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Costs, Efficacy Are Basis of Delivery Model

BY DAVID CHADWICK, M.D.

The National Institute for Clinical Excellence (NICE) develops clinical guidelines and formulates advice on when and how new drugs and procedures should be used in the National Health Service in England and Wales (but not Scotland and Northern Ireland).

Why should this be of any interest to neurologists practicing outside of the United Kingdom? Because NICE, which marks its first decade this year, is an innovative, transparent model for the application of evidence-based medicine to the provision of health services that is now well recognized and being copied worldwide, so it is or will become relevant to many of you.

COURTESY DR. DAVID CHADWICK

Dr. David Chadwick says the NICE model supports equity.

I am writing this from the perspective of someone who has seen NICE at work as a clinician as well as being a member of one of its appraisal committees. It is important to understand its methods before passing judgment on it.

The institute produces clinical guidelines that are largely uncontroversial. This work is undertaken by guideline development groups that include professional and patient interest groups (stakeholders) that are supported by dedicated information specialists.

The methodology for literature searching is comprehensive. Although systematic reviews and randomized controlled trials have greatest impact on advice, formalized processes for consensus development can be used where there is a lack of such evidence. The guidelines on epilepsy, multiple sclerosis, and Parkinson's disease will be seen as generally helpful by most neurologists, and because of the methodology, they probably represent guidelines as high in quality as any available worldwide.

NICE's technology appraisals of new drugs are undoubtedly the most difficult and controversial, as can be seen from reaction to appraisals of disease-modifying treatments for multiple sclerosis and symptomatic treatments for dementia. Here, methodology involves external academic units either producing a comprehensive review of evidence of clinical and cost-effectiveness of a number of treatments, or doing a critique of evidence submitted by the manufacturer of a single treatment. This work is then considered by a multidisciplinary appraisal committee, which hears expert clinical witnesses and patient representatives before it produces a preliminary appraisal document for review by stakeholders, after which a final appraisal is issued.

The preferred tool to assess effectiveness—quality-adjusted life-years (QALY)—is the EQ5D, which asks questions about mobility, self-care, usual activities, pain, and anxiety and depression. It is a generic tool that allows the comparison of health gains across different therapeutic areas. Its use can be supported, if it is accepted that the perspective for health economic decision making is societal. EQ5D may, obviously, lack sensitivity for neurological disorders such as epilepsy.

In England and Wales, technologies that deliver QALYs of £20,000 or less are likely to be approved. Those with QALYs of £30,000 are unlikely to be approved, although exceptions can be made on the basis of patient or expert input. These thresholds are, of course, immediately open to criticism as being arbitrary in the absence of clarity on the

See **Model** • *page 12*

INSIDE

Patient Age Affects Carotid Intervention Outcomes

BY MITCHEL L. ZOLER

SAN ANTONIO — The largest-ever, head-to-head comparison of stenting versus surgery for treating severe carotid artery stenosis showed a marked effect of age, with patients older than 70 years having fewer adverse outcomes after carotid endarterectomy and patients younger than 70 having fewer complications following carotid angioplasty and stenting.

Although the highly anticipated results from the decade-long Carotid Revascularization Endarterectomy vs. Surgery Trial (CREST) seemed, in simplest terms, to show a dead heat between carotid stenting and surgery (see p. 14), the results reported at the International Stroke Conference actually revealed statistically significant and clinically important differences between the two treatments.

The statistically significant interaction between patient age and outcome will likely play a key role when physicians and patients decide on an intervention.

The results showed another significant difference between carotid surgery and stenting: Surgery led to a 1.2% increased absolute rate in the incidence of periprocedural MIs, whereas stenting produced a 1.8% increase absolute rate of periprocedural strokes, a finding that will make patients and physicians think about which complication they would rather risk.

The patients in CREST answered that question, at least in part, via another outcome measure. Assessment of patient physical and mental quality of life with the 36-item Short Form (SF-36) Health Survey a year after treatment showed that patients who developed new strokes, even "minor" strokes, had statistically significant reductions in their mental and physical well-being compared with baseline, whereas those who developed new MIs

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EDITOR IN CHIEF'S COLUMN

MARK HALLETT, M.D.

Talking About Health Care Delivery and Cost

The goal of neurologists worldwide is to bring the best neurological care to all of our patients and to improve their quality of life. We face different problems in different countries. However, it is always the same basic question: Given the amount of resources available, what are the most useful services to deliver?

In developing countries, resources are low, and the problem is delivering any neurological services at all (see pp. 3 and 10). What are the most important diseases; how can the best therapies be delivered at the lowest cost (see p. 14)? At the most basic level, can we find the patients with epilepsy and at least make phenobarbital available?

In developed countries, there are lots of resources and much health care is delivered. Modern medicine has much to offer, but it can be expensive. We now frequently hear that the cost of health care is too high and that it has to be contained. Why not spend more money making everyone healthier? It is a laudable goal to be able to deliver the best to everyone. But we do not have enough money to pay for this (nor the will to actually do it). Moreover, it is not clear that the most expensive is always the best. It seems to make sense to find the most cost-effective procedures and therapies and deliver the most we can within the resources available. Easier said than done. This requires decision making, and often tough decisions are left undone. Politics appears to make rationing a dirty business.

On page 1, Dr. David Chadwick describes a process of controlling medical care delivery in the United Kingdom, based on a model developed by the National Institute for Clinical Excellence, or NICE. Evidence-based clinical guidelines are developed and efficacy is analyzed on the basis of quality adjusted life-years. There are problems, as he points out, but the system has been in place for a decade and seems to be helping. On the face of it, at least, it seems a good idea, and certainly worth knowing about. We certainly need such solutions to problems of health care delivery, which do seem to be getting progressively more difficult—certainly in the United States. ■

TRAVELLING FELLOW

Much to Learn, Many Contacts to Make

I attended the European Federation of Neurological Societies Congress in Florence, Italy, last year, as a World Federation of Neurology Junior Travelling Fellow.

I learned much from the lectures and courses and came to value the importance of having contact with neurologists from around the world who practice the same specialty under a range of different conditions.

The teaching course on stroke and especially current concepts in stroke rehabilitation was very useful. Stroke incidence is high in Georgia, but we have no stroke unit dedicated to treating these patients. I was grateful to learn about the European stroke guidelines. Also useful were sessions on movement disorders as well as cerebral small-vessel diseases.

BY SOFIA APRIDONIDZE, M.D.

Dr. Apridonidze is in the department of neurology at the State Medical University Clinic, Tbilisi, Georgia.

I presented a poster on a retrospective study of 34 patients with cerebellar infarction. Some received conservative treatment; others, surgical treatment (ventricular drainage or decompressive craniotomy). We compared clinical outcomes of the two treatments at 3 months and found that neurosurgical intervention reduced mortality and improved clinical outcomes in patients with cerebellar infarction deteriorated by occlusive hydrocephalus and/or brainstem compression. ■

WFN Dues For 2010

To maintain affiliation with the World Federation of Neurology, member societies are requested to send payment of their annual dues for 2010 as soon as possible, together with a current membership list of the names and addresses of individual neurologists.

For assistance, please contact Keith Newton or Laura Druce at the WFN Office.

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PERSPECTIVE—ZAMBIA

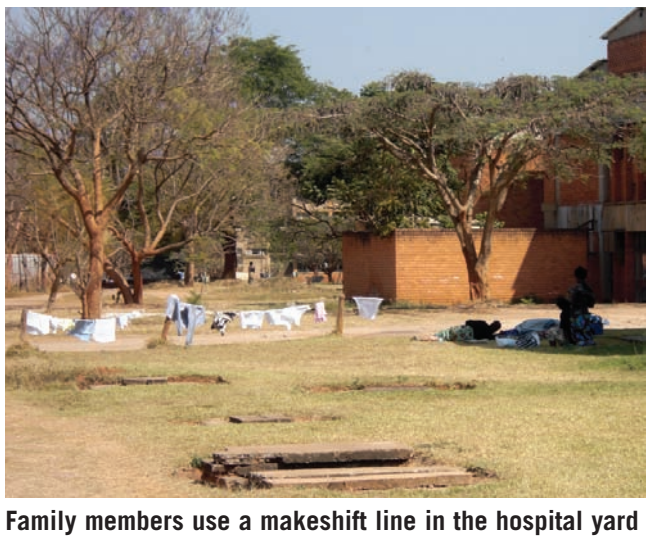
HIV/AIDS Is a Constant Subtext to Daily Rounds

BY WILLIAM H. THEODORE, M.D.

Dr. Theodore is chief of the Clinical Epilepsy Section at the National Institute of Neurological Disorders and Stroke, Bethesda, Md., U.S.A. (theodorw@ninds.nih.gov).

In the summer of 2009, I spent a month at the University of Zambia's teaching hospital in Lusaka as part of the World Federation of Neurology's Visiting Professor Program, co-ordinated by Dr. Gretchen Birbeck of Michigan State University, East Lansing. While I was there, I saw patients in the neurology clinic of the University Teaching Hospital (UTH), gave lectures to house staff, participated in ward rounds, and provided neurology consultation to the general medical service.

Zambia is a developing country in Southern Africa with a population of about 12 million. It is beset by social and economic problems and limited resources for social services. The World Health Organization puts its gross national income per capita at about $1,000 (purchasing power parity), although most people live on $1-$2 per day. Annual per capita health expenditure in 2006 was $62.



Family members use a makeshift line in the hospital yard to dry clothes and bedding for their inpatient relatives.

In particular, HIV/AIDS presents a major health and socioeconomic challenge, with an estimated infection rate of 15%-16% in the adult population. However, the UTH medical house staff estimated informally that 70% of patients admitted to the medical service are HIV positive, as were about 30% of those I saw at the neurology clinic. Even if a patient's illness is not due to HIV, the need for antiretroviral treatment might complicate other therapies because of overlapping toxicity and drug interactions.

