cities and villages do not have practicing neurologists.

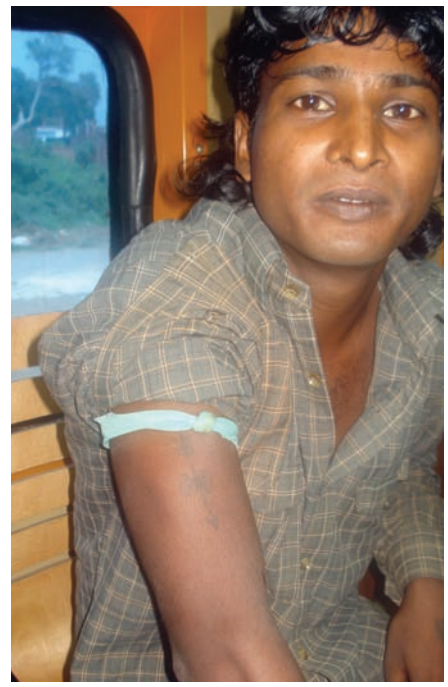
Many of these neurologists are working individually to improve circumstances for PWE. However, it is important that we take our services to regions where people are the least informed about the disease and where health facilities are the most rudimentary. This is the situation in almost all Indian villages, especially in the northern and central regions—the situation is somewhat better toward the south of the country.

I work on the Lifeline Express with a team of dedicated workers. We strive to educate people about epilepsy and will screen as many as 200-300 PWE at any given location. Whenever possible, we will initiate epilepsy treatment based on our clinical diagnoses. We also counsel patients and/or their families, provide the patients with free starter packs of 1-2 months of therapy, and try to persuade them to follow up either at the local hospital or at the All India Institute of Medical Sciences, New Delhi.

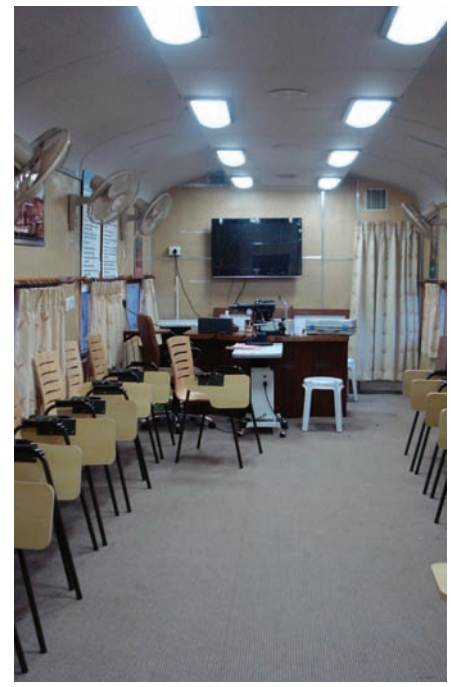
The LLE makes about 10 excursions a year, stopping for about 3 weeks at each project destination. It is run by the Impact India Foundation, a Mumbai-based nongovernmental organization that works toward reducing the incidence of curable or treatable conditions such as epilepsy, blindness, deafness, physical handicaps, and deformities.

Running expenses are borne by the LLE and its sponsors. Patients do not have to pay for any services, including surgery, because physicians volunteer their time for free. I must also acknowledge here that this work would not have been possible without encouragement and support from Prof. R.C. Deka, director of the All India Institute, and Prof. Madhuri Behari, head of the institute's neurology department; as well as the advocacy tools provided to me by the American Academy of Neurology's Palatucci Advocacy Leadership Forum.

Our excursions are meticulously planned ahead of our arrival. As much as is possible, we try to enlist support from the local administrations. We will send out information notifying people we will be coming to their area and informing them of the dates earmarked for seeing patients with certain conditions. For example, all cataract surgery will be done on particular days, and all PWE will be seen on different days. This helps streamline our efforts and means we can get a lot done in a relatively short time.



The rag and tattoo on this young man's arm indicate faith healer intervention.



The clinic doubles as a venue for the patient-caregiver education sessions.

Photos courtesy Dr. Mamta Bhushan Singh

We generally work 12-14 hours a day during the 2-3 days we spend at a project. The PWE and their accompanying caregivers or family members are divided into smaller groups of 15-20 for orientation and awareness sessions. We provide information about epilepsy and also encourage discussion about any unresolved issues they might want to share.

After this initial session, the patients have a one-on-one consultation with a neurologist member of the team.

The first-choice antiepileptic drugs (AEDs) for most epilepsy patients would be phenytoin, carbamazepine, and to a lesser extent, valproic acid. Use of newer AEDs is very limited because they are so expensive. We often have to deal with patients who have consulted faith healers for alternative treatments. Healers tend to play on the desperation of gullible rural people and will pass off anything—charms or plant juices—to "treat" epilepsy. They are largely uncontrolled and unaccounted for in India, so it is difficult to establish contact with them and unrealistic to expect them to participate in any meaningful way with our program, as has been achieved in some countries.

Now that we have initiated this unique rural epilepsy program, we are trying to expand and improve its scope. We plan to install basic investigation facilities for epilepsy on the LLE. An EEG machine has been donated by a neurologist colleague; next on our list is a CT scanner.

