

WORLD NEUROLOGY

THE OFFICIAL NEWSLETTER OF THE WORLD FEDERATION OF NEUROLOGY

Neurological Fallout in German Epidemic

BY GÜNTHER DEUSCHL,
M.D., AND ROBERT
STINGELE, M.D.

During the enterohemorrhagic *Escherichia coli* (EHEC) epidemic in northern Germany earlier this year, the neurological features of this rare condition quickly became acutely apparent, and neurologists found themselves working side by side and around the clock with nephrologists and gastroenterologists to manage patients with the life-threatening infection.

The epidemic seems to have been one of the most extensive and deleterious in recent years. So far, 3,602 EHEC infections have been reported, including 838 cases of hemorrhagic uremic syndrome (HUS). Thirty patients with associated HUS died, and 17 without HUS died, according to data from the Robert Koch Institute, a federal institute that oversees the prevention and control of disease.

The institute has said that the epidemic was caused by an

EHEC contamination of sprouts. This *E. coli* strain is known to produce Shiga toxin, which initially affects the epithelium of the intestine, leading to hemorrhagic diarrhea, but it subsequently also affects kidney epithelia, which can put the patient at risk for renal failure. This leads to HUS, a life-threatening condition. Erythrocytes and thrombocytes are also affected by Shiga toxin, which in severe cases can lead to disseminated intravascular coagulation and multiorgan failure, which can be fatal.

However, neurologists were surprised to see a new and severe neurological disease manifest in some of the EHEC patients and we soon realized that the nervous system could also fall prey to the infection – most likely as a result of the Shiga toxin. About a third of the EHEC patients developed HUS, and half of the HUS cases developed neurological symptoms. Very few of the patients who did not have HUS developed the neurological symptoms.



Infection with EHEC led to hemorrhagic uremic syndrome in one-third of patients, half of whom developed neurological symptoms.

The symptoms were sometimes fairly mild but often dominated the clinical syndrome. They started with slight and transient symptoms such as confusion and irritability, which sometimes developed into a full confusional and delirious state. Motor symptoms with myoclonus or jerky tremors were quite frequent, and often the myoclonus was stimulus sensitive. This stage sometimes led

to seizures or even status epilepticus. Some patients slipped into a coma and needed ventilation, which was why there was such high demand for intensive care treatment during this epidemic. Other patients manifested with focal symptoms such as aphasia or apraxia.

Brain stem symptoms with loss of cranial nerve functions

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Representatives from the World Federation of Neurology and Cairo University School of Medicine have signed an agreement to establish a center for training neurologists from Africa.

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Researchers gathered for the International Conference on Transcranial Magnetic and Direct Current Stimulation in Rome.

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Bashkortostan

A clinic integrates its continuing professional training into its existing routines and has sought local and international collaboration to bolster its impact.

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Neurologists Describe Responses to Disasters in Japan

BY SATOSHI TAKAHASHI,
FUMITOSHI HAMATO, MASASHI
AOKI, OKUJOU IWAMI,
YOSHIKAZU UGAWA, KATSUMI
NAKATA, OSAMU YAMAMURA,
MIEKO OGINO, HIDEHIRO
MIZUSAWA, AND GEN SOBUE

The most devastating earthquake ever to hit Japan struck on March 11. It was quickly followed by a giant tsunami that sent people frantically scrambling to

higher ground. Terrified children and older adults panicked as many struggled to evacuate their families and friends from the swiftly flooding stricken areas. For days, blocked and damaged roads cut off medical and emergency assistance access to where it was most needed, and communications came to a near standstill.

At this year's annual meeting of the Japanese Society of Neurology, we held a special forum in which the neurologists

who struggled during the disaster shared their experiences, and with the attendees, tried to come up with some solutions for delivering medical care during a crisis. Given the overwhelming chaos, medical services were forced to focus less on physical examinations or medications and more on food, shelter, water, clothing, warmth, and compassion – a challenge worthy of Florence Nightingale. The afflicted remained incredibly calm, patient, and cooperative despite the un-

mitigated destruction and loss around them.

One neurologist spoke of how his clinic near the northeast coastal city of Kamaishi was completely destroyed by the tsunami. The neurologist escaped to higher ground with a number of terrified people, but in the chaotic retreat, he lost his own parents. That evening, he started administering medical care in the

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Local Organizers Gear Up for WCN 2011

Members of the Moroccan Society of Neurology have taken an active role in organizing this year's Congress and are proud to be associated with the landmark event, which will be held in Africa for the first time.

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EDITOR IN CHIEF'S COLUMN

Catastrophic Neurology

Neurology is often thought to be a contemplative field of medicine. The brain is complex, and patients are frequently difficult. We spend a lot of time thinking. Of course, neurology is changing with the burgeoning fields of interventional neurology and intensive care neurology. In the setting of acute stroke, for example, the patient might need tissue plasminogen activator within 3 hours. But this is still generally one patient at a time.

In this issue of WORLD NEUROLOGY are two articles, one from Japan and one from Germany, which describe how neurologists have been called on to deal with catastrophes. Massive events came without warning, and neurologists were called into action.



BY MARK HALLETT, MD

Our Japanese colleagues are generally prepared for earthquakes and tsunamis, but not on the scale of the disaster that struck on March 11. Neurological clinics were flattened and put out of action, but neurologists worked long hours and pulled together to do their best. The aftermath still poses problems as recovery continues.

Our German colleagues have had to deal with a new neurological disorder that manifested in some of their patients infected with enterohemorrhagic *Escherichia coli*. Neurological units have been filled to capacity, ad hoc intensive care units set up, and staff from hospitals in regions that were not affected by the epidemic were brought in temporarily to help.

In both circumstances, cooperation between neurologists and hospitals across the countries has been critical in coping with the crises. We have seen other similar examples in recent years of countries helping other countries with similar large-scale disasters, such as the earthquake in Haiti last year. It is nice to see such cooperation, but it would also be useful to have some disaster planning in advance. It is better to be prepared as best as we can.

TALK BACK

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WFN to Collaborate With Cairo University Training Center

In April, Dr. Raad Shakir, the Secretary-Treasurer General of the World Federation of Neurology, represented the Federation at the Cairo International Neurological Congress. While he was there, he met with Prof. Lamees Ragab, dean of the Cairo University School of Medicine, and the school's vice-dean for postgraduate studies and research, Prof. Ahmed Zohdi, to discuss the establishment of an English-medium WFN center at the Cairo University Hospital for African neurology trainees. The initiative was made possible by the efforts of Prof. Mohamed S. El-Tamawy, president of the Egyptian Society of Neurology, Psychiatry, and Neurosurgery.

They signed a memorandum of understanding for setting up a pilot training program, which if successful, could be rolled out elsewhere in Africa. The agreement

set the seal on an initiative that began 2 years ago during the presidency of Prof. Johan Aarli when Dr. Ragnar Stien of the University of Oslo, Norway, went to Cairo on a fact-finding mission. As a result of that trip, he was able to prepare a comprehensive report on the training opportunities and facilities available in Egypt.

The 3-year program is intended for doctors from elsewhere in Africa who will join the Cairo University training program. They will train and work in the way Egyptian trainees do.

The expenses will be met by the WFN and Cairo University. The memorandum of understanding also paves the way for the detailed accreditation and inspection of the training program. Recruitment will begin after it has been approved by the WFN's specialist committee.

Despite the recent political unrest and prevailing un-

certainty in the region, Dr. Shakir returned from his visit confident that the WFN's perseverance in going ahead with the program will be rewarded.



From left, Prof. Mohamed S. El-Tamawy, Dr. Raad Shakir, Prof. Lamees Ragab, and Prof. Ahmed Zohdi.