Economic factors limit the availability of diagnostic resources and treatment. At present, EEG and EMG are not available at the hospital, and there is no MRI in Zambia. (It is possible, but costly, to go to South Africa or Malawi for MRI.) The hospital has a 1.5-T Philips AURA, single-slice spiral CT scanner, but the scans are interpreted by general radiologists. Moreover, a CT scan costs US$200 at the current exchange rate; plain films can cost US$5-$25.

Some medications, such as bromocriptine, are provided free by the hospital, whereas others, such as sinemet, have to be bought by patients at a cost of US$50-$75 for a month's supply. There are often shortages of other medications, including antibiotics, so that a patient's family might have to try getting them from an outside pharmacy. Supplies such as blood culture bottles are frequently in short supply, and procedures such as bedside spirometry are simply not available.

UTH opened in 1979 and has about 1,600 beds. There is no charge for a basic ward cot, though admission to a slightly better ward costs $10 a day, and mosquito netting is provided. Because of the high patient volume and limited nursing staff, families often provide much valuable hospital care. English is the official language, but in many instances, I needed help from interpreters—often, other patients—because there are about 70 indigenous languages.

Most neurology patients are cared for on the general medical service. There are no neurology trainees at the medical school, where Dr. Masharip Atadzhanov, who is a Moscow-trained professor of neurology, is the only adult neurologist.

The full range of neurological disease is represented at UTH, though the prevalence of HIV/AIDS affects distribution (see p. 12). On a typical clinic day, I might see an elderly woman with a clinical picture of subacute combined degeneration and low vitamin B_{12} levels; a patient with Huntington's disease (Dr. Atadzhanov has found nine cases in Zambia); peripheral neuropathies and chronic inflammatory polyneuropathy in HIV/AIDS patients; others with Parkinson's disease, altered mental status due to a frontal lobe meningioma (possibly complicated by HIV/AIDS), and various presentations of epilepsy and nonepileptic events, hemisensory pain and paresthesias after thalamic infarction, and headaches.

Cases of patients with complications of HIV/AIDS, particularly presumed opportunistic central nervous system infections, are common. However, the aforementioned limited diagnostic resources often preclude reaching a definite diagnosis, and the limited availability of drugs or support services such as intensive care facilities leads to increased mortality.

Inpatients tend to be very sick because they often don't present until they can no longer be cared for at home. In addition, patients might delay seeking medical care and first consult with traditional healers.

Indigenous customs and beliefs present special problems for treating neurological disorders. In Zambia, witchcraft is considered an important cause of epilepsy. Dr. Birbeck's research has shown that people with epilepsy suffer serious stigmatization, which can lead to social ostracism; reduced educational, social, and economic opportunities; and even reduced food aid during periods of dearth. Her program strives to develop evidence-based interventions to reduce epilepsy-associated stigma; lower seizure-related morbidity and mortality; educate policy makers about the burden of epilepsy and cost-effectiveness of treatment; create programs for teachers, clerics, and police officers; present continuing medical education to nonphysician health care workers, who provide much of the health care in Zambia; and facilitate relationships between traditional healers and formal health services.

Patients' relatives, seen here outside UTH, often provide valuable hospital care because of a limited nursing staff.

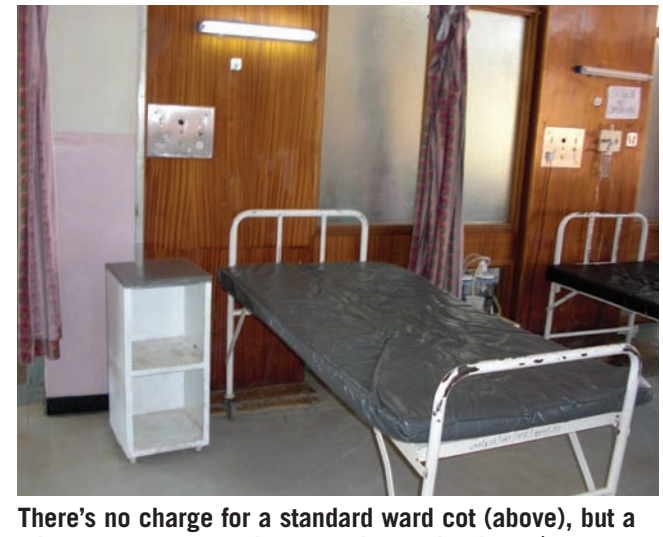
Teaching neurology in a developing country presents a special challenge when one is used to working in an environment rich in technology. However, the UTH house staff were very interested in recent therapeutic and diagnostic developments, and a few of them were better informed about particular areas of interest than I was.

There is an extensive research effort in Zambia devoted mainly to HIV/AIDS and other infectious diseases. Research in developing countries presents special scientific, practical, and ethical problems. Among the scientific challenges are the effects of social structures and the environment on subject participation and data collection and interpretation, and the presence of comorbidities (particularly if HIV/AIDS is not the main subject of a project). Potential pharmacokinetic and pharmacodynamic effects of environmental and genetic diversity could complicate data interpretation. At a practical level, researchers have to work in a research environment with limited infrastructure and facilities and recruit, train, and support local research collaborators.

Ethical issues include disparities in education, economic, and social conditions, and health care systems between developed countries and the study population, which makes "informed consent" difficult. In some cases, financial compensation for research participation might exceed annual wages and access to care outside a trial could be limited or nonexistent. Standards and procedures for research review may be insufficient to assure subject protection.

Despite these obstacles, working in developing countries, in addition to humanitarian imperatives, could have scientific value for developed countries, especially those that are becoming increasingly diverse because of rising immigration. At a personal level, although a month is a very short time, I gained a better sense of the challenges facing neurology in developing countries as well as the opportunities available to contribute to patient care and education. ■

DR. BIRBECK *initiated the visiting professor program in Zambia in 2001. In 2006, it expanded to include the University of Malawi College of Medicine, Blantyre. For more information, e-mail Dr. Birbeck at GretchenBirbeck@ hc.msu.edu.*



PHOTOS COURTESY DR. WILLIAM H. THEODORE

There's no charge for a standard ward cot (above), but a slightly better ward with mosquito netting is US$10 a day.

VIEW FROM BRNO

Seek Out Unity as Specialization Narrows

Neurology is changing: where will it go, and what should we prepare for? Will it prevail and prosper as a unified speciality or will it split into independent subneurologies the way internal medicine split into endocrinology, rheumatology, cardiology, and so on.

In the 19th and early 20th centuries, neurology was defined mainly in terms of its separation from psychiatry and internal medicine. Its boundaries seemed distinct: It comprised all the organic diseases of the nervous system, both central and peripheral, with a few poorly defined interdisciplinary issues, particularly those shared with psychiatry.

Porous Borders

The concept of neurology was based on the prerequisite of functional integrity of the nervous system, with logical projections to some related types of illnesses, such as muscle diseases and headaches. However, the scope of neurology has become less well defined, and as new subspecialties emerge, the question arises whether there is a need for a general neurology, at least at the university level.

This development has been largely due to the emergence of neuroscience. In the last quarter of the 20th century, there were nine Nobel prizes for neuroscience. Of course, basic research does not distinguish between the specialties: there is no such thing as a "neurological brain" or a "psychiatric brain." The borders between neurology and psychiatry, cardiology, immunology, neurosurgery, and so on, have become porous.

Recent developments in neuroscience have been quite revolutionary, not only in the basic research, but also in the various fields, such as cognitive neuroscience, imaging and metabolic techniques, invasive techniques, pharmacology, and, of course, genetics. The time from laboratory to clinic has sometimes been rather fast, as with the deep brain stimulation therapy for Parkinson's disease (PD); at other times, that transition takes longer.

Although neurology remains a contemplative discipline, it is becoming an invasive and sometimes intensive-care medical speciality that includes acute stroke treatment, neuromodulation, neurotransplantation, and other functional neurosurgical techniques, as well as developments such as stem cell and gene therapy and the use of growth factors, vaccines, and nanotechnology.

Redefining the Specialty

Genetics and molecular neurobiology will probably fundamentally change the understanding, diagnosis, and treatment of nervous diseases. The amount of information provided by research has grown to the extent that it is no longer possible for a clinical neurologist to consistently follow the literature covering the whole area of clinical neurology, from cognitive disturbances to the muscle diseases. It is even difficult for one clinician to fully cover one of the many subfields.

Where does this lead us?

Beyond any doubt, the trend is towards narrower specialization. A specialist in peripheral nerves should be interested in neuroimmunology; however, that specialist will probably not master the whole topic of dementia. Neuroradiology left neurology in favor of radiology; neurorehabilitation is no longer considered a part of neurology in many countries.

BY IVAN REKTOR, M.D.
Dr. Rektor is head of the First Department of Neurology and vice-rector of Masaryk University, Brno, Czech Republic and president of the European Society for Clinical Neuropharmacology (irektor@med.muni.cz).

Will neurology lose more subspecialties? I do have not a definite answer, but let me share with you the Brno experience.

Brno is the second-largest city in the Czech Republic, and Masaryk University Medical Faculty is among the largest medical schools in the country, with two departments of neurology as well as a department for child neurology.

United as Neurologists

In the 1990s, the newly appointed heads of the two adult neurology departments decided to focus their respective departments. One department, under Prof. Zdenek Kadanka and his successor, Prof. Josef Bednarik, who both have EMG backgrounds, became more peripheral-nerve and spine oriented; the other, which focused on the functions and diseases of the brain, was led by me (my own background is in EEG and CNS neurophysiology).

In both departments, clinical neurology has been performed in all aspects as needed for patient treatment and educational purposes, but the focus of our research and most sophisticated methods were developed according to this division.