We have also started a basic epilepsy orientation course for local doctors at every destination. We hope to provide them with information that will allow them to continue caring for persons with epilepsy whose treatment is initiated on the LLE, and to build a network of epilepsy caregivers over time, from the village level to the cities, to help sustain care so that patients do not have to make frequent long-distance trips for their treatment.

The task of raising awareness of epilepsy and improving the treatment of PWE in India is huge. This is just the beginning of our efforts, and advancing the project will take perseverance on our part and cooperation and collaboration from as many willing and committed physicians as possible. ■

Dr. Singh *is assistant professor in the department of neurology at the All India Institute of Medical Sciences, New Delhi.*

Any physician who is interested in contributing to or participating in the epilepsy project can contact Dr. Singh at mbsneuro@gmail.com. or become an "India Control Epilepsy" fan on Facebook.

To share your comments on this article, write to us at worldneurology@elsevier.com.

Patients and their caregivers at a stop in West Bengal wait outside the Lifeline Express for their consulations.

A question-and-answer session helps inform villagers about epilepsy and dispel the myths surrounding the disease.

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Honduras Pilots WFN Training Program in Latin America

BY MARCO T. MEDINA, M.D., AND THEODORE MUNSAT, M.D.
WFN Education Committee

Prof. Medina (left) is dean of the School of Medical Sciences at the National Autonomous University of Honduras, Tegucigalpa.

Prof. Munsat (right) is professor emeritus, Tufts University, Boston.

One of the primary goals of the World Federation of Neurology is to help provide low-resource countries with meaningful training and education for their neurological health care providers and in doing so, to improve the neurological health of the population.

These efforts in developing countries are beset with challenges, ranging from socioeconomic and structural problems—such as inadequate continuing medical education (CME) and limited access to educational and reference resources—to technical or financial constraints that make it difficult for neurologists to attend educational activities. However, the major barrier to the provision of quality care for patients with neurological disorders is that these countries have a neurologist-to-inhabitant ratio that is often far below the World Health Organization's recommended 1 neurologist per 100,000 people.

A number of strategies can be implemented to improve neurology training and education, but the first step should always be to evaluate the conditions pertaining to the specialty in a particular country. This should include looking at demographics data and information about the availability of health care, the number of physicians and neurologists per capita, the epidemiologic profile of neurological diseases, and the existence of neurology training programs, CME, and/or accreditation programs.

Over the past 12 years, the WFN has promoted neurology education in Latin America by establishing training programs and promoting CME and certification processes.

Training Takes Root ...

Honduras was the pilot country for the WFN's training effort, which started in 1998. Since then, Guatemala, Peru, and Mexico have also benefited from the training program.

At the start of the WFN's training effort, Honduras had 1 neurologist per 325,000 inhabitants, and all of its neurologists had trained outside the country (see WORLD NEUROLOGY, June 2010, p. 10). The WFN Education Committee, in collaboration with the Postgraduate Direction of the National Autonomous University of Honduras, the Honduran Neurological Association, and the Honduran Secretary of Health, helped establish a neurology training program that was overseen by an external WFN review board.

By this year (2010) there was a 50% increase in the number of neurologists per capita in Honduras, which has significantly improved the quality of patient care and promoted research in the neurosciences.

The training program provided a valuable model that could be adapted and applied to other developing countries in the region with similar needs for neurological care.

The neurology department at the National Autonomous University of Honduras, Tegucigalpa, is considered one of the best in Central America, and every one of its graduates has stayed in Honduras. Faculty members are currently developing a doctoral program in neuroscience with the support of the University College London, and it is attracting the better medical school graduates from Honduras and Nicaragua.

In addition, secondary cities are now getting well-trained neurologists for the first time. This has led to greatly improved outcomes, with some assessments showing a notable reduction in deaths from status epilepticus, for example. Furthermore, preventive programs for neurocysticercosis, a scourge of the country, are beginning to show results. A vigorous stroke prevention program is also showing encouraging results.

In 2001, the Federation initiated a CME project based on content from its in-house publication, *Seminars in Clinical Neurology*, and the American Academy of Neurology's CME journal, *Continuum: Lifelong Learning in Neurology*. The two organizations each provide six specially designed educational courses annually, either in hard copy or online.

Twelve countries—Argentina, Brazil, Chile, Columbia, Cuba, Guatemala, Honduras, Mexico, Panama, Peru, Uruguay, and Venezuela—take part in the program. Participants in each country review *Seminars* and *Continuum*, then meet as a study group to discuss the issues, review cases, and examine how practice might differ in their respective countries. The president of the national neurological society in each country appoints a WFN education coordinator who distributes the courses and arranges the discussion groups. Participants have to submit an evaluation form and belong to a national society if they wish to receive a certificate.

... Continuity Takes Hold

This program is now being used increasingly for certification purposes, grand-round presentations, educational retreats, and the education of non-neurologists. In Honduras, for example, residents read one to two chapters of the two CME publications and meet for weekly discussions with their professors, sometimes inviting residents and specialists from other areas, such as internal medicine, to join. Some meetings also include patient evaluations.

The WFN has formed an education subcommittee to focus on Latin America, with the goal of improving education about neurological disorders.