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PRESIDENT'S COLUMN

Planting the Seeds of Our Future



BY VLADIMIR HACHINSKI, MD

We aim to make the World Federation of Neurology (WFN) more participatory. This year, in a first round of 21 grant applications, the WFN Trustees have approved 10 projects totaling about US\$270,000.

Interested parties submitted their letters of intent through WFN committees, continental initiatives, and task forces to a small grants committee that I chaired. We referred the applications to expert reviewers and prioritized them on the basis of their rankings and comments, making recommendations to the Trustees for final ratification.

Our criteria for selection included return for invested effort, funds, and time; the viability of the proposed project; whether outside partners would be involved in (synergy); and how the outcome would be measured.

Funds are available for a second year in some cases, but are dependent on a satisfactory report at the end of the first year. There will be a second, smaller round of grant applications later in 2011 as the WFN embarks on its program of planned disbursement of funding following its successful Bangkok World Congress and the healthy state of its finances reported in previous issues of *WORLD NEUROLOGY*.

Congratulations to the following successful candidates (the project titles follow the candidates' names):

Prof. Masharip Atadzhanov (Zambia), Bringing EMG/NCV Capacity to Zambia's University Teaching Hospital

Dr. Thomas Bak (Scotland), Cognitive Clinics Worldwide

Dr. Donna Bergen (USA) and Dr. Raad Shakir (UK), Revision of ICD-10 – Neurology Chapter and Beta Field Testing

Dr. Philip Gorelick (USA), Prototype Survey of Diagnostic and Management Capabilities for Neurological Disorders: Stroke Survey

Dr. Douglas Postels (USA), Paediatric Neurology Electronic Training Tool and Site

Dr. Barbara Scherokman (USA), Neurological Education for Non-Neurologists in Developing Countries: A Web-Based Initiative

Prof. Ryuji Kaji (Japan), Educational Grant for Asian Neurology

Dr. Mohammad Wasay (Pakistan), Neurology Training in Afghanistan: A Short Course

Prof. Jo Wilmshurst (South Africa), Children With Epilepsy in Developing Countries, and Training and Retaining Child Neurologists

UN Summit Meetings

The planned summit meeting on Sep. 19-20 of the United Nations' General Assembly on Noncommunicable Disease

offers the WFN the opportunity to put the brain on the agenda. To this end, the Federation has led an initiative to form a World Brain Alliance, comprised of the WFN, the International Brain Research Organization, the World Psychiatric Association, the European Brain Council, the World Federation of Neurological Surgeons, the World Federation of NeuroRehabilitation, the International Child Neurology Association, the International League Against Epilepsy, the Alzheimer's Disease International, and the World Stroke Organization.

I participated in meetings in Moscow and New York earlier this year on behalf of the World Brain Alliance. The Moscow meeting proved intriguing, not just because of its setting, but because of its historic importance as the first global gathering in the effort to control noncommunicable disease (NCD).

Moscow

The First Global Ministerial Conference on Healthy Lifestyles and Noncommunicable Diseases Control was called to help shape the agenda for the UN Summit in September. It was organized by Ala Alwan, the World Health Organization's assistant director-general of noncommunicable diseases and mental health, and Veronika Skvortsova, deputy minister of health and social development of the Russian Federation. The day before the ministerial conference, the WHO held a meeting to refine the wording of the Moscow Proclamation, which had been precirculated.

When we arrived for the ministerial conference the next day, we were surprised to see that tight security restrictions were in place.

Once we assembled, the reason became clear: There was to be a "mystery guest."

The meeting began with a rousing address by Dr. Margaret Chan, the secretary-general of the WHO. This was followed by addresses from the ministers of health or their representatives and a panel discussion. Then a hush from the chattering crowd signaled the arrival of the well-protected guest: Prime Minister Vladimir Putin.

His speech focused on how much was being done for health care in Russia and complimentary remarks about those assembled. Afterward, he took questions and spoke engagingly for longer than his formal presentation.

The meeting was attended by 93 ministers of health, representatives from over 150 ministries of health, employees from the WHO and other organizations, and a few physicians.

It was a combination of plenary sessions, followed by parallel sessions, with deliberations summarized at the end of the day. The presentations ranged from

general to specific issues. Although they concentrated on the extent of NCD as a health challenge, they were sparse in offering specific solutions. Kuwait's minister of health, a vascular surgeon, put it well: It was like seeing a patient – we have taken the history, done an examination, carried out confirmatory tests, and now what do we do for treatment?

If ministers of health are to be persuaded, the message has to be that preventing NCD is not only good for individuals and society, but for the economy.

I participated in both the WHO meeting and the ministerial conference. I came to realize that the NCD summit had been 10 years in the making and that it was unlikely at this late stage that those who had formulated the priorities – cardiovascular

in two versions, one that makes the individual risk and pleasure prone and one that makes the individual risk adverse. Neuroscience may be able to identify modulators of these receptors that could help control all of the targeted risk factors. In addition to empiric measures, we need to invest in brain research. "Our brains are our future" (Draft document, World Brain Alliance, 2011).

On behalf of the World Brain Alliance (Draft document, World Brain Alliance, 2011). I offered our joint expertise to assure that the campaign to control the targeted risk factor would be successful. I received verbal assurances from the two senior organizers that the messages had been heard. How this may translate into action remains to be seen.

New York

The New York meeting was a 1-day consultation of the president of the United Nations General Assembly, Joseph Deiss, with civil society – that is, the voluntary, civic, and social organizations components of society, excluding government and the private sector.

This meeting went into some depth about different approaches, and a small committee will prepare a brief summary to guide Dr. Deiss when he sets the agenda for the summit. I was asked to submit a short document, which I did in a one-page letter that included the following:

► The World Brain Alliance asks that "cerebrovascular disease" be specified as "heart disease and stroke" and offered a document, "Stroke: Working toward a prioritized world agenda" (*Stroke* 2010;41:1084-99), as a helpful guide toward implementing the General Assembly's decisions.

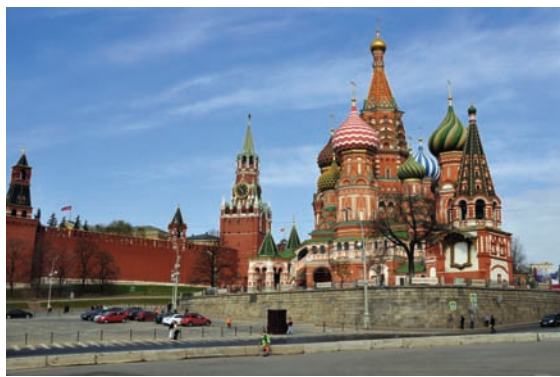
► The World Brain Alliance offers its ongoing global collaborations across more than 130 countries as a platform for building the global collaborations that will be required to implement the NCD resolutions.

► The World Brain Alliance offers a three-person panel comprised of an expert on brain science, an expert on human behavior, and an expert on brain diseases to give high-level advice to help assure the successful implementation of the identified priorities in the fight against NCD.

Conclusion

The seeding grants may grow into larger enterprises, and given the individuals involved, will likely lead to tangible results. It is hard to know if we'll be able to influence the UN summit at this late stage. What we can do is to build on the World Brain Alliance to develop a World Brain Agenda that with effort and luck might become the subject of a future UN General Assembly Summit meeting.

The seeding grants will find fertile ground, but the terrain to the UN summit is rocky. We are planting seeds whenever we can; one never knows where a seed may sprout. ■



The First Global Ministerial Conference on Healthy Lifestyles and NCDs Control was held in Moscow.

COURTESY DR. VLADIMIR HACHINSKI

diseases, cancer, pulmonary disease, and diabetes – would be willing to add the brain and mental disorders to the agenda.