Based on my own interests and experience, I started by creating two centers, one for epilepsy and another for movement disorders. They are currently in many aspects the strongest centers in the country, for example, in the number of epilepsy surgeries and deep brain stimulation procedures performed in close cooperation with neurosurgeons, neuroradiologists, and so on. The movement disorder center gradually extended into a new cognitive neurology center; the epilepsy center expanded into an advanced MR unit; clinical need led to the development of invasive techniques in the stroke center and the creation of a multiple sclerosis center; the clinical neuropsychology unit became indispensable for the whole department.

This is all unexceptional: Similar developments have occurred in other departments. For the purpose of this article, however, it might be of interest to note that we maintained a sense of unity as "neurologists," despite the subspecializations among the staff. We all meet every morning for at least a few minutes to discuss difficult cases and share our experiences, all the while keeping in mind the conceptual unity of neurology.

Our awareness and knowledge of our common background means we can share research and clinical interests that overlap the various subspecialties.

For example, in addition to research in epilepsy and movement disorders, we are interested in the role of the basal ganglia in epilepsy and in the occurrence of dystonia in epileptic seizures. In the course of stroke and PD research, we have been interested in the role of vascular impairment in parkinsonian syndromes, including PD. We use similar or identical protocols for studying cognitive or motor physiology in epilepsy surgery candidates via intracerebral electrodes implanted mostly in the cortex as we do for movement disorders patients implanted in subcortical structures within the DBS programs.

The advanced MR techniques, as well as transcranial magnetic stimulation, neuropsychology, and electrophysiology, are used by various teams in mutual cooperation under ongoing discussions, which enrich the experience of the individual teams with a critical but friendly consideration of each research topic from the aspect of the other teams. The research reflects the clinical practice in the department where the experts meet and discuss difficult patients with diagnostic and therapeutic problems reaching beyond the boundaries of individual subspecialities.

Although there will be narrow specializations, there still will be a need for broadly educated neurologists on all levels, from the front line and back to university departments. These general neurologists will provide treatment covering the gamut of neurological topics in close co-operation with subspecialized neurologists.

Be Flexible—and Prepared

At the same time, the subspecialists should keep in mind the shared background of various neurology branches. The demand for education will certainly grow dramatically. Both pre- and postgraduate education in neurology will be more demanding and comprise a deeper knowledge of the core subject as well as its borders, in particular, with internal medicine and psychiatry.

We have to be flexible in our response to the results of science and remember that our priority is the best achievable care for our patients. We must prepare for the forthcoming changes. ■

New Group Is a Global Platform for Young Neurologists

BY WALTER STRUHAL, M.D., KATE AHMAD, M.D., JASON BURTON, M.D., CHRISTIAN FALUP-PECURARIU, M.D., RUFUS AKINYEMI, MBBS, FAUSTIN YEPNJIO, M.D., SURAT TANPRAWATE, M.D.

The International Working Group of Young Neurologists and Trainees held its inaugural meeting at the World Congress of Neurology in Bangkok last year.

The new platform was established to advocate for young neurologists within the Federation.

At each WCN since the London congress in 2001, members of the European Association of Young Neurologists and Trainees (EAYNT) have organized meetings for young neurologists, covering topics of common interest such as career development and promoting contact between delegates from different countries.

The EAYNT is an independent, nonprofit association based in Brussels that represents young neurologists in Europe. It was founded in 1999 and since then, its membership has grown and it is now an established partner to European organizations such as the European Federation of Neurological Societies, the European Neurological Society, and the European Union of Medical Specialties/European Board of Neurology.

However, within the EAYNT we felt that it would be more appropriate to form a new, worldwide representation of young neurologists that would consist of delegates from all the continents and regions already represented in the WFN.

Our plan was well received by the federation's officers, especially from the President, Dr. Vladimir Hachinski, and trustee, Dr. Wolfgang Grisold. Since there was no allowance within the existing WFN framework for the type of structure we were proposing, we were advised to form an external, international entity for young neurologists, with the long-term goal of being incorporated into the WFN.

And so the International Working Group of Young Neurologists and Trainees (IWGYNT) was born. The WFN invited IWGYNT to send one delegate to the committee, and Dr. Walter Struhal was elected in that capacity.

The first organization after the EAYNT to join the new body was the Australian and New Zealand Association of Neurologists (ANZAN).

The two groups compiled the bylaws for the IWGYNT, which include that:

► Organizations representing young neurologists from a given continent have the right to send two delegates each to represent that continent to the IWGYNT;

► One chair is elected within the international working group;

► The chair will hold the position for 4 years; and

► Delegates should be aged under 40 years or be in residency or subspecialty training.

Currently Africa, Asia, the Australia–New Zealand region, and Europe are represented in the IWGYNT.

To increase networking in this community, we will organize meetings and social activities at future WCNs. In addition, the Web offers a range of online possibilities for global networking and document exchange.

To that end, we are currently developing an online presence and we are already on Facebook. We also plan to have a Web site, which we hope will reside on the WFN site, and to keep our members current with developments in the specialty.

Finally, to support international exchange and collaboration between our members, the IWGYNT will also collect information on exchange programs, grants, and opportunities for working or studying abroad and post it online. ■

DR. AHMAD *and* DR. BURTON *are delegates for ANZAN; Dr. Falup-Pecurariu and Dr. Struhal, for EAYNT; Dr. Tanprawate, for the Asian Neurological Society; and Dr. Yepnjio and Dr. Akinyemi , for the Pan African Association of Neurological Sciences.*

For more information, visit www.facebook.com/pages/IWGYNT/351778649052 or e-mail Dr. Struhal at walter.struhal@akh.linz.at or iwgynt@aesculapian.net.

CLINICAL REPORT—RABIES

Immune Responses Might Guide Therapeutic Strategy

Researchers are probing the nature and types of infection, disease progression, and new therapies.

BY THIRAVAT HEMACHUDHA, M.D., HENRY WILDE, M.D. AND SUPAPORN WACHARAPLUESADEE, PH.D.

We do not yet fully understand the complete mechanism that would explain why patients who develop symptoms of rabies are doomed (Curr. Neurol. Neurosci. Rep. 2006; 6:460-8; *Principles of Neurological Infectious Diseases*, edited by K. Roos, McGraw-Hill, New York, 2005, pp.151-74). Even patients who have received state-of-the-art rabies postexposure prophylaxis succumb to rabies (Clin. Infect. Dis. 2010;50:77-9).

Data derived from magnetic resonance imaging (MRI) of the brains of several patients and from brain biopsies have shown that the virus reaches the brain before symptoms actually develop (Lancet Neurol. 2002;1:101-9). These abnormalities on MRI were evident at a time when rabies patients had no brain symptoms, only pain at the bite sites (http://pier.acponline.org/physicians/diseases/d267/d267.html [accessible by password only for members of the American College of Physicians]).

Furthermore, electrophysiological studies have confirmed the presence of abnormalities of cells in the spinal cord, even though patients with furious rabies had no demonstrable weakness (Curr. Neurol. Neurosci. Rep. 2006;6:460-8).

Bat vs. Dog Rabies Virus

Novel strategies using coma-induction therapy to counteract excitotoxic mechanisms are said to have saved one human life—though that result was not reproducible in at least 16 other patients, including 1 in Thailand (Trans. R. Soc. Trop. Med. Hyg. 2008;102:979-82; J. Neurovirol. 2006;12:407-9). The cases of two complete rabies survivors in the United States (including the coma-therapy patient) were associated with bat rabies virus, and both patients developed rabies antibody in the cerebrospinal fluid (CSF) and blood early in the course of their disease. However, no virus could be recovered from these patients' tissue or biological fluid specimens.

In the most recent rabies case in the United States—also associated with bat variant—the patient recovered without receiving any specific treatment and did not receive any intensive care (MMWR 2010;59:185-90).

Researchers have found that rabies virus from bats elicited more immune response in infected humans than was the case with rabies virus from dogs (http://pier.acponline.org/physicians/diseases/d267/d267.html In: PIER [online database]. Philadelphia, American college of Physicians, 2009).

Comfort care is still recommended as the mainstay of treatment in human rabies patients until more scientific knowledge and effective drugs become available. Intensive care support is recommended only in noncomatose rabies patients, and in particular, in those associated with bat virus and who have rabies antibody in the blood and spinal fluid on admission despite having no history of prior vaccination (PIER online database).

Distinguishing Furious and Paralytic

Rabies in humans manifests as a furious or paralytic form; the former patients succumb rapidly within 5-6 days without intensive care support, the latter succumb within 11-12 days. The weakness in paralytic rabies is caused by abnormalities in peripheral nerves (J. Neurovirol. 2005;11:93-100). Studies in dogs that had been naturally infected with rabies revealed much higher viral loads in the brains of furious dogs than in paralytic dogs. Conversely, a higher local immune response was found in the brains of paralytic dogs than in those of furious dogs, which might explain why paralytic dogs survive longer (J. Neurovirol. 2008;14:119-29).

In addition, brain MRIs showed distinct abnormalities in the specific parts of the brain mostly responsible for classic rabies symptoms, that is, they were greater in the hypothalamus, hippocampus, and brainstem. However, the MRI disturbances were more prominent in the brains of paralytic dogs than they were in the brains of furious dogs (J. Neurovirol. 2008;14:119-29). These differences also correlated with the extent of the brain immune response, which was greater in paralytic dogs. There is also no evidence that the barrier between blood vessels and the brain is compromised during the early stage of the disease, which might explain why immune defenses, if they develop, cannot gain access into virus-infected brain cells.

An intra vitam diagnosis of rabies can be made by detecting viral RNA in a patient's saliva, extracted hair follicles, or biopsied skin at the nape of the neck (including hair follicles), urine, and spinal fluid. However, these samples from different sources should be examined simultaneously because of the intermittent shedding of virus (Expert Rev. Mol. Diagn. 2010 [in press]).