The WFN has recently introduced a certification process for training programs to be reviewed externally. So far, programs in Honduras, Guatemala, Mexico, and Peru have met the criteria to qualify for certification.

The process is useful for confirming that the program is functioning effectively, and for notifying the medical community that it meets international criteria of performance.

Several countries have requested that the WFN provide a process of external evaluation of their residents when they graduate. A logical extension of that process could lead to a more formal certification and recertification process. ■

Hypertension Tops the List

Stroke • *from page 1*

60834-3]). The findings were published online in *The Lancet* and reported simultaneously at the World Congress of Cardiology in Beijing.

To establish the association of conventional and emerging risk factors with stroke, the INTERSTROKE researchers set out to perform a study similar to the INTERHEART study published in 2004, which identified nine modifiable risk factors that explained the majority of myocardial infarctions worldwide.

Between March 1, 2007, and April 23, 2010, they studied 3,000 patients from 22 countries, and 3,000 sex- and age-matched controls with no stroke history. Case patients (2,337 with ischemic stroke; 663 with intracerebral hemorrhagic stroke) presented with acute first stroke and were enrolled within 5 days of symptom onset and 72 hours of hospital admission. A structured questionnaire and physical examination, including routine neuroimaging, were performed in all patients.

"Our study provides essential information on the importance of common, potentially modifiable vascular risk factors, and builds on previous epidemiological studies," they wrote. Although the risk factors identified in this study are similar to those identified as being associated with myocardial infarction in the INTERHEART study, hypertension, physical activity, apolipoproteins, and alcohol intake seem to have different relative importance for stroke compared with myocardial infarction, they noted.

"These findings are important to help guide optimum selection of risk-factor targets for population-based programs to prevent all cardiovascular diseases," they concluded.

Phase II of the INTERSTROKE study, which is expected to include an additional 10,000 case-control pairs to more reliably characterize the importance of individual risk factors in different geographical regions, ethnic groups, and stroke subtypes, is underway and should be completed within 3 years. The researchers noted that the phase I findings confirm the feasibility of the scale of the second phase.

INTERSTROKE phase I was funded with unrestricted grants from the Canadian Institutes of Health Research, Heart and Stroke Foundation of Canada, Canadian Stroke networks, Pfizer Cardiovascular Award, AstraZeneca, Boehringer Ingelheim, and Merck & Co. Multiple authors reported receiving grant or research support, honoraria, expenses, and/or fees from numerous pharmaceutical firms and other sources and/or being associated with the American Heart Association as a board member and officer. ■

MY TAKE

Stroke is the second-leading cause of death globally, and the cause of more than 85% of deaths in developing countries. Therefore, research on risk factors for stroke around the world is imperative for addressing the problem.

The INTERSTROKE investigators confirmed that hypertension is the leading risk factor for stroke not only in high-income countries, but also in developing countries. This finding is especially relevant because it highlights the need for regional health authorities to develop strategies to screen the general population for high blood pressure and offer affordable treatment to reduce the burden of stroke.

Although the current study is limited by its matched case-control design vs. a prospective cohort approach, it nonetheless represents an efficient approach to obtaining useful information about stroke risk. The findings of this study should help inform worldwide stroke prevention strategies and reduce the global burden of stroke.

JACK V. TU, M.D., *is with the Institute for Clinical Evaluative Sciences, the Sunnybrook Health Sciences Centre, and the University of Toronto. His comments on this topic were originally published in* The Lancet *(2010 June 18 [doi:10.1016/S0140-6736(10)60975-0]). He reported having no conflicts of interest.*

FROM THE JOURNAL OF THE NEUROLOGICAL SCIENCES

Aspirin May Have Role in TB Meningitis

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

Tuberculosis is a major cause of morbidity and mortality. The World Health Organization estimates there are 2 billion cases worldwide.

In recent years, the disease has become a formidable challenge, with increased prevalence in the context of HIV disease and social breakdown in many regions. It is protean in its manifestations, can affect any of the body's organs, and is difficult to treat, requiring long-term medication that must be taken correctly.

One of the more common target organs of tuberculosis (TB) is the central nervous system. This involvement has high morbidity and mortality, even with the standard treatment, which includes a four-drug antituberculous regimen (isoniazid, rifampin, pyrazinamide, and ethambutol) and possibly corticosteroids. The reason for these high rates is not clear, but probably involves the thick exudate in the basal meninges, which damages the cranial nerves and blood vessels passing through the subarachnoid space; and the effects on the arachnoid villi, which causes hydrocephalus. The resulting cranial nerve damage and strokes can be devastating.

This inflammatory reaction is an important potential therapeutic target (which has been exploited with some success in acute bacterial meningitis), and many cases of tuberculous meningitis (TBM) are treated with dexamethasone (or other corticosteroids). The efficacy of steroids is not clear and the effect of adding an anti-inflammatory and antiplatelet agent such as aspirin is reasonable to investigate, as was done for the current paper (J. Neurol. Sci. 2010;293:12-7).