So during my formal presentation, participation, and discussions from the floor and in person with a number of participants, I tried to make three points:

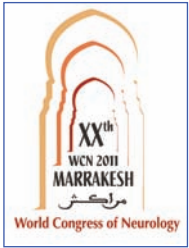
► "Cardiovascular disease" should be spelled out as "heart disease and stroke" for clarity and action. We made this point in line with a policy article (*Lancet* 2001;377:1438-47) and in concert with Bo Norrving, president of the World Stroke Organization, and Marc Fisher, editor of the journal *Stroke* and official delegate of the American Heart Association.

► World stroke leaders, with the support of the major stroke organizations, have developed a prioritized world stroke agenda that can help implement strategies to prevent stroke and treat and rehabilitate stroke patients when it occurs (*Stroke* 2010;41:1084-99).

► Healthy lifestyles depend on human behavior and therefore the brain, and cognitively impaired, depressed, or anxious individuals cannot do what is required without addressing these issues. In summary, "There is no health without brain health."

The targeted behaviors, tobacco, salt, and alcohol use, unhealthy diet, and physical inactivity, have a common denominator in the brain. All produce activation of the brain reward system. The nucleus accumbens is a key component of this system, and its chemical messenger is dopamine. Receptor type IV comes

WGN 2011



The Moroccan Society of Neurology (MSN) is proud to partner with the World Federation of Neurology in this year's landmark World Congress of Neurology (Nov. 12-17), which will be taking place in Africa for the first time.

Aside from serving as the hosts, MSN members are taking an active role in developing the Congress's scientific content, under the leadership of society and Congress president Prof. Mostafa El Alaoui Faris.

"We are delighted to host the upcoming Congress," said Prof. El Alaoui Faris. "The neurology community in Morocco has much to be proud of, and we look forward to exchanging knowledge and information at the Congress with our colleagues from around the world."

In addition to promising a rich scientific program and social events at the Congress, which will take place Nov. 12-17, MSN members have also been working on other exciting activities, such as the Tournament of the Minds competition, for which they have prepared 120 cases to challenge participants as they vie for the top honor.

"MSN members have also submitted 200 of the total 1,497 abstracts that have been submitted so far and have been working assiduously both in planning the

Moroccan Hosts Gear Up

Congress and in promoting it at home and abroad," Prof. El Alaoui Faris added.

The society was founded in 1996. It presently has 170 members, including 50 trainees, and they comprise all of the practicing neurologists in Morocco. They represent all fields of adult and child neurology, including epilepsy, stroke, dementia, headache, movement disorders, neuromuscular diseases, and multiple sclerosis.

The MSN is also an umbrella body for the country's specialized neurological societies such as the Moroccan League Against Epilepsy, the Moroccan Society of Neuropsychology, the Moroccan Movement Disorders Society, the Moroccan Association Against Myopathy, and the Moroccan Society of Neurogenetics.

Half of MSN members work in private

practice, while 30% work in regional hospitals and 20% work in university hospitals. "We are lucky to represent all of the neurologists in the country," said Prof. El Alaoui Faris. "As such, we have created a platform for rich professional exchanges among our members who specialize in different fields and who bring with them different levels of training and experience."

The MSN organizes training courses for general

practitioners, in which they learn how to treat the most common neurological disorders, as well as two annual scientific seminars and a biennial national congress. Each year, it participates in the Maghreb Neurology Congress with its regional neurology colleagues from Algeria, Tunisia, Libya, and Mauritania.

The MSN looks forward to welcoming neurologists from around the world to Marrakesh. ■



The Moroccan local organizing committee, from left, Reda Ouazzani, Mounia Rahmani, Chafiq Hicham (vice-president), Khadija Al Zemmouri, Mostafa El Alaoui Faris (Congress president), Maria Benabdeljilil (Congress secretary), Abdellatif Medejel, Faouzi Belahsen, Ali Benomar (Congress Scientific Committee chair), and Hamid Ouhabi.

FROM THE JOURNAL OF THE NEUROLOGICAL SCIENCES

Cardiac Dysfunction Causes Most Friedreich's Ataxia Deaths

BY SHARON WORCESTER
Elsevier Global Medical News

Cardiac dysfunction remains the most common cause of death in patients with Friedreich's ataxia, according to the findings of a retrospective study.

The majority (59%) of 61 deceased patients studied died as a result of cardiac dysfunction, most often congestive heart failure, with arrhythmia the next most common cause, at 16%; another 3% died of probable cardiac dysfunction, Dr. Amy Y. Tsou of the University of Pennsylvania, Philadelphia, and her colleagues found (*J. Neurol. Sci.* 2011;307:46-9).

Cardiac dysfunction is widely accepted as the leading cause of death in patients with Friedreich's ataxia (FRDA), but this has not been well studied in the years since clinical and genetic diagnostic criteria were developed and led to improved diagnostic accuracy for this inherited ataxia, Dr. Tsou and her associates said.

FRDA is characterized by dysarthria, areflexia, and loss of vibratory and proprioceptive sensation. Systemic manifestations of the disease can include cardiomyopathy, diabetes, and scoliosis.

Noncardiac deaths accounted for 28% of the 61 deaths, and unknown causes accounted for the remaining 10%, the investigators reported.

In a comparison with patients who suffered noncardiac deaths, patients who died from cardiac causes died at younger ages (median of 26 years vs. 41 years) and with shorter disease duration (mean of 19.6 years vs. 30.1 years). Those with a disease duration of 20 years or more had

significantly lower odds of death from cardiac dysfunction, compared with a disease duration of less than 20 years (odds ratio 0.19). Patients who died from cardiac dysfunction also had a significantly longer mean GAA triplet repeat length than did patients who died from a noncardiac cause (687 vs. 508).

In a case-control analysis of 20 of the deceased patients whose records were particularly detailed and 40 living age- and sex-matched control patients with FRDA, deceased patients were significantly more likely to have arrhythmia (75% vs. 15%), dilated cardiomyopathy (65% vs. 5%), congestive heart failure (65% vs. 5%), stroke (20% vs. 0%), or be wheelchair bound (75% vs. 48%). However, the presence of hypertrophic cardiomyopathy did not differ significantly between the groups.

"As cardiac hypertrophy in FRDA is common but not associated with mortality in our study, further investigation to identify factors that predict development of dilatation may allow improved prognostication and targeting of future research. In addition, while hypertrophy has been used as a primary end point in several clinical trials, our results suggest that other manifestations of cardiac dysfunction such as a dilated cardiomyopathy or arrhythmia are more relevant indicators of clinical significance," the investigators wrote.

They noted that because their cohort had a young mean age of onset (12 years) and mean age of death (37 years) in comparison with large living cohorts, the study may not be "entirely repre-

sentative of the general FRDA population," despite the fact that they drew patients from a wide geographical area that included patients from a community group as well as multiple academic medical centers. "The difficulties with selection in our study highlight how relevant the problem of selection bias in FRDA studies continues to be, particularly when working with smaller numbers of patients."

The study was supported by a grant to coauthor David R. Lynch from the Friedreich's Ataxia Research Alliance.

Alex Tselis, M.D., Ph.D. comments: Friedreich's ataxia is an autosomal recessive ataxia with mutations in the gene that codes for frataxin, a protein which is involved in mitochondrial function. The mutation affecting the gene consists of an excessive number of GAA triplet repeats in the first intron of the gene. The protein is expressed in most tissues, but it is particularly abundant in the spinal cord, muscle, liver, and heart; the disease particularly affects these organs. These are also the organs, along with retina, ear, and pancreas that are affected in mitochondrial disease.

The disease behaves like many neurodegenerative diseases, with the most prominent manifestation being progressive gait ataxia, eventually leading to inability to walk. Dysarthria can lead to unintelligible speech. Given this level of disability, one would expect that FRDA patients would have difficulties with nutrition, hydration, urinary tract infections, infected decubitus ulcers, and

pneumonia. However, the impression in the community was for many years that FRDA patients had a high risk of cardiac death. This would be unusual for a purely neurological disease. On the other hand, with FRDA being a mitochondrial disease, involvement of the organs that have high expression of frataxin would be expected, and this includes the heart, as mentioned above.