Tapping In to Nerve Fiber Integrity

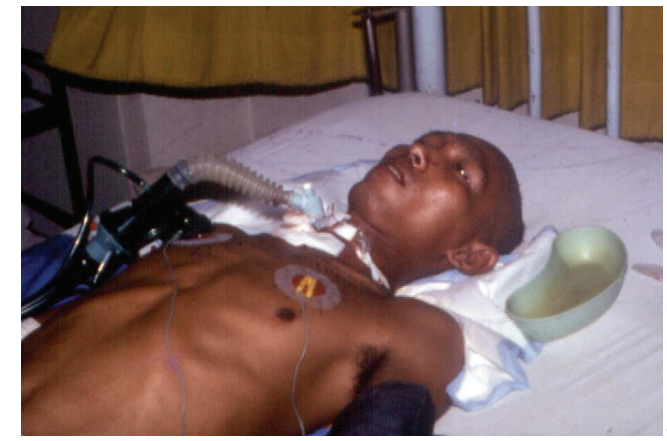
Although brain MRI has proved useful in diagnosing rabies and differentiating it from some other brain infections, abnormal signals are not very prominent. To overcome this, Laothamatas, Sungkarat, and Hemachudha reported in an unpublished study how they applied a special technique to examine the nerve fiber tract integrity and the status of water diffusion along the tract in various regions of the brains of rabies-infected dogs. Because there was a high degree of distortion and variability in the dog brains (as is commonly found in elderly people and in patients with Alzheimer's disease), the researchers first created whole brain probabilistic tractography maps of normal dogs as a template. This was then compared with maps from rabies-infected dogs.

The researchers found that tract integrity was compromised especially at the brainstem area adjoining the spinal cord and in the brain of paralytic dogs. This also confirmed the absence of water leakage through the blood vessel into the brain substance. Such impaired tract integrity at the brainstem suggests that it may be one of the mechanisms that retard the dissemination of virus throughout the whole nervous structure, particularly in the paralytic form of the disease.

Immune Response

These research techniques are promising and might be applicable in diagnosing brain diseases other than rabies in humans. Studies of the proteins (called proteomic profiling) in rabies-infected dog brains confirmed a poor immune response, although trace amounts of immune effectors could be detected. A unique cell death process, called autophagy, might also be associated with rabies pathogenicity, according to an unpublished study by Thongboonkerd and his colleagues. As for therapeutics, they employed a technique using microRNAs, which are small RNA molecules that can inhibit viral synthesis of proteins and ultimately multiplication (Antiviral Res. 2009;84:76-83). The use of this strategy has shown that microRNAs, which are designed to interact with multiple targets of a rabies viral gene at the same time, were effective as a potential therapeutic. The researchers noted that further study in experimental animals is underway.

In a paper presented in October 2009 at a World Health Organization (WHO) meeting of rabies experts in Annecy, France, researchers reported on findings from a preliminary study suggesting that it is highly likely that rabies postexposure prophylaxis (PEP) can be completed within 1 week instead of using the 1-month vaccine course that is now recommended (Clin. Infect. Dis. 2010;50:77-9). PEP consists of rabies vaccine and rabies immunoglobulin. The latter is injected in and around the wound where the infection is concentrated so that it can kill the virus at the wound site before it can enter peripheral nerves where it might not be accessible to the circulating antibodies and immune effectors that originate from the vaccine series.



COURTESY DR. THIRAVAT HEMACHUDHA

In paralytic rabies, the motor weakness of the arms, legs, and respiratory muscles resembles Guillain-Barré syndrome.

Exploring an Intradermal Regimen

This new intradermal (ID) regimen consists of three different visits—on days 0, 3, 7—at which patients received four ID injections at four different lymphatic drainage sites each time. The regimen resulted in higher initial antibody titers that lasted for the same duration as seen in previous WHO-approved PEP regimens. It is now undergoing further studies and appears extremely promising (Clin. Infect. Dis. 2010;50:56-60; Asian Biomedicine 2009;3:751-4).

The US Centers for Disease Control recently also introduced a reduced-visit new PEP schedule. It requires one intramuscular (IM) injection on days 0, 3, 7, and 14, omitting a fifth injection on day 28 or 30 and eliminating an additional clinic visit on day 28 or 30. This reduction in the number of visits for both the ID and IM regimens has been shown to be as immunogenic as the traditional methods and are more convenient for patients and may help avoid noncompliance (Asian Biomedicine 2009;3:751-4). Both of these reduced dose/visit regimens should soon be approved and announced by the WHO.

Another development in rabies vaccination, also to be announced by the WHO, is the use of a new and effective booster regimen in which four ID doses of 0.1 mL each of any WHO-recognized tissue culture rabies vaccine are injected at four different sites during one session. This could replace the conventional one injection (IM or ID) on days 0 and 3. Boosters are currently recommended for re-exposed previously vaccinated subjects (Asian Biomedicine 2009;3:751-4). ■

DR. HEMACHUDHA, DR. WILDE, *and* DR. WACHARAPLUESADEE *are staff members at Chulalongkorn University Hospital, Bangkok, Thailand. Dr. Hemachudha presented the Bharucha Oration at the World Congress of Neurology in October 2009, also in Bangkok.*

BOOK REVIEW

History of Epilepsy League Is a Valuable Resource

International League Against Epilepsy, 1909-2009: A Centenary History

Simon Shorvon, Giselle Weiss, Giuliano Avanzini, Jerome Engel, Jr., Harry Meinardi, Solomon Moshe, Edward Reynolds, Peter Wolf

(Chichester, U.K.: Wiley-Blackwell, 2009)

This well-researched historical work reviews the first century of the International League Against Epilepsy. Among its numerous highlights is an account of the league's history, based on the authors' meticulous original research into the political dynamics of its formation and evolution, and their comprehensive account of the history of the disease during that time.

Another highlight is their attention to the origins of the league's journal, *Epilepsia*, which was published sporadically, during 1909-1915, 1937-1950, and 1952-1955, until the fourth series began in 1959 and has continued to the present.

BY ORRIN DEVINSKY, M.D.

Dr. Devinsky is a professor of neurology, neurosurgery, and psychiatry at the New York University Langone School of Medicine. He directs the NYU Epilepsy Center and the Saint Barnabas Institute of Neurology and Neurosurgery (od4@nyu.edu).

The nine-chapter book is generously illustrated with photographs of many of epilepsy's medical and scientific leaders during the past century, and includes detailed accounts of the classification of the epilepsies and the league's relationships with lay organizations, as well as others dedicated to specific ILAE meetings, commissions, and task forces.

It is also an important scholarly contribution to the history of epilepsy. Some chapters, such as those on the disease's early history, its classifications, and *Epilepsia*, are easy to read and provide informative as well as fascinating details and insights. Many of the other chapters and the six appendices are more likely to be references.

For those who love the history of epilepsy, this book should be added to your shelf. It uncovers new facts and untangles details about people and relationships that greatly influenced academic epileptology.

The great standard for any volume on the history of epilepsy is Owsei Temkin's *The Falling Sickness: A History of Epilepsy From the Greeks to the Beginnings of Modern Neurology* (Softshell Books; 1945, 1971), which begins in antiquity and ends shortly before this ILAE volume starts with the English neurologist, John Hughlings Jackson.

In contrast to Temkin's history, the current work on the ILAE's first centuary focuses on an organization and tells the story of epilepsy through that lens. It is not a history of epilepsy during that period, but a history of the ILAE.

Yet the inclusion of so many leaders in the subspecialty in this organization, as well as the ILAE's central role in *Epilepsia* and academic epilepsy, makes this volume an invaluable resource for understanding the advancement of epileptology in the past century. ■

Correction

The headline for a comment by Dr. Danielle M. Andrade accompanying the article, "Implant Short-Circuits Some Epileptic Seizures" (WORLD NEUROLOGY, February 2010, p. 1) should have read "Improvement Offsets Risks."

Calendar of International Events

2010

International Congress of Child Neurology
May 2-7
Cairo, Egypt
www.icnc2010.com

Association of British Neurologists Annual Meeting
May 11-14
Bournemouth, England
www.theabn.org

Second International Conference "Advances in Clinical Neuroimmunology"
May 31–June 1
Gdańsk, Poland
www.bokiz.pl/neuroim2010

15th Annual Meeting of the International Society for the History of the Neurosciences
June 15-19
Paris
www.ishn.org

20th Meeting of the European Neurological Society
June 19-23
Berlin
www.congrex.ch/ens2010

14th Congress of the European Federation of Neurological Societies
Sept. 25-28
Geneva
www2.kenes.com/efns2010/Pages/home.aspx

23rd Scientific Meeting of the International Society of Hypertension
Sept. 26-30
Vancouver
www.VancouverHypertension2010.com

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 Society of Pain Clinicians Congress and 1st Asian Congress on Pain
Oct. 28-31
Beijing
www2.kenes.com/wspc/Pages/Home.aspx

MEETING ROUND-UPS

IBRO's Work Leaves Its Mark in Africa

BY RAJ KALARIA, M.D., AND PIERRE M.K. LUABEYA, M.D.

The International Brain Research Organization's collaboration with the World Federation of Neurology has thrived since Dr. Johan A. Aarli, the former WFN President, convened the inaugural meeting of the Africa Initiative in 2006.

Since then, the European Federation of Neurological Societies (EFNS) has joined forces with us, and with impetus from the World Health Organization, we have targeted joint activities to increase neurology training and research with a particular focus on sub-Saharan Africa.

Two events last year show how IBRO is having an impact on the Africa Initiative.

► **Neurological sciences schools.** IBRO Africa has been hosting the highly subscribed schools in the neurological sciences for nearly a decade. Last year, the 20th IBRO African Region Neuroscience School was held at the Nemba Hospital Training Centre in Ruhengeri, Rwanda.