Dr. Usha K. Misra of the neurology department at Sanjay Gandhi PGIMS, Lucknow, India, and colleagues randomized 118 patients (mean age, 30 years) with TBM to receive either aspirin (150 mg) or placebo. All patients were put on the four-drug anti-TB regimen. The critically ill who were encephalopathic, losing vision, or herniating also received the corticosteroids prednisolone or dexamethasone.

Primary outcome was a stroke, as seen on an MRI, at 3 months; secondary outcomes were mortality and functionality as assessed by the Barthel index, also at 3 months. The groups were well balanced in baseline demographics.

For the primary outcome of new stroke at 3 months, aspirin resulted in a 19.1% absolute risk reduction of stroke, with 25% of patients in the aspirin group developing stroke, compared with 45% in the placebo group—not statistically significant. (Some studies have put this risk at roughly 50%).

Absolute risk reduction in mortality following aspirin was 22%. In all, 22% of aspirin-group patients died, compared with 44% in the placebo group (statistically significant). There was complete restoration of functionality in 40% of the aspirin group and 25% of the placebo group.

A post hoc analysis comparing patients on corticosteroid plus aspirin with placebo patients showed statistically significant decreases in death and stroke, though such analyses are most useful for hypothesis generation, suggesting this study deserves to be followed up.

Should this result be upheld, it would provide another medication—an affordable one—for treating the disease, and it is likely to have implications for the pathogenesis of TBM and so provide another therapeutic target for this common and dangerous disease. The authors made no disclosures of conflicts of interest relating to the study. ■

DR. TSELIS *is associate professor of neurology at Wayne State University in Detroit, USA, and book review editor for the* Journal of the Neurological Sciences.

Time to Relapse May Predict Neuroblastoma Survival

BY PATRICE WENDLING
Elsevier Global Medical News

CHICAGO — In children with neuroblastoma, time to relapse is highly predictive of overall survival post relapse, according to an analysis by Wendy B. London, Ph.D., and her colleagues.

The researchers identified other factors that are also prognostic of overall survival post relapse as well as a small proportion of relapsed patients who are salvageable.

Currently, clinicians do not know how to identify which patients are more likely to respond to post-relapse therapy and they have difficulty in interpreting time to relapse because neuroblastoma is a heterogeneous disease, Dr. London said in a presentation at the meeting.

The median time to relapse in the 2,266 children was 13.2 months, with a range from 1 day to 11.4 years.

All told, 73% of children who relapsed were aged 18 months or older, 72% were International Neuroblastoma Staging System (INSS) stage 4, and 33% had amplified MYCN oncogene expression.

Overall survival at 5 years was 20%.

It was not possible to categorize time to relapse using a simple 1-year cutoff, said Dr. London, director of biostatistics at Children's Hospital Boston.

The risk of death was about the same for children who relapsed within the first 6 months as it was for those who relapsed at 18-24 months. The risk of death was highest in those who relapsed between 6 and 18 months.

All three groups had a significantly higher risk of death, compared with patients who relapsed after 36 months (*P* less than .001).

The association between time to relapse and overall survival appears to be driven by stage 3, 4, and MYCN-amplified patients, Dr. London said.

In a survival tree regression analysis that adjusted for time to relapse, disease stage was identified as the most highly significant variable for survival post relapse. INSS stage 4 patients had a 5-year survival of 8%, compared with 52% for those who were stage 1, 2, 3, or 4S.

Upon further analysis, three cohorts emerged as salvageable after relapse:

- Patients who are stage 4, with nonamplified MYCN, and less than 18 months of age;
- Patients who are stage 1, 2, 3, or 4S with MYCN amplification; and
- Patients who are stage 1, 2, 3, or 4S with nonamplified MYCN and undifferentiated grade histology.

Patients who had stage 4 disease and MYCN amplification had a 5-year survival of 4%, compared with 12% for stage 4 patients with nonamplified MYCN.

Time to first relapse as a predictor of survival is important for two reasons, said discussant Dr. Andrew Pearson, chair of pediatric oncology at the Institute of Cancer Research and the Royal Marsden Hospital in London: It can be used to stratify and/or describe patients in early clinical trials and to identify a salvageable population post relapse.

"In the past, I'm sure that some agents have had a negative response in early clinical studies because a group of very poor prognosis patients were included," he said. "In evaluating early clinical studies, it's important that we understand the population that is being investigated."

The study findings will also be used by the International Neuroblastoma Risk Group, which is nearing completion of standardized international criteria for eligibility and response for phase II studies in neuroblastoma, he said.

In multivariable analysis, factors at diagnosis that were independently predictive of overall survival post relapse were stage 4 (hazard ratio, 6.9); stage 3 (HR, 4.3); stage 4S (HR, 3.5); MYCN amplification (HR, 2.4); age less than 18 months (HR, 1.6); and time to relapse less than 12 months (HR, 2.0)—all with a *P* value less than .0001, Dr. London said.

Time to relapse was predictive of survival post relapse in patients with stage 1, stage 2, or no MYCN amplification, but it was not independently predictive, she added.

The study was supported by the Little Heroes Pediatric Cancer Research Foundation, the Forbeck Foundation, and a grant from the National Institutes of Health. Dr. London and her associates reported no conflicts of interest. ■

MY TAKE

Given the unique biology of neuroblastoma and the extreme clinical heterogeneity that impacts its natural history despite therapy and initial response to therapy, this finding will be important as new agents become available for investigation in this disease and especially when nontraditional end points such as time to progression and progression-free survival are considered.