This study, the first done in the modern molecular era, confirms this impression. The results suggest that FRDA patients need to be followed not only for their neurologic problems, but also the heart, since this seems to be the main determinant of the risk of death. Thus, serial echocardiograms, electrocardiograms and Holter monitors, would be reasonable to do to anticipate structural cardiac disease and arrhythmias, and thus consider inotropic drugs, pacemakers, and even heart transplantation, if the patient's underlying condition permits.

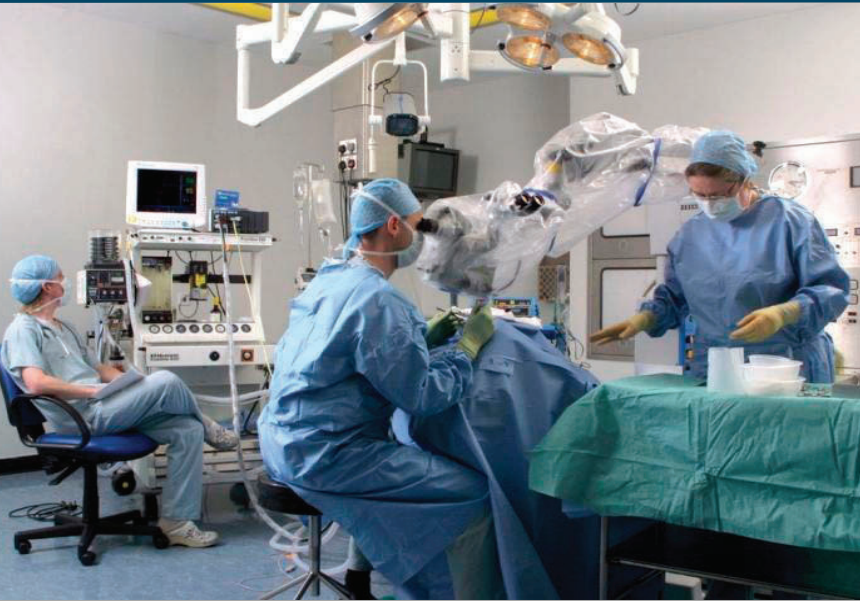
It would be interesting to know why some patients develop severe cardiac problems, while others don't. The latter have fewer GAA repeats than the former, but it is not clear why this would explain selective cardiac involvement. It is possible that because the heart demands a lot of energy, it would be relatively more sensitive to dysfunction of compromised mitochondria. Further work is important. ■

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*.

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MEETING REPORT

Interest Grows in Transcranial Stimulation Techniques

Progress in applying transcranial stimulation techniques to basic research in human neuroplasticity and the treatment of neurological and psychiatric diseases has evolved rapidly ever since the first international conference on repetitive transcranial magnetic stimulation and transcranial direct current stimulation was held in Göttingen, Germany, in 1998.

Growing interest in the field led to successive meetings in Göttingen in 2003 and 2008 and many clinical studies. At present, 165 repetitive transcranial magnetic stimulation (rTMS) and 86 transcranial direct current stimulation (tDCS) clinical studies have been registered at the U.S. National Institutes of Health's clinical trials Web site, www.clinicaltrials.gov. Based on this interest, I organized the fourth International Conference on Transcranial Magnetic and Direct Current Stimulation, which was held June 21-25 in Rome in conjunction with the 14th European Congress on Clinical Neurophysiology. The congress was chaired by Prof. Paolo Rossini and Prof. Vincenzo di Lazzaro and attracted more than 900 participants.

Development in this area is accelerating so quickly that a fifth meeting has been requested to be arranged at an even shorter interval than before.

In recent years, important progress in TMS research has been achieved for clinical practice. Treatment of depressive disorders by rTMS is now approved by the U.S. Food and Drug Administration. Other larger ongoing multicenter trials will reveal in the next few years which

technique may or may not be best suited for different indications. For example, trials are ongoing to see if rTMS may ameliorate tinnitus.

Great technical progress has been made with TMS. The width of TMS pulses can now be varied. The sequence of rTMS pulses has been refined for more efficient and selective induction of inhibition and excitation by the so-called theta burst and quadro-pulse paradigms. Electrical stimulation techniques have



BY WALTER PAULUS, MD

Dr. Paulus is head of the department of clinical neurophysiology at University Medical Center, Göttingen, Germany.

been expanded from tDCS to transcranial random noise stimulation (trNS) and transcranial alternating current stimulation (tACS). The tACS therapy is particularly interesting for frequencies in the beta and gamma range, allowing investigators to induce phosphenes. In the so-called ripple frequency range around 140 Hz, tACS is able to interfere with high-frequency oscillations, whereas in the low kHz range it can interfere with the membrane potential of neurons. With thoracic DCS, spinal cord functions can be influenced directly. Ultrasound stimulation for the purpose of cortical plasticity induction is now being investigated in animal models. An in-

creasing variety of other animal models are used to discover more about the mechanisms of rTMS and tDCS on a cellular and network level. Diffusion-tensor MRI data is allowing us to calculate the flow of electric current to target optimal electrode positions. Individuals' responses to rTMS also are being predicted based on brain-derived neurotrophic factor (BDNF) polymorphisms.

To learn about the basic mechanisms of neuroplasticity in normal subjects, most studies still target the motor cortex (M1). M1 investigations are of direct clinical relevance for the treatment of patients with stroke, pain, or dystonia, the latter presenting with altered center-surround inhibition in M1. Parkinson's disease patients show reduced neuroplastic responsiveness in M1 – probably among other factors –

which also depends on their dopamine level. Changes in the excitability of motor neurons can be quantified easily by the size of TMS-induced motor evoked potentials. Clinically relevant effects usually need repetitive stimulation over at least several days and often several weeks. Simply prolonging the duration of stimulation protocols in a single day may not improve efficacy but convert excitation into inhibition and vice versa. Modulating the amplitude of the stimulation also plays a role through preferentially inducing excitation with higher intensities and inhibition with lower intensities.

Drugs play a central role in modulat-

ing the aftereffects of rTMS and tDCS. By applying different drugs together with tDCS or rTMS, investigators can prolong or attenuate these aftereffects or reverse inhibition or excitation. Drugs may also selectively suppress nonspecific tDCS-induced plasticity and facilitate synapse-specific plasticity that was induced by paired associative stimulation (PAS). This technique can reveal the contribution of different transmitter systems.

Excitability changes induced in cortical areas other than M1, such as the parietal, visual, and dorsolateral prefrontal cortices are of central interest in many cognition or perception studies that test both enhancement and transient lesioning of a given function.