Of the 25 students who attended this UNESCO-sponsored event, 18 were neurology trainees, and 7 were postgraduate students in the biological or veterinary sciences, or medicine.

Dr. Pierre M.K. Luabeya (Belgium), Dr. Mariano Pérez Arroyo (Spain), and Dr. Raj Kalaria (England) convened the select group from 11 African countries. They were also part of the teaching faculty, which included Dr. Richard Mukendi-Kavulu (Belgium), Dr. Tharcisse Kayembe (DRC), Dr. Desire Tshala-Katumbay (United States), Dr. Evelyne Sernagor (England), Dr. Pascal Vrielynck (Belgium), and David Cechetto (Canada).

Dr Fidèle Sebera, an IBRO alumnus and the only Rwandan neurologist, was the local host.

The morning schedule consisted of sessions on nerve and muscle structure and neuromuscular disorders, epilepsy, spastic paraparesis, neurological complications of leprosy, stroke, neurodegenerative disorders, and the eye and retinopathies. At afternoon workshops, students were instructed in EEG and myography techniques and interpretation. They also made oral presentations on research projects or case reports on a range of topics including epilepsy, stroke, neurological manifestations of HIV, and cerebral malaria.

In the evenings, there were discussions on neuroethics, publishing, research, and obtaining support for clinical research.

► **Regional Teaching Courses.** The neurology teaching initiatives lead by Dr. Jacques De Reuck, EFNS president, have gone from strength to strength, and the regional teaching courses (RTCs) are a good example of such success.

In June last year, the neurology department of Addis Ababa University (AAU), chaired by Dr. Guta Zenebe, and the Association of Neurological Sciences of Ethiopia, led by Dr. Zenebe Melaku, cohosted the second regional teaching course at the Black Lion Hospital, one of the AAU's teaching hospitals.

This RTC, as with the first held in Dakar in 2008, was chaired by Jean-Michel Vallat (France) working with representatives from the EFNS, Pan African Association of Neurological Sciences (PAANS), IBRO, Pan Arab Union of Neurological Societies, and AAU.

COURTESY DR. RAJ KALARIA

Dr. Raj Kalaria (center left) and Dr. Mariano Pérez Arroyo (right) with students at the Rwanda school.

More than 100 neurology and neurosurgery trainees, IBRO alumni, and specialists from 13 countries attended. Morning sessions comprised lectures on epidemiology, pathophysiology, symptoms, treatment, and management; afternoon sessions focused on case study discussions. Neurology practice and research "in the bush" were also discussed.

The attendees were encouraged to support PAANS activities and to contribute to the African Journal of Neurological Sciences (www.ajns.paans.org).

Delegates from Kenya announced the first Annual Meetings of the Neurological Sciences, sponsored by IBRO and PAANS, will be in Nairobi, Sept. 8-10, 2010.

IBRO says "asante sana" ("thank you" in Swahili) to its EFNS, WFN, and PAANS colleagues for their collaboration. Neurological and mental health research should not be a luxury, even in Africa. ■

DR. KALARIA is deputy director of the Centre for Brain Ageing and Vitality and professor of neuropathology at Newcastle University, England. Dr. Luabeya is professor of neurology at the Hôpital Neuro-Psychiatrique Saint Martin, Namur, Belgium.

Mali Congress Emphasizes Collaboration

The First Bamako Neurosciences Congress last November in Bamako, the capital city of Mali, provided a valuable platform for neurologists in Africa.

The congress was organized under the leadership of Dr. Moussa Traoré, who, with chairman, Dr. Guy Rouleau of the University of Montreal; Dr. Jean-Marc Leger, secretary-general of the French Society of Neurology; and the US-based Movement Disorder Society (MDS), recruited the international faculty.

MOUSSA TRAORÉ, M.D.

Dr. Traoré is chief of the neurology department at the University of Bamako.

At the plenary sessions, the faculty lectured on movement disorders, neuro-epidemiology, dementia, epilepsy, neuromuscular and neurodevelopmental disorders, and neuro-oncology. Local physicians presented research on neurological disease during parallel sessions.

The MDS sponsored Dr. James H. Bower and Dr. Michel Gonce of Liege, Belgium, as society ambassadors to the congress. Dr. Gonce lectured on Tourette syndrome and treating Parkinson's disease, and presented a series of case studies on video; Dr. Bower gave an overview of gait disorders and neuroepidemiology in Africa.

Mali has a population of 13 million people and only six neurologists. They trained outside of Mali because the country does not have a neurosciences program. Several faculty members met with Prime Minister Modibo Sidibé to discuss neuroscience in Mali, and he emphasized the importance of collaboration in neurological research.

JAMES H. BOWER, M.D.

Dr. Bower is associate professor of neurology at the Mayo Clinic, Rochester, Minn., USA.

The delegates echoed his comments about collaboration, saying they hoped the congress would mark the beginning of strong collaboration between neurologists in developed countries and those in Mali. They discussed establishing a neurosciences training and research center in the city for the African region. ■

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PERSPECTIVE—CAMBODIA

Physical Exam Is Key in an Underresourced Setting

BY YAACOV ANZISKA, M.D.

Dr. Anziska is assistant professor of neurology at SUNY–Downstate Medical Center, Brooklyn, New York, and director of the Muscular Dystrophy Association Clinic at the center (Yaacov.Anziska@downstate.edu).

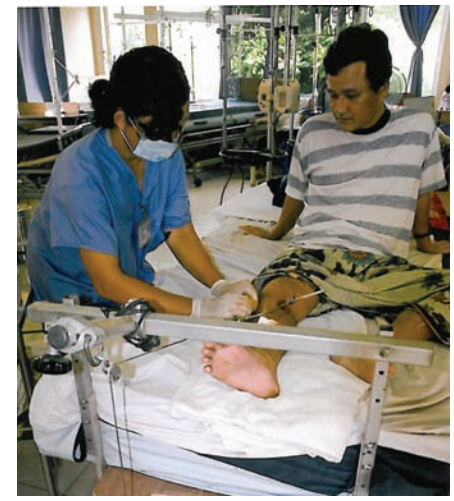
In October last year, I volunteered at a charity hospital in Phnom Penh, Cambodia, under the auspices of Health Volunteers Overseas, a Washington, D.C.–based network of health care interest groups.

The Sihanouk Hospital Center of Hope provides free care to thousands of impoverished Cambodians. I worked in its emergency department, its inpatient medical service, the general medicine clinic, the HIV ward, and a mobile medical clinic that serves an outlying village. I also joined the neurology rounds at an inpatient neurology service at another hospital in the city. I diagnosed and treated both in- and outpatients who presented with conditions ranging from minor headaches to neurological emergencies.

Cambodia has a population of 14.7 million, but there are only four neurologists, all of whom are based in Phnom Penh. Most neurologic disorders are treated by internists. The diagnostic equipment used by the average neurologist in the United States is not available in Cambodia. There are no EEGs, EMGs, or ultrasound machines, and only one CT scanner and one MRI machine in the country.

Although older medications such as phenobarbital and phenytoin are found in pharmacies, many patients consult local healers and use herbal supplements. New medications, such as interferon beta, are not available. And because of the lack of health insurance, patients have to pay cash for each test. For some, US$58 for a CT scan of the head does not seem expensive, but for a family earning just a few dollars a month, as many Cambodians do, it is astronomical. This lack of payment limits testing, so I was forced to rely more on my physical examination.

As a neurologist, I was stunned by the prevalence of stroke in Cambodia, with at least 1,000 cases in the main hospitals in Phnom Penh. It is the second most common reason for hospital admissions in the country and likely involves different causes than those seen in the United States. Obesity is less common in Cambodia, yet hypertension and hyperlipidemia are widespread, and there also may be an overrepresentation of intracranial disease. However, there are no facilities for stroke rehabilitation, and I treated many outpatients with severe spasticity and disability.



COURTESY DR. YAACOV ANZISKA

The country has only four neurologists, so patients are usually treated by internists.

Treatment for HIV-positive patients is one of the medical success stories of Cambodia, with HIV prevalence having halved over recent years. Internists are aware of the neurological diseases that come with HIV and they follow patients longitudinally. In addition, most HIV patients are on antiretroviral therapy and are living longer, whereas many stroke patients don't even use aspirin.

What can be done for neurology in Cambodia? Neurologists there are trying to arrange specialized training within the country so that candidates don't have to travel overseas to train. Primary care physicians need to learn more about neurological disease, and this can start in the training phase, with residents rotating on neurology inpatient services. After training, there can be continued medical education programs run by neurologists and conferences that focus on specific diseases. And finally, more equipment, such as additional CT machines, should be purchased.

Moreover, Cambodian neurologists feel isolated from the global neurological community. This could be remedied by encouraging them to join organizations such as the World Federation of Neurology and the American Academy of Neurology and possibly waiving registration fees to facilitate their participation.

It was a privilege to treat the patients and teach the house staff. I look forward to returning and hope to see more neurologists practicing there in the future.■

For more information about Health Volunteers Overseas and its volunteering program, visit www.hvousa.org.

Thrombolysis Is Effective, Appropriate for Octogenarians

BY MITCHEL L. ZOLER

SAN ANTONIO — Intravenous infusion of a thrombolytic drug helped octogenarian ischemic stroke patients as much as it did middle-aged adults with stroke in a meta-analysis of data collected from more than 1,700 very elderly patients.

Octogenarian stroke patients "show significant benefit" from intravenous treatment with recombinant tissue plasminogen activator (rt-PA) and no excess harm compared with younger patients, Dr. Kennedy R. Lees said at the International Stroke Conference.

And stroke patients aged 75 years and older are also, in general, the best candidates for rt-PA treatment, according a second report presented by Dr. Dawn O. Kleindorfer, director of the division of vascular neurology at the University of Cincinnati.