In addition, refining and enriching patient populations for some degree of biological homogeneity is important, not only for the purpose of accurately defining activity of a specific investigational agent in this specific disease, but also for potentially identifying a group of patients with relapsed disease who may be candidates for more conventional or standard salvage therapy approaches. This will also aid in defining eligibility criteria and estimating accrual requirements for investigational approaches.

GREGORY H. REAMAN, M.D., *is chair of the US-based Children's Oncology Group. He is also a professor of pediatrics at George Washington University School of Medicine and Health and member of the Division of Hematology-Oncology at the Children's National Medical Center, both in Washington, D.C.*

FROM THE LANCET NEUROLOGY

Limbic Encephalitis Autoantibodies Might Target LGI1

Recent findings in patients with limbic encephalitis and antibodies against voltage-gated potassium channels indicate that the target of autoantibodies is not the VGKC but the synaptic protein leucine-rich, glioma-inactivated 1.

In a report on the study, the researchers suggest new diagnostic tests and the reclassification of the disorder as an autoimmune synaptic encephalopathy. The findings could also change understanding of related disorders and major neurological disorders that share similar symptoms (Lancet Neurol. 2010 June [doi:10.1016/S1474-4422(10)70137-X]).

Autoimmune synaptic encephalopathies are disorders in which patients develop antibodies against synaptic proteins. Autoantibodies against voltage-gated potassium channels (VGKC) have been implicated in limbic encephalitis and disorders involving neuromyotonia, including Morvan's syndrome. However, Dr. Josep Dalmau of the University of Pennsylvania, Philadelphia, USA, and his American and Spanish collaborators failed to find reactivity of patient samples exposed to cells expressing VGKC subunits. Using previously established methods to identify autoimmune synaptic encephalopathies, the team set out to identify the true autoantigen of limbic encephalitis with VGKC antibodies and related disorders.

Dr. Dalmau and his colleagues analyzed the serum and cerebrospinal fluid (CSF) of 57 patients with limbic encephalitis and antibodies attributed to VGKC, and 148 patients with other disorders with or without VGKC antibodies. To the researchers' surprise, they precipitated leucine-rich, glioma-inactivated 1 (LGI1), a secreted protein known in epileptic disorders, as the target of the autoantibodies. All of the serum or CSF from patients with limbic encephalitis and VGKC antibodies, but not from controls, recognized LGI1. Because LGI1 interacts with presynaptic ADAM23 and postsynaptic ADAM22 proteins, the investigators used an assay with HEK293 cells transfected with LGI1 and ADAM22 or ADAM23 to show that cotransfection improved antibody visualization. Furthermore, immunoabsorption with LGI1-expressing cells abrogated reactivity of patient samples, which also failed to react to brains of LGI1-null but not wild-type mice. The serum of a patient with encephalitis, seizures, and positive 125I-alpha-dendrotoxin radioimmunoassay (specific for the putative VGKC antibodies) precipitated another protein, contactin-associated protein 2 (CASPR2), expressed in the peripheral nerves and hippocampus.

The findings indicated reliable immunological tests to confirm the diagnosis in limbic encephalitis, said the authors, who speculated that "antibody-mediated disruption of LGI1 function causes increased excitability resulting in seizures and other symptoms of limbic encephalopathy." Moreover, a change in diagnostic classification is required, with the term "limbic encephalitis associated with VGKC antibodies" changed for "limbic encephalitis associated with LGI1 antibodies." The researchers proposed including limbic encephalitis among the autoimmune synaptic encephalopathies.

In an interview, Dr. Dalmau noted that the existence of a disorder related to VGKC autoantibodies still has to be demonstrated, because different autoantigens might be found in other disorders included in this current classification.

"The reason all these patients have a positive 125I-alpha-dendrotoxin radioimmunoassay is because LGI1 and CASPR2 form part of different protein complexes that include VGKC, although the latter are not the real target autoantigens. Therefore, different clinical phenotypes that were difficult to explain as a result of a single immune response against VGKC are now explained by the identification of antibodies against two different molecular targets," he said.

The study was supported in part by grants from the US-based National Institutes of Health and National Cancer Institute and Germany's Euroimmun. Dr. Dalmau disclosed that he has filed a patent application for the use of LGI1 antibody determination in patients' sera and CSF as a dignostic test. None of the other authors reported any conflicts of interest related to the study.

—Kelly Morris, M.D.

Dr. Morris is a freelance writer for The Lancet Neurology.

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BOOK REVIEW

A Range of Viewpoints Lends New Perspective

History of Neurology: Handbook of Clinical Neurology
(Series editors: Aminoff, Boller, and Swaab), Vol. 95. Edited by Stanley Finger, Francois Boller, and Kenneth L. Tyler.

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

Some years ago, a paper was published on the history of the *Handbook of Clinical Neurology* (J. Hist. Neurosci.2008;17:46-55) describing its roots in the Centralblätter (published in German before World War II) and Excerpta Medica (published in English after the war), which were abstract services for physicians written to make medical literature more accessible.