Imaging techniques such as functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG) may be used in these studies to determine the effects of tDCS and tACS. A newly developed stimulator allows tDCS and tACS to be applied during fMRI and EEG. Multi-channel EEG recordings can now pick up TMS-induced cortical electric activity, which may be traced by source-analyzing techniques. Classical fMRI measurements and analyses using block designs are further refined by longer fMRI recordings, providing the data that investigators use in sophisticated connectivity analyses. The trace changes in intracerebral propagation and connectivity patterns that occur after transcranial electric and magnetic stimulation may potentially allow us to detect neuroplastic alteration in conditions such as multiple sclerosis or Alzheimer's disease. ■

Calendar of International Events

2011

4th International Congress of the World Association of Sleep Medicine and 5th Congress of the Canadian Sleep Society

Sept. 10-15
Quebec City, Canada
www.wasm2011.org

World Congress on Huntington's Disease

Sept. 11-14
Melbourne, Australia
www.worldcongress-hd2011.org

American Association of Neuromuscular & Electrodagnostic Medicine Annual Meeting

Sept. 14-17
San Francisco, USA
www.aanem.org/Meeting/Annual-Meeting.aspx

Asia Pacific Stroke Conference

Sept. 29 to Oct. 1
Colombo, Sri Lanka
www.apsc2011.com

Association of British Neurologists Annual Meeting

Oct. 5-7
Gateshead, UK
www.theabn.org/Meeting.aspx?type=1

43rd International Danube Neurology Symposium

Oct. 6-8
Dresden, Germany
www.danube2011.org

6th World Congress of the World Sleep Federation

Oct. 16-20
Kyoto, Japan
www.worldsleep2011.jp/index.html

5th Joint Triennial Congress of the European and Americas Committees for Treatment and Research in Multiple Sclerosis

Oct. 19-22
Amsterdam, Netherlands
www.congex.ch/ectrims2011

5th International Dystonia Symposium

Oct. 20-22
Barcelona, Spain
www.internationaldystoniasymposium.org

7th International Congress on Vascular Dementia

Oct. 20-23
Riga, Latvia
www.kenes.com/vascular

20th World Congress of Neurology

Nov. 12-17
Marrakesh, Morocco
www2.kenes.com/wcn/Pages/Home.aspx

European Charcot Foundation Symposium: Towards Personalized Treatment in Multiple Sclerosis

Dec. 1-3
Villa Padierna, Marbella, Spain
www.charcot-ms.eu/symposia/symposium-2011.html

2012

5th European Neurological Conference on Clinical Practices: Neurovascular and Neurodegenerative Diseases

Jan. 27-29
Krakow, Poland
www.enccp.net

Aspiring Neuroscientists Face Off in Florence

Thanh-Liem Huynh-Tran of USA, won the 2011 International Brain Bee Championship, which was held during the International Brain Research Organization World Congress of Neuroscience in Florence, Italy.

The competition was established to motivate young students between the ages of 14 and 18 years to learn about the brain and inspire them to consider careers in the neurosciences, according to its founder and director, Dr. Norbert Myslinski of the University of Maryland, Baltimore, USA.

Mr. Huynh-Tran won US\$3,000, a trophy, and the opportunity to represent the Brain Bee around the world. Ben Thompson of Australia was a close

the local competitions then compete in their respective national championships, and the national winners go on to represent their countries in the international championship.

For more information about starting a Brain Bee in your country, go to www.internationalbrainbee.com, or contact nmyslinski@umaryland.edu. ■



COURTESY DR. NORBERT MYSLINSKI

Thanh-Liem Huynh-Tran of the United States (front center) won the Brain Bee Championship. Participants took an oral test, a neuro-anatomy exam, a neurohistology test, analyzed brain MRI scans, and diagnosed diseases in student actors posing as patients.

THE INTERNATIONAL BRAIN BEE MOTIVATES YOUNG STUDENTS TO LEARN ABOUT THE BRAIN AND CONSIDER CAREERS IN THE NEUROSCIENCES.

second to Mr. Huynh-Tran. The other finalists were: Wojciech Bochenek, Poland; Kyeong Rok Choi, Korea; Rita Di Censo, Italy; Silvia Valentina Gogu, Romania; Abha Jain, India; Vishnu Naidu, United Arab Emirates; Jimoh Hafeez Olafisayo, Nigeria; Soohyun Park, Canada; Rachael Wiltshire, New Zealand; and Katarina Zimmer, Germany.

Last year's 2010 winner was Ritika Chohani of India.

The students were tested on their knowledge of the human brain, including topics such as intelligence, emotion, memory, sleep, vision, hearing, sensation, Alzheimer's disease, Parkinson's disease, schizophrenia, addictions, and brain research. The primary reference source for the competition is *Neuroscience: The Study of the Brain* (European Dana Alliance and the British Neuroscience Society).

The competition is comprised of an oral test, a neuroanatomy laboratory exam of the human brain, a neurohistology test with tissue specimens and microscopes, MRI brain imaging analysis, and a patient diagnosis component with student actors. Some of the questions participants have to answer include: What kind of molecules are semaphorin, ephrin, neuropilin, and plexin? Sonic hedgehog is important for the development of what part of the nervous system? What is the medical term for when you start dreaming before you fall asleep? Stargazer mice are experimental models for which type of epilepsy?

The competition, launched in 1999, has three tiers. It begins at the local level, with over 100 competitions in the participating countries, each one involving pupils from different schools. Winners of



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Our fast track service publishes qualified original research faster than any other neurology journal



Experts Review Sudden Epilepsy Deaths

BY JEFFREY S. EISENBERG
Elsevier Global Medical News

The overall risk of sudden unexpected death in people with epilepsy is more than 20 times higher than in the general population. Although it has been recognized since the 19th century, only in the past 2 decades have researchers established the full extent and risk that this clinical event will occur.

In a review paper, Dr. Simon Shorvon of the Institute of Neurology at University College London and Dr. Torbjorn Tomson of Karolinska Institute and Karolinska University Hospital, Stockholm, discussed risk factors, likely mechanisms for sudden unexpected death in epilepsy (SUDEP), and the focus of current research.

SUDEP (defined as the sudden, unexpected death of a seemingly healthy individual with epilepsy) has an incidence rate of 0.09-9.3 per 1,000 person-years, depending on the type of epilepsy population, according to the authors (Lancet 2011 July 6 [doi:10.1016/S0140-6736(11)60176-1]). Several mechanisms exist, and most research has focused on seizure-related respiratory depression, cardiac arrhythmia, cerebral depression, and autonomic dysfunction.

The Task Force on Epidemiology of the International League Against Epilepsy (ILAE) pooled data from four major case-control studies of SUDEP, for a total of 289 cases and 958 living epilepsy control patients, and found the following:

- ▶ The odds of SUDEP was 1.4 times higher in male patients than in female patients.
- ▶ The odds were 1.7 times higher in those with the onset of epilepsy before age 16 than in those in whom the onset of epilepsy occurred between ages 16 years and 60 years.
- ▶ The odds were two times higher in

those who had epilepsy for longer than 15 years.

▶ The odds were three times higher in patients on combination antiepileptic drug therapy than in those on monotherapy.

Several case-control studies and the ILAE task force analysis did show an increased risk of SUDEP in patients on multiple therapies, although the authors say this might reflect the severity of epilepsy rather than the medications themselves.

One case-control study showed that individuals using no drug treatment had nearly 22 times greater odds of SUDEP than did those taking one or two antiepileptic drugs. The ILAE task force found that monotherapy was more protective than no treatment, although this was not statistically significant. Also, noncompliance with therapy or frequent changes in the prescribed dose may increase the risk of SUDEP, probably because of poor seizure control.

The most important risk factor, the task force found, was the frequency of generalized tonic-clonic seizures. Additional studies have shown that among patients who have a high number of tonic-clonic seizures, the relative risk of SUDEP ranges from 7 in those with a history of 3-12 seizures in the previous year to 10 in those with a history of more than 50 seizures in the previous year. The relative risk was 23 overall, compared with those patients who were seizure free, although SUDEP may occur in patients with infrequent seizures or even those patients experiencing their first seizure.

However, most people with frequent seizures do not experience SUDEP, which suggests individual susceptibility. "Furthermore, in most cases, even the predisposed individual will usually have had many non-fatal seizures before the final fatal one, which suggests that there are modulating factors that establish whether the course of the seizure will be benign or

will lead up to SUDEP," the authors wrote. "Various aspects have been studied, but a satisfactory unitary explanation of the mechanisms of SUDEP remains elusive."

The researchers suggested that clinicians should inform patients and relatives about the risk of SUDEP. They also recommend cardiac pacing in patients with evidence of marked cardiac arrhythmia, close observation after a tonic-clonic seizure until the patient regains full consciousness, and caution in prescribing

antiepileptic drugs with potential cardiorespiratory adverse effects.