That analysis of 1,774 adult ischemic stroke patients who presented to the emergency department at the University of Cincinnati during 2005 showed that the percentage of patients eligible for acute treatment with intravenous rt-PA reached the highest level, 10%, in patients 85 or older; 75-to-84-year-olds comprised the subgroup with the next highest percentage of good rt-PA candidates, 9%. These rates compared with an 8% eligibility level for all adult stroke patients in the study.

Many younger adults were ineligible for treatment because their strokes were too mild, the analysis showed.

Despite this new evidence of the appropriateness, efficacy, and safety of rt-PA in patients aged 75 and older, this demographic subgroup stands out as undertreated with intravenous thrombolytics, even more than the low rate of intravenous rt-PA use in all adults with stroke.

"There is a bias at the bedside of a 90-year-old patient," Dr. Kleindorfer said in an interview. "In the United States, we place no upper age limit [on rt-PA treatment], but there still is inherent tentativeness for treating extremely elderly patients."

To assess the efficacy of rt-PA in octogenarians, Dr. Lees and his associates used data collected in the Virtual International Stroke Trials Archive (VISTA), a compilation of data from more than 20 stroke trials involving more than 15,000 patients (Stroke 2007;38:1905-10).

They narrowed the database to ischemic stroke patients with complete follow-up assessment by a modified Rankin scale score, which yielded nearly 6,000 patients, including almost 1,200 patients who were older than 80. The total group included 1,703 patients who received intravenous rt-PA and 4,114 who did not.

In the octogenarians, treatment with intravenous rt-PA led to a statistically significant 34% improvement in outcomes in an analysis that adjusted for age and baseline NIH Stroke Scale score. This relative benefit closely matched the 42% benefit from rt-PA seen in patients younger than 80, said Dr. Lees, professor of cerebrovascular medicine at the University of Glasgow (Scotland).

In the rt-PA eligibility by Dr. Kleindorfer and her associates,the average patient age was 70, and 142 patients (8%) were judged eligible for intravenous rt-PA treatment based on a retrospective review of the patients' records. Seventy-two of the rt-PA–eligible patients actually received the drug.

Among the more than 1,600 patients judged ineligible for rt-PA treatment, the most common reason, in 77%, was that their time at presentation exceeded the 3-hour time window for intravenous rt-PA treatment that existed in 2005. (The American Stroke Association last year issued guidelines that expanded the rt-PA treatment window to 4.5 hours after stroke symptom onset.)

The extent of patient eligibility and the actual rate at which eligible patients received rt-PA varied significantly by age (see chart). The overall pattern of increased eligibility for rt-PA with increased age, and decreased treatment with rt-PA with increased age were both statistically significant, Dr. Kleindorfer said. The analysis also showed that patients aged 75 or older had a significantly higher rate of an international normalized ratio above 1.6, a legitimate reason for rt-PA ineligibility. But those patients also had a significantly higher rate of more severe strokes that qualified them for rt-PA treatment.

Dr. Lees said he has received honoraria from Boehringer Ingelheim Corp. and Thrombogenics Inc. Dr. Kleindorfer said she has served on the speakers bureaus for Boehringer Ingelheim and Genentech Inc. ■

Rt-PA Eligibility, Use in Stroke Varies by Age

Patient age in years	Eligible for IV rt-PA	Eligible Patients Receiving IV rt-PA
18-44 (n = 90)	3%	67%
45-54 (n = 197)	7%	36%
55-64 (n = 305)	7%	57%
65-74 (n = 372)	8%	67%
75-84 (n = 507)	9%	49%
85 or more (n = 303)	10%	35%

Note: Data from 1,774 stroke patients seen at the ED of the University of Cincinnati in 2005.
Source: Dr. Kleindorfer

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THE LEADER IN NEWS AND MEETING COVERAGE

Polymorphism Predicts Age of Late-Onset Alzheimer's

BY JEFF EVANS

The age at which individuals at risk for developing late-onset Alzheimer's disease begin to show symptoms of dementia may now be accurately predicted to within 7 years, according to a phylogenetic analysis of three cohorts of individuals with and without the disease.

Dr. Allen Roses of the Deane Drug Discovery Institute at Duke University, Durham, N.C., and his colleagues found that carriers of a long poly-T polymorphism in the translocase of outer mitochondrial membrane 40 (TOMM40) gene and the e3 allele of the apolipoprotein E (APOE) gene on the same chromosome developed late-onset Alzheimer's disease (LOAD) an average of 7 years earlier than those who carried a shorter poly-T polymorphism in TOMM40 and the APOE e3 allele (Pharmacogenomics J. 2009 Dec. 22 [doi:10.1038/tpj.2009.69]).

Most people who develop LOAD are APOE e3 carriers, and these results may explain their risk. The length of the poly-T variant in TOMM40 also could help to determine the risk of LOAD in carriers of APOE e4 and e2 alleles. The APOE e4 allele is the strongest genetic risk factor for developing LOAD and is known to be associated with a younger age of LOAD onset, whereas the e2 allele is thought to be relatively protective against LOAD.

The protein encoded by TOMM40 is a subunit of the outer mitochondrial membrane pore, which allows cytoplasmic peptides and proteins to pass through during mitochondrial biogenesis. Mitochondrial dysfunction is an early defect in LOAD pathogenesis.

Previous genetic studies of LOAD, including genome-wide association studies, may have missed the association between TOMM40 and APOE because of strong linkage disequilibrium between the two genes, which are separated by about 2,000 nucleotide bases on chromosome 19.

To work around that problem, the researchers constructed a phylogenetic analysis of the chromosomal region in one cohort of white patients to see if they could identify collections of related haplotypes with common ancestral history that were enriched with LOAD-causing polymorphisms. The approach is normally used for evolutionary analyses, "but is ideally suited for analysis of regions of the genome where there is high sequence diversity and low levels of recombination," the authors wrote.

They showed they could match the phylogenetic structure of the APOE-TOMM40 chromosomal region in the first cohort with two additional case-control cohorts of white individuals. A key poly-T polymorphism in TOMM40 distinguished the age of onset of LOAD in patients who were homozygous for APOE e3 or carried both e3 and e4 alleles.

In patients from one cohort for whom disease-onset data were available, repeats of 27 or more thymidine bases were associated with disease onset at a significantly younger age than were shorter poly-T alleles (77.6 years vs. 70.5 years).

The distribution of the lengths of the poly-T variant seemed to be inherited faithfully along with specific alleles of APOE, suggesting that they "do not represent dynamic mutations as observed in other neurological diseases."

All of the subjects homozygous for the APOE e4 allele had poly-T polymorphisms with lengths of 21-30 thymidine bases, except for two who had lengths of 15 bases. Those two had a later age of LOAD onset than would normally be expected. Subjects with APOE genotypes of e2/e2 or e2/e4 also seemed to carry variable-length, poly-T repeats similar to those of APOE e3 carriers, but "further investigation is needed to verify this preliminary finding and determine whether the poly-T repeat affects the very late stage of disease onset for carriers of APOE e2," said the researchers.

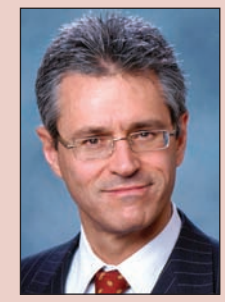
"It is highly probable that African, Asian, Caucasian and other ethnic groups have very different phylogenetic patterns in the APOE-TOMM40 region. This may affect the clinical usefulness, for non-Caucasians, of the data presented here and this could be especially problematic in the pharmacogenomic interpretation of global clinical trials. This factor must be considered when large Phase III trials do not confirm the efficacy found in original Phase II experiments based solely on Caucasians," they cautioned.

Dr. Roses is president of Zinfandel Pharmaceuticals Inc., which is conducting the trial. Its results are open for validation, but patent applications have been filed for using polymorphism as a genetic marker for AD. The National Institutes of Health, the National Science Foundation, the Arizona Alzheimer's Consortium, and the State of Arizona funded the research through grants. It also was supported by an anonymous gift and the Deane Drug Discovery Institute. ■

MY TAKE

Discovery May Untangle Genetic Role

Dr. Roses was the team leader for the discovery in the early 1990s that allelic variants of APOE influence susceptibility to Alzheimer's disease, so his assertion that TOMM40 may underlie part or all of APOE's effect is startling.



Although the e4 APOE allele was initially found in familial cases of LOAD, it was then found in "sporadic cases," providing evidence that even patients without a family history could have genetically determined (or influenced) disease.

The APOE e4 allele also is common, so screening normal people could identify those at elevated risk levels, including e4 noncarriers (further subdivided by the protective e2 allele), e4 heterozygotes, and e4 homozygotes who could then be studied prospectively. It is still not clear if TOMM40 explains the entire APOE effect, or only a part of it. If it is the latter, then further questions arise as to the synergistic interactions of several genes in linkage disequilibrium, possibly including other genes in this region as well.

RICHARD J. CASELLI, M.D., *is a professor of neurology at the Mayo Clinic, Scottsdale, Arizona. He is collaborating with Dr. Roses on a follow-up study exploring the relative contributions of APOE and TOMM40 to AD age of onset, but he has no financial interest in the discovery.*

A Utilitarian Approach

Model • *from page 1*

value society or individuals would place on an additional year of perfect health (Med. Decis. Making 2000;20:332-4).

Some will immediately part company with this approach, believing that clinicians shouldn't be constrained by cost considerations. But such an argument ignores the fact that within resource-limited systems—that is, in probability, all health care systems worldwide—interventions with limited cost-effectiveness have opportunity costs for other therapeutic areas.

Aiming for the Greatest Gains

NICE is essentially utilitarian in its approach; it seeks the greatest health gains for the community as a whole, without regard to disease or therapeutic area and by doing so, supports equity in the NHS.