The founding editors of the *Handbook of Clinical Neurology* (HCN), Pierre J. Vinken and George W. Bruyn, worked for Excerpta Medica, where Vinken subsequently became director. They thought about starting the HCN in the 1960s, based on their experience at Exerpta Medica and inspired by another prewar German publication, *Handbuch der Neurologie* (1935-1937, 17 volumes, edited by Bumke and Foerster), for which there was no English counterpart.

Between 1964, when the project started, and 2002, Vinken and Bruyn produced a comprehensive overview of neurology in 1,909 chapters (46,000 pages in 78 volumes) with contributions from 28 volume editors, a temporary third editor, the neurologist Harold Klawans, and almost 2,800 authors. The original edition (1968-1982) is considered to be of important historical value.

Perhaps this history of the HCN is one of the few omissions of the present volume (No. 95), which is entirely devoted to the history of neurology. It is a substantial book (952 pages), edited by psychologist and neurohistorian Stanley Finger, and two neurologists with experience in writing neurohistory, Francois Boller and Kenneth Tyler. As the editors admit in the preface, they are "aware that some topics are missing."

However, their choice of structure has resulted in a fairly comprehensive overview of the history of neurology by starting from several viewpoints, for example, a chronological, a regional, and a nosological perspective. The chronological perspective occupies the first two sections, including nine chapters on the traditional period to about 1900, followed by the "Origins of Modern Neurology" on the evolution of neurology in the 19th century, with chapters on localization, experimentation, neuroanatomy, and neurophysiology. The nosological perspective is in a fourth section, with chapters on the main neurological diseases. Despite choosing several perspectives, the editors have carefully avoided the risk of overlap.

IT'S USEFUL TO KNOW ABOUT THE HISTORY OF MEDICINE AS IT HELPS 'KEEP US HUMBLE AND KEEP IN PERSPECTIVE OUR OWN EFFORTS.'

How does this volume compare with standard books on the history of neurology and neuroscience, such as Lawrence C. McHenry's *Garrison's History of Neurology* (1969) and Finger's *Origins of Neuroscience* (1994)?

Besides containing more information and being a multiauthored work (by 60 experienced contributors), almost all topics are dealt with more extensively. Moreover, several new topics are found—for example, in chapters on "Visual Images and Neurological Illustration," and "Neurological Illustrations: From Photography to Cinematography," starting with the daguerreotypes, illustrations from Guillaume Duchenne's *Physionomie*, images from Albert Londe's (Jean-Martin Charcot's medical photographer) studio at the Salpêtrière hospital in Paris and Eadweard Muybridge's photographic works on motion, and the rise of cinematography (a popular subject in recent literature and presentations).

There are chapters on special hospitals, child neurology, and neurodisability, and an excellent, well referenced chapter on movement disorders. As the perspective of "Regional Landmarks" was chosen for a separate 13-chapter section, information on parts of the world that have been rarely dealt with elsewhere is now more readily available. This section includes chapters on Chinese, Japanese, South American, and tropical neurology. But a few important references are missing, such as the rich contents of Bruyn and Charles Poser's *History of Tropical Neurology* and Alla Vein's edited work on Russian neuroscience (J. Hist. Neurosci. 2007;16[1-2]:42-57).

What do we miss? I miss a chapter on the evolution of neurology between psychiatry and internal medicine and a chapter or introduction on the term neurology and its evolution. The section on "Regional Landmarks" would have been enriched by a chapter on Spanish and Portuguese neurology, with a more extensive discussion of the work of Spaniard Ramón y Cajal (which receives scant attention in the chapter "The Anatomical Foundations") and that of Portugal's Egas Moniz (touched on in a short section on lobotomy in "Frontal Lobes"). And Polish neurology deserved more space than the few sentences in the chapter on Russian neurology. Finally, a chapter on synthesis would have enhanced one's understanding of the history of neurology, but that would not be an easy job. A few chapters, such as the one on frontal lobes, now and then cross the boundary of past and present too much.

The publication of this volume among the many others on clinical neurology marks the importance of the history of neurology, as is well described in the foreword: "It is interesting to see … how the small steps achieved by so many clinicians and scientists throughout the centuries have enabled a few to make the giant leaps forward." It is useful to have some knowledge of the history of medicine, the editors write, not in the least as "it helps to keep us humble and keep in perspective our own efforts, as well as the 'breakthroughs' that reach us daily via the media." This interest in the history of neurology has been acknowledged by the World Federation of Neurology since the early 1980s by an active History of the Neurosciences Research Group, now chaired by George York.

The editors of the current work have succeeded in carefully assembling a wealth of information. It may be used for teaching and enjoying, but also as a starting point for further study into the rich history of our specialty. ■

Dr. Koehler and Dr. Finger are coeditors of the Journal of the History of the Neurosciences.

TALK BACK

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LETTERS TO THE EDITOR

Child Neurology and the WFN

Thank you for highlighting child neurology ("Crisis in the Child Neurology Workforce," June 2010, p. 14). It is time we acknowledge that neurology is one field of care and research. Yes, some of us are concerned with the neurological health of infants and children, with the majority of neurologists focusing on the rest of the life span. But many diseases, such as stroke, can occur at any time, from intrauterine life to old age. Epilepsy is a disorder of all ages. Degenerative diseases of the senium start in youth. Neurologists for adults and children use similar tools and think about neurological diagnosis in similar ways.