Dr. Shorvon has received consultancy fees from Janssen Cilag, UCB Pharma, and Eisai, and has received speaker's honoraria from GlaxoSmithKline, Janssen Cilag, and UCB Pharma. Dr. Tomson has received research grants from Eisai, GlaxoSmithKline, Janssen-Cilag, Novartis, Sanofi-Aventis, and Pfizer, and has received travel expenses from UCB Pharma. ■

Epilepsy Deaths in West China

Probable sudden unexpected death in epilepsy is second only to drowning as the leading cause of premature death among patients with convulsive epilepsy in rural West China, who die early at a rate nearly five times higher than that of the general population, according to a prospective study.

Dr. J. Mu of Sichuan University in Chengdu, China, and colleagues reported that 106 of 3,568 patients with active convulsive seizures from an epilepsy management program in the Sichuan Province died during a median 28 months of follow-up (Neurology 2011;77:132-7). From an original total of 4,976 patients who were screened, the researchers excluded 1,408 patients who were already on treatment, had not had seizures in the previous year, had a doubtful diagnosis or refused to participate.

Drowning was the leading cause of death (46 patients), followed by probable SUDEP (15 patients), status epilepticus (7 patients) and malignant neoplasm (7 patients).

The mean duration of epilepsy in patients was shorter in patients who

died than in those who survived. And at the last follow-up, the mean dosage of phenobarbital – the first treatment option available – was lower in patients who died.

In 2007, the highest proportional mortality ratios (defined as the proportion of deaths from a specific cause) were 59% for accidental death, including 45% for drowning; 15% for probable SUDEP; and 7% each for status epilepticus and malignant neoplasm.

The standardized mortality ratios (SMRs), which refer to the ratio of the observed number of deaths among patients with convulsive epilepsy to those expected, were 4.92 for men and 4.52 for women, and were especially high among younger patients.

SMRs showed that patients with convulsive epilepsy have an 82-fold higher risk of drowning than does the general population.

Some of the authors reported relationships with government agencies, patient advocacy groups, philanthropic and international organizations, and pharmaceutical companies that manufacture antiepileptic drugs.

Shiga Toxin Link

Epidemic • from page 1

(eye muscles, swallowing) were seen, and a few patients even developed acute coma with absent brainstem reflexes, but nevertheless recovered over time. It is too early to report on the neurological outcome of this epidemic, but we have seen many patients who had favorable outcomes despite the severe neurological infection.

The treatment for EHEC was plasmapheresis in the patients with HUS, though it did not always improve the neurological symptoms. Many patients were treated with eculizumab, a new complement-binding monoclonal antibody that was administered when plasmapheresis did not improve HUS or the neurological symptoms. The assumed mechanism of this new treatment is that it blocks the Shiga toxin-induced activation of the complement, though effects of this treatment need to be carefully analyzed. Additional neurological therapies were for seizures and for sedation in patients with confusional syndromes. Complex treatments were necessary whenever uremia, thrombopenia, and neurological symptoms occurred in the same patient.

The disease was concentrated in a region that is home to four university hospitals – in Hamburg, Hannover, Kiel, and Lübeck – and many of the patients received care at

one of these institutions. From early on, the hospitals devised plans to handle the epidemic catastrophe. In Kiel, more than 150 patients were admitted in less than 3 weeks. The patients were considered highly infective based on earlier data suggesting that fewer than 100 bacteria could cause an infection. They were placed in special wards that were isolated from the patients in the rest of the hospital. The care for these patients was complicated by the high demands for in-hospital control of the infection.

Because patients with HUS and the neurological syndrome needed ventilation and intensive care, there was an urgent need for more intensive care units (ICUs) than were available in Kiel. In addition, the patients with HUS had to be isolated in separate intensive care units because of the high infective potential, so new ad hoc ICUs were opened in the wake-up rooms of operating suites.

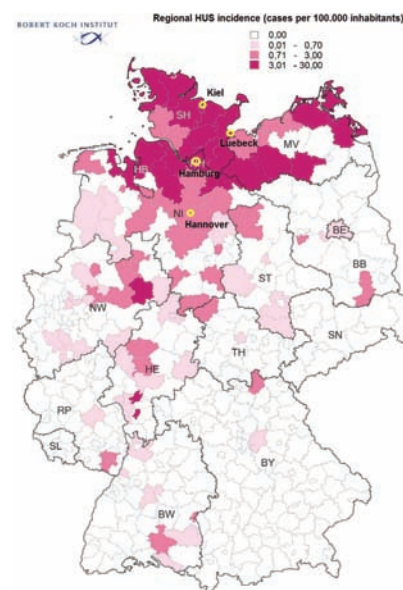
Interventional disciplines such as surgery, cardiology, and neurology had to limit their interventions to emergencies for sev-

eral days during the peak of the infection. The nursing staff was not able to handle the patient load, so the local ministry of health advertised for temporary help in large clinical facilities in south Germany. Neurologists in the attending teams compiled an in-house manual for the

treatment of EHEC-caused neurological disease and updated it daily.

We learned two lessons for neurology from our experience with this epidemic. First, catastrophe medicine is usually not within the spectrum of neurology (Economic encephalitis and poliomyelitis may have been similar examples in the past), but when it is, team work between neurologists and other attending specialists is essential; and second, in dealing with a completely unknown disease, the combination of the classic neurological approach to such diseases and intensive care neurology is invaluable in treating it effectively. ■

DR. DEUSCHL and DR. STINGELE are in the department of neurology, Christian Albrechts University, Kiel, Germany.



This map shows the incidence of EHEC according to the region where the infection most likely took place.

DATA FROM THE ROBERT-KOCH-INSTITUTE, BERLIN, WITH PERMISSION

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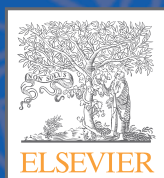
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Support Networks Proved Crucial

Japan • from page 1

emergency evacuation areas. Ten days after the earthquake, he opened a makeshift clinic in an abandoned medical office. When faced with a tragedy of such proportions, he said, it was essential to have a forward-looking attitude toward life.

Another neurologist told of a neurological clinic near Miyako Bay that was flattened as a wall of sea water nearly 30 feet high inundated the first floor, destroying all the neurological tools, and equipment, including the MRI scanner.

learned they should have provided a mobile medical service in the stricken areas so that they could travel to the patients when the roads allowed it.

The discussants at the forum agreed that there is an urgent need for ongoing research in disaster medicine in the field of neurology to prevent disaster-related neurological disease from progressing and intractable disease from worsening in the aftermath of such crises. They agreed that a large-scale epidemiologic study was also warranted to provide an effective safety net for neurological disease patients.

Hospital Activities in Crisis

At Tohoku University Hospital in Sendai City, which is usually the lifeline of the area, the elevators were damaged and declared unsafe, meaning that patients and medical supplies could not be taken to the upper floors for a while. Laboratories were without power for a week, and all clinical specimens were lost because there was no refrigeration. At least seven hospitals with 723 beds along the Miyagi Prefecture

coastline were so devastated they could no longer function, leaving only two hospitals able to accept patients. Phones and wireless networks were knocked out in most hospitals, and many of the severe injury cases had to be brought to the university hospital from the two hospitals that were in operation. Based on this scenario, the forum participants noted that two things were crucial if teams were going to be effective in coping with the demands for assistance: Communication channels had to be maintained and regional transport needed to be restored.

Local Support Network

In Iwate Prefecture, one of the three areas hit hardest by the earthquake, a complete team of doctors, dentists, public health doctors, nurses, and pharmacists, together with police and self-defense forces was established. A medical support network was set up to investigate disaster treatment in real time, with neurologists on the ready. In response to some of support network's observations, patient transport, clinical treatment at shelters, measures against infectious disease, and psychological counseling were added to the care system.