Inevitably, adverse guidance from NICE is accompanied by outcries from patient support groups, which blame the institute and the appraisal process—rather than the lack of a "value-for-money" pricing policy from industry—for reduced access to a treatment. They are rarely asked to and don't address the question: If you want this treatment to be available, then which treatments for which patients are you going to withhold?

How has NICE guidance had an impact on the care of neurological patients?

Its baseline is set at the present time, which can be a problem. Thus, therapeutic areas that have enjoyed incremental benefits in improving treatments over many years will have already drawn to themselves considerable health care resources that have never been subject to its rigorous appraisal process. This could disadvantage neurological patients where disease-modifying treatments are a recent innovation. There are strong arguments that the NHS may be providing older treatments that would not now be considered to meet its requirements and that these should be reviewed (BMJ 2009;338:b181).

Warding Off Excessive Costs

Most importantly, neurological disorders are longer-term conditions, giving rise to much greater uncertainty in the estimation of cost-effectiveness. This was well illustrated in the appraisal of beta-interferons and glatiramer acetate in the treatment of MS.

As is universally the case, the clinical outcomes available from short-term licensing studies aren't informative of the potential effects over 10 or 20 years. This gave rise to estimates of costs per QALY ranging, depending on assumptions, between £40,000 and £90,000, if gains from treatment extended over 20 years, but £380,000 and £780,000 if the gains from treatment extended over 5 years.

What good has NICE done? Although it would deny that it is involved in pricing, it has certainly begun a process that bears down on excessive costs charged by industry for its newly licensed treatments. Its first steps in this direction came from its rejection of beta-interferons and glatiramer acetate for MS. This led to a scheme that identified a cohort of patients to be treated and followed. Full prices were to be paid by the NHS but if the outcomes in the cohort fell below a threshold of benefit, then the NHS would be refunded money to recognize the fact. Initial results have just been published illustrating the practical problems of historical comparison (BMJ 2009;339:b4677).

NICE can claim to have supported equity in the delivery of care within the health service and to have contributed much needed transparency to this.

It has, directly, limited the availability of new treatments to patients with MS and dementia, but these have been treatments with borderline clinical effectiveness, as illustrated by divided opinion within clinical neurology. But its work across all therapeutic areas can be seen as protecting neurological patients from the adverse opportunity costs of the introduction of new poorly cost-effective treatments in other therapeutic areas.

Equitable and Effective

It has to be seen as a force for good in health care if you agree that: "The NHS should, above all, be aiming to provide equitable access to effective health care for those who need it," (Independent Inquiry Into Inequalities in Health [also known as the Acheson Report], 1998). I recognize from the controversy over health care reform in the United States that this might not be an aspiration universally shared. ■

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FROM THE JOURNAL OF THE NEUROLOGICAL SCIENCES

Charting the Burden of Neurological Disease in Zambia

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

The burden of neurological disease in the underserved areas of the world is high and comprises several disease types. As populations increase and migrate, the climate changes, and new habitats are used, new diseases emerge and old ones reemerge.

It is important to know the spectrum of neurological diseases. First, it is necessary for the allocation of resources, instituting preventive measures, and treating disease. If HIV is responsible for a substantial proportion of disease, authorities can begin preventive campaigns and negotiate therapies with the drug industry, or if arthropod-borne disease is prominent, mosquito eradication programs can be used. An idea of their relative importance will better guide the allocation of funds.

Second, many of these diseases are of global concern. Tuberculosis, AIDS, and malaria, even "forgotten" diseases such as measles are among the most important causes of mortality in the tropics. They all have neurological manifestations that can be lethal and have a global impact. Again, consider AIDS: It probably was first manifested in humans in Africa, spread slowly and then rapidly worldwide.

The effects of such disease are great: they are difficult to diagnose, treat, and prevent, and mortality is high. In many countries, there are few neurologists to evaluate and advise (see p. 3).

The researchers in the study under review here examined the spectrum of neurological disease at the University Teaching Hospital in Lusaka (J. Neurol. Sci. 2010;290:1-5). They reviewed the records of all inpatient and outpatient neurological consultations in 2006. The patients were seen by a senior general physician, who obtained evaluation from a consultant neurologist as needed. The diagnostic methods were very limited. CT (but not MRI) scans were available, as were simple laboratory studies of blood and CSF, but there was no viral polymerase chain reaction testing of the CSF.

In all, 443 inpatients and 368 outpatients were classified. The classifications were not in any standard form, but a mixture of clear-cut nosologic categories and descriptions that seemed to capture the on-site picture very realistically. They included neurological infections, cerebrovascular disease, dementia, headache, trauma, herpes zoster neuralgia, myelopathy, and encephalopathy. Patients were also analyzed by HIV status, which affects the distribution of diseases, especially in outpatients.

Of the total, 125, or 15%, were known to be HIV positive. The greatest proportion of HIV-positive inpatients (38.8%) were in the "neurological infections" category, and this was significantly higher in the HIV-positive group than in the HIV-negative group. Cryptococcal meningitis, toxoplasma encephalitis, and tuberculosis were the most common entities in the HIV-positive group. This is similar to what was seen in North America up to 10 years ago. The second and third categories, neuropathy/radiculopathy and cerebrovascular disease (14.9% and 8.9%) were just as common in HIV-negative inpatients. Myelopathy was more common in HIV-positive inpatients than the HIV negative.

In the outpatient groups, more clear-cut differences were found, with neuropathy, cerebrovascular disease, dementia, encephalopathy, headache, myelopathy, and seizures more common in the HIV-positive than HIV-negative group. That encephalopathy, neuropathy, and myelopathy are more common in the HIV-positive outpatients reflects the long-term complications of the infection (also are seen in North America). So although the acute neurological complications of HIV are no longer seen in North America, the long-term problems persist and resemble those in Europe and North America. ■

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.*

Stenting Expertise Key

Carotid Intervention • *from page 1*

had, on average, no significant changes in their SF-36 mental and physical scores, Dr. Wayne M. Clark noted while presenting the CREST results.

Dr. James C. Grotta, professor and chairman of neurology at the University of Texas in Houston, said the study was "was an endorsement for surgery."

The findings also renewed concerns about the appropriateness of any invasive intervention, be it stenting or surgery, for patients with asymptomatic carotid stenosis. In addition, some experts also emphasized that the stenting results in the trial came from selected, experienced operators and that it would be a leap to expect comparable results from physicians who were not trained as well as the more experienced operators.

CREST randomized 2,502 patients with either symptomatic carotid stenosis or asymptomatic, severe carotid stenosis (at least 60% blockage) at 108 sites in the United States and 9 in Canada. The average age was 69; a third of the patients were women and 47% were asymptomatic. The analysis showed no significant effect from either gender or symptom status on outcomes.

The age effect produced the sharpest distinction between stenting and surgery, and confirmed evidence that began emerging a few years ago that carotid stenting poses a special problem for elderly patients.

"As we went into this [trial], most of us thought that the less invasive procedure would be best suited for the older patients," said Dr. Thomas G. Brott, professor and director of neurology at the Mayo Clinic in Jacksonville, Fla., and coprincipal investigator for CREST.

In fact, some of the first suggestions of safety problems that can occur when stenting elderly patients came from the lead-in phase of CREST that involved nearly 1,600 patients who underwent carotid stenting in the early 2000s as operators in the study established their stenting expertise. The problem has been attributed to the increased difficulty and danger of placing stents and embolic protection devices through elderly patients' tortuous and atherosclerotic arteries.

Dr. Clark, a CREST participant and professor of medicine and director of the Oregon Stroke Center at the Oregon Health & Science University in Portland, reported the age effect as a continuous variable, without specifying any point estimates of the effect. But based on the line graph he showed, patients who underwent stenting at age 65 had a roughly 20% reduced risk for an adverse perioperative or long-term outcome compared with those who underwent surgery, whereas at age 60 the relative benefit from stenting was about 35% and at age 50, the rate of adverse outcomes after stenting was less than half the rate after endarterectomy.

The primary adverse-event measure used in CREST was the composite rate of any stroke, MI, or death during the 30 days following treatment plus the rate of any ipsilateral stroke during long-term follow-up of up to 4 years.

This rate was 7.2% for stenting and 6.8% for endarterectomy, with similar rates of ipsilateral strokes occurring from 31 days to 4 years (2.0% vs. 2.4%, respectively).

In contrast to younger patients, at age 75, the rate of adverse outcomes after stenting rose by about 35% compared with surgery; at age 80, the adverse-outcome rate was more than 50% higher with stenting than with surgery; and at age 85, the adverse event rate was roughly doubled by stenting in comparison with endarterectomy. In patients who were 70 years old, the adverse event rates were essentially identical regardless of which procedure was used.

The finding that stenting produced a significant increase in periprocedural strokes compared with endarterectomy, whereas surgery led to a significant increase in MIs over stenting, led some experts who heard the report to speculate on which of these adverse events was worse. "I'm a neurologist, so I think strokes are worse," said Dr. Grotta.

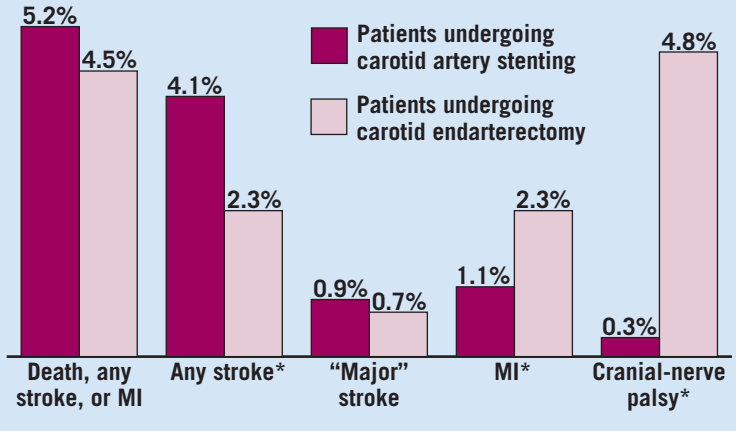
"An MI in a patient who already has poor cardiac function might push them into a state where their quality of life is severely affected, whereas a patient with a relatively normal heart will be unscathed," noted Dr. Mary E. Jensen, a professor of radiology at the University of Virginia in Charlottesville. "In general, I suspect that a stroke affects quality of life more profoundly than an MI, but it is an individual and specific event."