As to the crisis in the child neurology workforce, there are several issues. Length of training and lower earning potential compared with other medical specialties might be part of it, but most child neurologists love what they do—witness more than a few of us who cannot bear to retire. There is no shortage of child neurologists in and around major cities in the United States—as opposed to rural areas and inner-city neighborhoods—but two issues contribute to their overly long waiting lists, excluding the few practitioners who do unnecessary tests and overschedule return visits.

The first is that residents in general practice and pediatrics often receive inadequate training in neurology, even though they will see many neurological conditions in their practices. Many don't know how to do a quick neurological assessment and interpret neurological findings, and they perceive neurology as "too complicated" precisely because they have not been taught the basics.

The second issue is that the Internet has created the impression that developmental problems are brain problems, which they are of course. Often, children are sent to neurologists, even though the treatment of choice more often should be specialized education rather than medication. Further, few graduates in child neurology have received sophisticated training in cognitive-developmental neurology. Borderline referrals end up inflating many child neurologists' waiting lists, while children with more serious neurological problems might be relegated to waiting along with these borderline referrals.

In resource-poor countries, the issue is not distribution and type of referral, but the virtual absence of child neurologists.

The International Child Neurology Association organizes collaborative open topical educational symposia in those regions and supports short visits by professors of child neurology to countries that invite them for hands-on teaching (and learning). ICNA, the Child Neurology Society, the American Academy of Neurology, the American Neurological Association, and other subspecialty neurological societies invite a few trainees, young practitioners, or faculty members to their annual meetings. Occasionally, programs in developed countries will support a trainee for a few months or longer. Sometimes, countries that lack neurologists recognize the need to have

Continued on following page

OBITUARIES

Fred Plum (1924-2010)

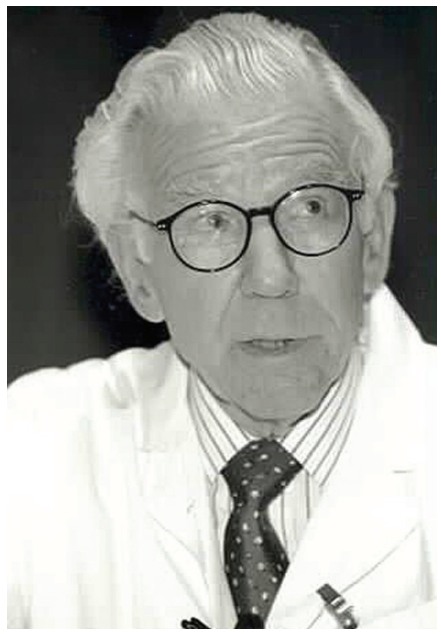
BY JEROME B. POSNER, M.D.

The world of neurology lost a giant when Dr. Fred Plum died on June 11, 2010. Before his death, he was incapacitated for several years by primary progressive aphasia, an illness that robbed him first of his most striking asset, his language and way with words, and then ultimately, his finely organized and incisive mind.

Nevertheless, although unable to work, he remained in the memories of all of those who knew him and of many who had only heard of him. Fred Plum stories still abound, one of which was published as an article by Dr. Robert Daroff in the August 2009 issue of WORLD NEUROLOGY (p. 12).

Dr. Plum was born and raised in Atlantic City, N.J., USA. He matriculated first at Dartmouth (N.H.) College and then at Dartmouth Medical School, which was a 2-year medical school at that time. He graduated from Cornell Medical College in New York, in 1947, after which he served as an intern and resident in medicine and neurology under the direction of Dr. Harold Wolff until 1951. That was followed by a 2-year stint at the US Naval Hospital in St. Albans, N.Y.

In 1953, Dr. Plum was selected by Dr. Robert Williams, who was then chairman of the department of medicine at the University of Washington in Seattle, USA, to head up the department's neurology section, even though he had never held an academic position. He was one of a series of young section chiefs, almost all of whom achieved international recognition over time. Dr. Plum's interest in poliomyelitis led to his forming a respiratory center at Harborview Medical Center in Seattle, where chronic polio patients were taken for treatment.



COURTESY DR. JEROME B. POSNER

Dr. Plum was a pivotal in the study of consciousness.

Because of Dr. Plum's skills in artificial respiration and the use at that time of barbiturates as a preferred method of attempted suicide, Harborview would admit first all comatose and subsequently all encephalopathic patients to the neurology unit. Emergency imaging was not available at the time, so a rapid and correct clinical diagnosis of stuporous or comatose patients was essential for their survival. Together with Dr. Don McNealy, one of his residents, he published a seminal paper on brainstem dysfunction with supratentorial mass lesions (Arch. Neurol. 1962;7:10-32). It was that work that eventually led to the publication of the first edition of *The Diagnosis of Stupor and Coma* (Plum & Posner, 1966).

In 1963, after the death of Dr. Wolff, Dr. Plum assumed the position of chairman of the department of neurology at Cornell Medical College. The department eventually became the department of neurology and neuroscience.