Nationwide Network

Medical facilities that escaped direct damage had no choice but to receive injured patients beyond their capacity. The absence of a disaster coordinator to match up the needs of those sending and receiving patients, such as doctors on the ground and personnel from the ministry of health, labor, and welfare; defense agency; and fire department, was a source of frustration for both those wanting to assist and those seeking help.

The Japanese Society of Neurology quickly spearheaded a move to provide

countries offered to assist. We offer our heartfelt thanks!

Not surprisingly, Tokyo and its vicinity, which were not directly in the path of the quake or tsunami, were nevertheless plagued by power losses due to the nuclear plant accident. The crisis thus severely crippled medical capacity, with blackouts and energy shortages even at considerable distances from Fukushima.

Planning for Recovery

We should research disaster medicine in the field of neurology, and prevent neurological disease from progressing after an earthquake. For stable recovery of these devastated areas, where a lack of doctors has long been a problem, a grand plan must be worked out and put in place as quickly as possible.

Long-term recovery and ongoing assistance remain daunting tasks for afflicted people and medical professionals, not to mention the government; countless patients, evacuees, and homeless and jobless people must now rebuild their lives in the wake of the disaster. We are sure that the dignity, patience, fortitude, and benevolence of our own patients that truly inspired us will eventually mean the successful recovery of Japan. ■

DR. TAKAHASHI, associate professor, division of neurology and gerontology,



COURTESY DR. MIEKO OGINO

A military helicopter lifted five ventilation-assisted neuromuscular disease patients to safety.

Fortunately, the second floor of the building was set up as a clinic for tsunami casualties and was able to reopen after 2 days. But all power, water, and gas supplies as well as cable phone service came to a halt for 2 weeks. Cell phone service, where it was available, was so overloaded that it was difficult to get through or the sound was subpar.

First-Aid Support Team

Help soon came from medical and emergency crews in areas that had not been af-



Areas of Japan where neurologists and other health care workers responded.

ected by the disaster. The Fukui University medical support team set up an emergency first-aid station in hard-hit Watari-cho, where it treated over 18% of patients with disaster-related neurological disease for 8 straight days. Headache and dizziness were the chief complaints, but no patients with neurological intractable diseases came to the station because they were immobile due to progression of their symptoms. Indeed, neurologists



COURTESY DR. FUMITOSHI HAMATO

The tsunami completely destroyed a clinic near the northeast coastal city of Kamaishi.

a nationwide list of hospitals that could take in more patients. Government agencies and the defense force joined hands to transport patients needing ventilation support.

At the request of Iwaki Hospital, a defense force helicopter lifted five ventilation-assisted neuromuscular disease patients to safety. The medical transfer team faced several problems such as intense noise and oscillation of the helicopter. The importance of this kind of on-the-ground knowledge being recorded and disseminated for use in future emergencies cannot be overestimated. We also came to appreciate the value of having emergency coordinators and a well-planned system for clinical treatment in place for emergencies such as this one.

Power Plant Crisis

Fukushima, both a prefecture and a city located not far from the damaged nuclear power plants, suffered the triple blow of earthquake, tsunami, and the effects of a nuclear plant accident. The onsite experience of many medical teams taught them to give top priority to the transfer of all serious patients to safer ground, especially those on ventilator support.

One neurologist said that he simply did all that he could rather than lose time and opportunities while awaiting directives. He proposed the following to expedite patient transfer:

► **Build on personal relationships.** Doctors who know each other can quickly communicate by phone, text messaging, or e-mail to reserve patient beds and arrange transfers.

► **Network with professional societies.** Most medical societies have online resources designed for or adaptable to disaster response. Specialists can thus network faster among themselves to arrange beds and transfer methods.

► **Access doctor-driven electronic networks.** An example of this is the Google group Jishin Iryo (earthquake medical treatment) – jisin-iryoo@googlegroups.com.

► **Reach out to patient support groups.** These nonprofit organizations support specific categories of patients, and many of them have relationships with the ministry of health, labor, and welfare. In addition to the local help, volunteers from across Japan pitched in, and over 150



COURTESY DR. OKUJOU IWAMI

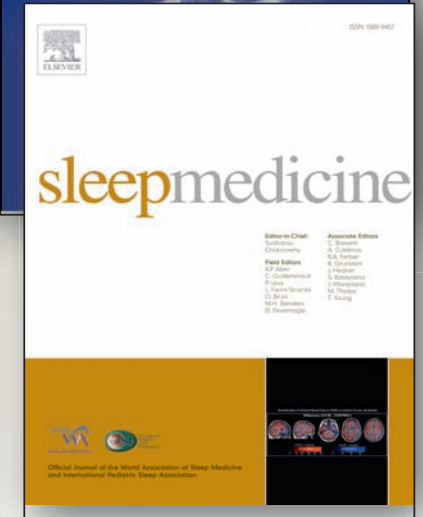
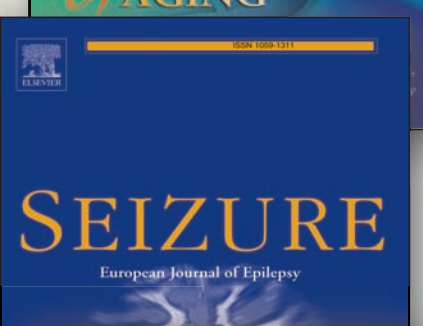
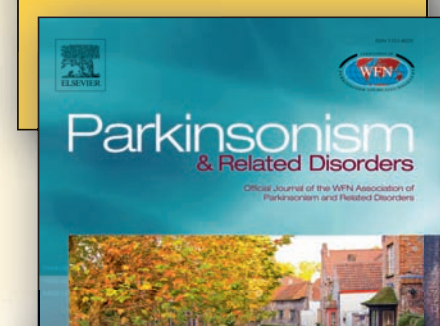
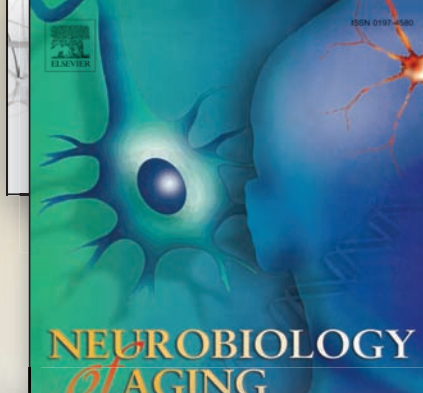
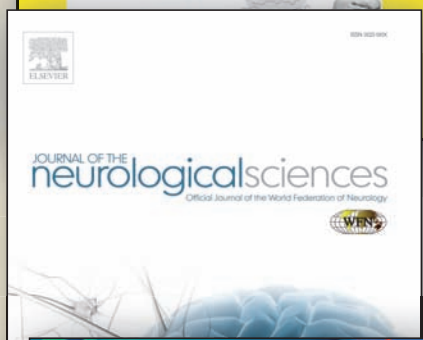
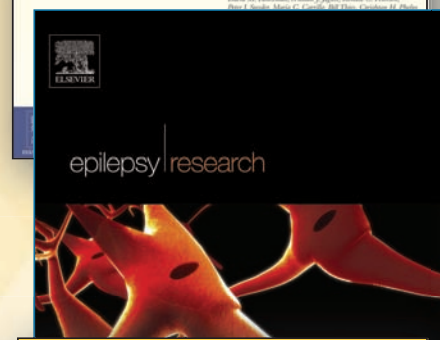
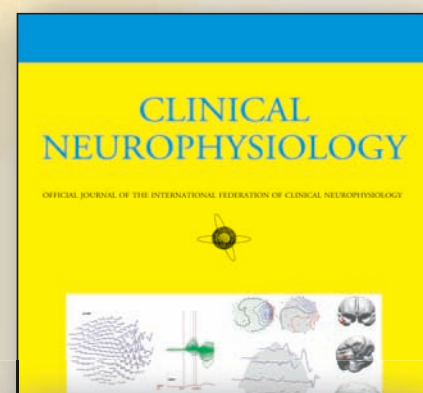
A wall of water nearly 30 feet high inundated the first floor of a neurological clinic near Miyako Bay.