The CREST results reported so far gave no details on how endarterectomy and stenting fared in asymptomatic patients compared with patients who already had symptoms of carotid disease. In the absence of these data, several experts cautioned that the findings should not be taken as an endorsement of aggressive carotid interventions for asymptomatic patients, especially at a time when medical therapy has become very effective.

In contrast to CREST, results from another comparison of stenting and surgery, the International Carotid Stenting Study (ICSS), which also appeared online on the same day as the CREST report (Lancet 2010 Feb. 26 [doi:10.1016/S0140-6736(10)60239-5]), showed a clear benefit from endarterectomy over stenting.

There were numerous differences between the two studies, but perhaps the most important was that CREST included a lead-in phase for operators to hone their stenting skills, and ICSS did not. It was that training phase in CREST that raised issues on the study's generalizability.

Dr. Clark, Dr. Grotta, Dr. Jensen, and Dr. Brott, had no disclosures relevant to the study. ■



*Statistically significant difference between comparator groups
Note: Results based on 2,502 patients randomized at 117 medical centers.
Source: Dr. Clark

HISTORY—ARGENTINA

A Pioneering Role in Neurological Progress

BY OSAVALDO FUSTINONI, M.D.

In 1885, just 3 years after Jean-Martin Charcot established a neurology clinic at Hôpital de la Salpêtrière in Paris, a similar department was opened at the Hospital San Roque de Buenos Aires, launching the practice and scientific investigation in the neurosciences in South America (J. Neurol. Sci. 2008;271:29-33).

The new field took hold in Argentina, Brazil, Chile, Peru, and Uruguay, with many clinicians and researchers subsequently making groundbreaking contributions. In this article, we focus on scientists from Argentina who left their mark on neurology and its related fields.

Many of the traditional "firsts" in neuroscience can be traced to Argentina. José María Ramos Mejía was the first director of San Roque and in 1887 and became the continent's first professor of neurology at the University of Buenos Aires, according to Ricardo F. Allegri, author of the aforementioned article. In the early 1900s, Ramos Mejía, with Christofredo Jakob, José A. Estévez, and José Ingenieros, spearheaded the practice of clinical neurology.

In 1936, Vicente Dimitri published the first Spanish-language journal of neurology, Revista Neurológica de Buenos Aires, which is now Neurologia Argentina. In 1952, José Pereyra Käfer established the Sociedad Neurológica de Buenos Aires, now the Sociedad Neurológica Argentina.

Eduardo Braun Menéndez (1903-59)

After finishing his medical studies at the University of Buenos Aires in 1929, Eduardo Braun Menéndez pursued his interest in research. In the mid-1930s, he returned from postdoctoral studies in London and joined the research team with Juan Carlos Fasciolo, Luis Federico Leloir, Juan M. Muñoz, and Alberto C. Taquini to study nephrogenic hypertension. He used a technique devised by Harry Goldblatt, an American pathologist, to induce hypertension by placing ligatures on the renal artery, and found evidence supporting the renal origin of a humoral factor that could cause transient arterial hypertension. He named the substance "hypertensin." American Irving H. Page made the same discovery and used the term "angiotonin." In 1958, they agreed to rename it "angiotensin."

EDUARDO BRAUN MENÉNDEZ

Eduardo De Robertis (1913-1988)

In 1947, while Eduardo De Robertis was at the Massachusetts Institute of Technology in Cambridge, USA, he reported the first observation of the neurotubules as the ultrastructure of the axon. On his return to Buenos Aires, he discovered the synaptic vesicles and showed that they contained neurotransmitters, so proving they were a prime structural component of neuronal transmission. He later identified pre- and postsynaptic receptors, confirming Ramón y Cajal's neuronal theory of transmission at a subcellular level.

Raúl Carrea (1917-1978)

In 1951, the neurosurgeon Raúl Carrea, with Mahelz Molins and Guillermo Murphy, performed in Argentina the first documented human internal carotid artery surgery to prevent recurring transient ischemic attacks by surgically connecting the external carotid artery to the normal distal segment of an atheromatous internal carotid. Michael E. DeBakey in the United States performed the first endarterectomy in 1953, and in 1954, H.G. "Felix" Eastcott and his team performed the first endarterectomy in Europe. Dr. Carrea established FLENI in Buenos Aires in 1958 to meet the community's neurological medical needs. He also was instrumental in creating the first pediatric neurosurgical service at the Ricardo Gutiérrez Children's Hospital.

Nobel Laureates

► **Bernardo Houssay (1887-1971)** was the first Latin American to win a Nobel Prize in the sciences with the 1947 award for Medicine or Physiology for his work on hydrocarbon metabolism. He pioneered modern scientific research in Argentina and was the first director of the National Council for Scientific and Technical Research, which regulates scientific research in Argentina.

► **Luis F. Leloir (1906-1987)** worked with Dr. Houssay on the role of adrenalin in carbohydrate metabolism. In the late 1930s, after working in England, he returned to Buenos Aires where, together with Juan M. Muñoz, he studied the chemistry of physiological enzymatic processes. He subsequently became part of a larger team comprising Dr. Muñoz, Dr. Taquini, Dr. Braun Menéndez, and Juan C. Fasciolo. In 1942, a year after Irving H. Page and his colleagues suggested the renin substrate known today as angiotensinogen was of hepatic origin, Dr. Leloir and his colleagues proved conclusively that was the case after they conducted experiments in nephrectomized dogs with and without hepatectomy (Hypertension 2001;38:1246-9). Five years later, as part of a different team, he discovered how a malfunctioning kidney and angiotensin caused hypertension. Dr. Leloir received the Nobel Prize for Chemistry in 1970 for his work in charting the metabolic pathways in lactose.

LUIS F. LELOIR

► **César Milstein (1927-2002)** spent most of his professional life in England at Cambridge University. He was awarded the 1984 Nobel Prize in Medicine or Physiology jointly with Niels K. Jerne and Georges J.F. Köhler for their theories on the specificity in the development and control of the immune system and discovering the principle for production of monoclonal antibodies. Those findings were the basis of the production of alemtuzumab, a humanized monoclonal antibody. It originally was licensed for as a lymphocytic leukemia therapy, but also has been tested in diseases such as multiple sclerosis, where the immune system is overactive. ■

CÉSAR MILSTEIN

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JNS Continues Along Its Path of Growth and Expansion

I completed my third 4-year term as Editor-in-Chief of the Journal of the Neurological Sciences in December last year. During those 12 years, the journal showed enormous growth and improved impact throughout the medical world. The submission rate soared annually from 400 to 1,137. The impact factor (reflecting the average number of citations over the two preceding years) rose from 1.84 to 2.359, and the journal now ranks 68th of all 156 journals in Thomson Reuters' clinical neurology category.

These indicators are a reflection of the journal's growing importance as an international journal covering all aspects of neurology. The implementation in May 2006 of the Elsevier Editorial System, an online submission/review process software, acted as a catalyst for this growth.

The evolution of the journal continues to be reflected in the changing dynamics of authors and ad hoc reviewers. The five leading countries in submissions remain Japan, China, the United States, South Korea, and Italy. However, submissions from regions including Africa, Egypt, Iran, Jordan, Lebanon, Palestine, Qatar, the Russian Federation, and Saudi Arabia demonstrate the growing global impact on emerging markets.

Special issues and supplements, a regular feature of JNS, continued to focus on the latest research and developments in a specific field. Guest editors produced one supplement and two special issues dedicated to multiple sclerosis research and another special issue featured vascular dementia:

► Franz Fazekas of Graz Medical University, Austria, and Bernd C. Kieseier of Heinrich Heine University, Düsseldorf, Germany, produced the supplement, "Translating New Insights Into Treatment in Multiple Sclerosis" (J. Neurol. Sci. 2009;277[suppl. 1]:1-61).

► Robert Zivadinov of State University of New York at Buffalo and Alireza Minagar of Louisiana State University Health Sciences Center, Shreveport, focused on a special issue titled, "Evidence for Gray Matter Pathology in Multiple Sclerosis: A Neuroimaging Approach" (J. Neurol. Sci. 2009;282.1-2:1-124).

ROBERT P. LISAK, M.D.

Dr. Lisak is Editor-in-Chief of the Journal of the Neurological Sciences. He is a professor and chair of neurology at Wayne State University in Detroit, USA.

► Amos D. Korczyn, Natan M. Bornstein, and Laszlo Vecsei, all from Tel-Aviv Sourasky Medical Center, Israel, offered the special issue, "Vascular Dementia Proceedings of the Fifth International Congress on Vascular Dementia" (Budapest, Hungary, November 2007; J. Neurol. Sci. 2009;283.1-2:1-324).

► Otto R. Hommes, chairman of the European Charcot Foundation, and Mieke Friedrichs, managing director of the foundation, presented another special issue, "Multiple Sclerosis and Gender" (J. Neurol. Sci. 2009;286.1-2:1-120).

These featured articles and all other journal issues are readily accessed online through ScienceDirect, Elsevier's electronic information system for interdisciplinary research.

As Editor-in-Chief, I welcome this opportunity to thank the deputy editors Richard A. Lewis and Paula Dore-Duffy; the administrator and supporting editor, Susan E. Hutton, all associate and guest editors, and ad hoc reviewers for their commitment to the journal.

We will continue to promote the visibility of the journal worldwide by encouraging high-quality submissions and new authors in 2010. ■

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