At Cornell, he continued his work on consciousness and coma and expanded it to include studies of brain metabolism. He is known for coining the term "locked-in syndrome," and, with the Scottish neurosurgeon Bryan Jennett, the term "persistent vegetative state." With David E. Levy, Ph.D., and others, he published important papers on prognosis in nontraumatic coma.

Over the course of his career, Dr. Plum published more than 300 original research report reviews and trained several residents who subsequently went on to become chairs of departments. He served as chief editor of the *Archives of Neurology* from 1972 to 1976 and founding editor of *The Annals of Neurology*, which was first published in 1977. He served as president for research in the Association for Research in Nervous and Mental Disease, and was a member of the Institute of Medicine and the American Academy of Arts and Sciences.

Dr. Plum was one of the leaders of world neurology in his time. However, what made him a true giant was his bedside teaching. His rounds were electrifying as well as educational. It was a rare patient presented to him for whom he could not add something that the patient's physicians had not thought of.

On rounds, he could be very tough with the house staff. His critiques could be withering, and perhaps at times less than fair. But he also accepted criticism and challenges graciously. Once, when challenged by a young medical student who was able to prove his point, Dr. Plum backed down and happily related the story to several of us, giving the medical student, as he often did with others, somewhat more credit than he deserved.

The giant is gone; all of neurology will miss him sorely. ■

DR. POSNER *is an attending neurologist Memorial Sloane-Kettering Cancer Center in New York.*

Continued from previous page

their own trainers in child neurology and will support training abroad for a physician who is willing to return after the training and commit long-term to a teaching hospital or medical school in the home country. All of this is better than nothing, but it remains grossly inadequate.

Modest liaisons have been forged between the World Federation of Neurology and ICNA, and even with the World Health Organization. But these are essentially invisible to the grassroots child neurologist, and, I believe, barely visible to the executive of the WFN.

Child neurologists are few and would profit greatly in their global educational efforts from overt coordination with those of the WFN to promote better neurological care worldwide. Child neurology needs to be integrated into the Federation as a matter of course; child neurologists should be eligible to serve on its active committees and to participate in its governance. Now is the time!

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Melvin Greer (1929-2010)

BY KENNETH M. HEILMAN, M.D.

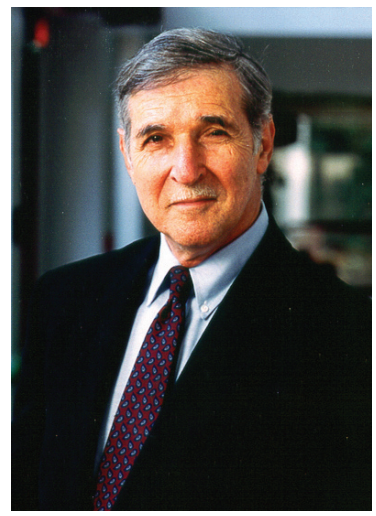
Dr. Melvin Greer, the first chairman of the department of neurology at the University of Florida and a former president of the American Academy of Neurology, died of heart failure on May 19, 2010, in Gainesville, Fla., USA.

He was born in 1929 in New York, where he attended public schools in the city's borough of Brooklyn before graduating from New York University in 1950 and from its medical school in 1954. Dr. Greer took his pediatric residency at the university's Bellevue Hospital, and following 2 years with the US Navy as a pediatrician in Guam, he took a neurology residency/fellowship at Columbia Presbyterian Medical Center, also in New York.

In 1961, he joined the faculty at the University of Florida's College of Medicine (UF-COM). Three years later, he was appointed chair of the neurology division, and in 1974, he became chair of the newly created department of neurology, a position he held for 26 years until he stepped down in 2000.

Members of the department called him "Chief," because he was more than an administrator—he led, protected, educated, supported, and enhanced their careers and lives.

Dr. Greer was a master clinician-educator who taught primarily by example and invited excellence. He trained more than 150 residents, as well as thousands of medical students and received multiple teaching awards.



COURTESY ARLINE GREER

Dr. Greer was a devoted clinican and masterful diagnostician.

Although he was a person of few words, he was a kind and empathetic clinician, who was always available, day or night, for the patients who needed him.

He was also a masterful diagnostician. Many of us would toil over a patient's diagnosis, and then, after a brief examination of the patient, he would make a diagnosis. He was almost always right. His research interests focused on the neurochemistry of neurological disorders, intracranial hypertension, and child neurology, and he wrote or cowrote many important papers on those topics.

Dr. Greer also played an important role in promoting and enhancing the speciality both nationally and internationally. He was president of the American Academy of Neurology from 1985 to 1987 and a member of the editorial boards of many publications.

He and his wife Arline had a wonderful marriage of 58 years. They had four children and have 11 grandchildren. He was a powerful and talented athlete. In the last months of his life, although his body weakened, he maintained his inner strength and continued to see patients until 2 weeks before his death.

Mel is physically gone, but his spirit lives in many of us, and his role in enhancing our profession is eternal. ■

DR. HEILMAN *is professor of neurology and health psychology at the University of Florida in Gainesville, USA.*

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