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MS May Relapse After Yellow Fever Vaccination

BY NASEEM S. MILLER
Elsevier Global Medical News

Patients with relapsing-remitting multiple sclerosis had a more than 10-fold increase in their relapse rate after they received vaccination against yellow fever, according to a small prospective study.

Although relapsing-remitting MS and yellow fever (YF) vaccination do not overlap often, “depending on specific patient travel plans, potential local epidemics, and length of stay, the final decision on whether to administer the vaccine should result from a careful balance between the risk of MS exacerbation and the likelihood of exposure to the YF virus, which can lead to death,” Dr. Jorge Correale, one of the authors of the study, wrote in an e-mail (Arch. Neurol. 2011 June 13 [doi: 10.1001/archneurol.2011.131]).

Dr. Correale added that most other vaccines do not increase the risk of new exacerbations in MS patients (J. Neurol. 2011;258:1197-206). “However, in contrast to other vaccines, YF vaccine is prepared with live attenuated virus, and probably for other vaccines prepared in the same way we need to consider this possibility,” wrote Dr. Correale and his coauthor, Dr. Mauricio F. Farez. Both work in the department of neurology at the Dr. Raúl Carrea Institute for Neurological Research, Buenos Aires.

YF is a potentially deadly disease found

in tropical regions of Africa and in parts of South America. It affects approximately 200,000 people each year and leads to 30,000 deaths annually. Although there are no treatments for the disease, the YF 17D-204 vaccine has been proven a safe and effective preventive measure.

Observations of two patients who presented with worsened MS after YF immunization prompted the authors to conduct the study. There are very little data available on the overlap of YF vaccination and MS.

The authors recruited seven patients – five women and two men with an average age of 45 years – with relapsing-remitting MS who received a single dose of YF 17D-204 before traveling. After vaccination, the patients underwent clinical, radiological, and immunological evaluations every 3 months for 2 years. The investigators asked the patients to return for examination within 72 hours if they had a relapse.

To serve as control subjects, the investigators recruited seven unvaccinated

patients with MS of the same age and sex; seven patients with MS of the same age and sex who had received influenza vaccinations; and seven healthy individuals of the same age and sex.

They defined an MS exacerbation as the development of a new symptom or worsening of preexisting symptoms lasting at least 48 hours and preceded by stability or improvement

lasting at least 30 days. They considered patients to be at risk between 1 to 5 weeks after immunization.

During the at-risk period, five of the seven patients who received YF 17D-204 had exacerbations. Four of those five patients had a significant and persistent increase in their Expanded Disability Status Scale score 1 year after the exacerbation, according to the study. Exacerbations

were transient in the other three patients.

The annual exacerbation rate in the at-risk period was significantly higher than during the non-risk period (8.57 vs. 0.67, respectively).

During 2 years of follow-up, the over-

all annual exacerbation rate was 0.99.

In contrast, immunization against influenza did not affect the annual exacerbation rate.

MRI showed a significantly higher mean number of new or enlarging T2 lesions at 3 months after YF vaccination, compared with the remaining follow-up period (2.6 vs. 0.1), as well as significantly more gadolinium-enhancing lesions (2.14 vs. 0).

The study’s limitations were the small number of patients and its unblinded design for clinical and radiological assessments.

The authors added that it is not clear how yellow fever immunization can trigger autoimmune reactions. They proposed molecular mimicry, epitope spreading, bystander activation, and polyclonal activation as possible mechanisms.

“Whether the more than 10-fold increase in the relapse rate observed in these seven patients can be confirmed by larger studies remains to be seen,” the authors wrote.

Dr. Correale is a board member of Merck Serono Argentina, Biogen Idec LATAM, and Merck Serono LATAM. He has received reimbursement to develop educational presentations for Merck Serono Argentina, Merck Serono LATAM, Biogen Idec Argentina, and Teva-Tuteur Argentina.

The study was supported by a research grant from his institution. ■



COURTESY DR. JORGE CORREALE

Before this study, there were very little data available on the overlap of yellow fever vaccination and MS, Dr. Jorge Correale said.

Deep Brain Stimulation Didn't Alter Course of Parkinson's

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

Subthalamic nucleus deep brain stimulation doesn't appear to change the course of Parkinson's disease when it is performed on patients with long-standing disease.

In the longest follow-up cohort study to date, Dr. Aristide Merola and his colleagues tracked patients who underwent the procedure at about age 60 years. They all showed similar declines in cognition, gait stability, and continence – marks of the disease's later stage, according to their study.

However, the study should not be construed as a negation of deep brain stimulation's (DBS's) potential therapeutic value, wrote Dr. Merola of the University of Turin (Italy) and his coauthors. Instead, they suggested that one can “speculate whether the subthalamic nucleus DBS surgical procedure should be proposed earlier, considering that Parkinson's disease progression might not follow a linear course, and it is possible that age might influence the development of non-motor features more than disease duration” (Brain 2011;134:2074-84).

The study comprised 19 patients who underwent subthalamic nucleus DBS after a mean disease duration of 22 years. The investigators compared the baseline results of clinical and neuropsychological testing to those at 1 year, 3 years, and 5 years. For 14 patients who underwent testing after more than 7 years post surgery, the mean follow-up duration was 8 years.

The cohort consisted of 9 men and 10 women. The patients had developed disease symptoms relatively early in life (at a mean of 39 years). Their mean age at the intervention was 61 years.

The patients were evaluated with the UPDRS (Unified Parkinson's Disease Rating Scale) at baseline and

after the procedure, when the scale was administered at each follow-up point in four disease states: stimulation on/medication off, stimulation off/medication off, stimulation off/medication on, and stimulation on/medication on.

The authors noted that they paid “particular attention to the main axial, non-motor, and psychiatric symptoms,” assessing subjects for falls, postural instability, non-levodopa responsive gait freezing, urinary incontinence, dysphagia, and speech difficulty. They used pharmacologic treatment as a measure of other symptoms, including constipation, postural hypotension, depression, and hallucinations.

Freedom from those symptoms is a prerequisite for DBS surgery; therefore at baseline, none of the patients showed evidence of them.

Follow-up considered not only the years out from surgery, but also the years of disease duration. The long-term follow-up evaluations showed a similar pattern of symptom progression in all patients, regardless of the disease state in which they were measured. However, the combination of stimulation on/medication on was consistently more effective at controlling symptoms than were the other states.

“The majority of patients progressively developed falls (64%), postural instability (100%), non-levodopa responsive freezing of gait (64%), dysphagia (86%), urinary incontinence (57%), severe postural hypotension (36%) and dementia (43%) during the course of follow-up,” the authors wrote. “On the other hand, neuropsychological data showed a gradual decline in the performance of all the main cognitive domains, in agreement with previous findings” that showed a five-fold prevalence of dementia in patients with Parkinson's disease, compared with the general population.

Complications of levodopa therapy significantly im-

proved initially after DBS. But this improvement gradually decreased over the follow-up time. The same pattern occurred in activities of daily living. The mean levodopa equivalent daily dose decreased in the first year after surgery (from a mean of 890 mg to 336 mg). Over the entire follow-up, the dose continued to increase, but only rose to a mean of 435 mg/day after more than 7 years.

When the investigators examined the progression of falls, postural instability, and gait freezing, a similar pattern emerged. There was a slight increase from 1 to 3 years, and then a sharper increase at 5 years. After more than 7 years – with 14 patients still being followed – 9 of them had postural instability, all had gait freezing, and 9 had fallen.

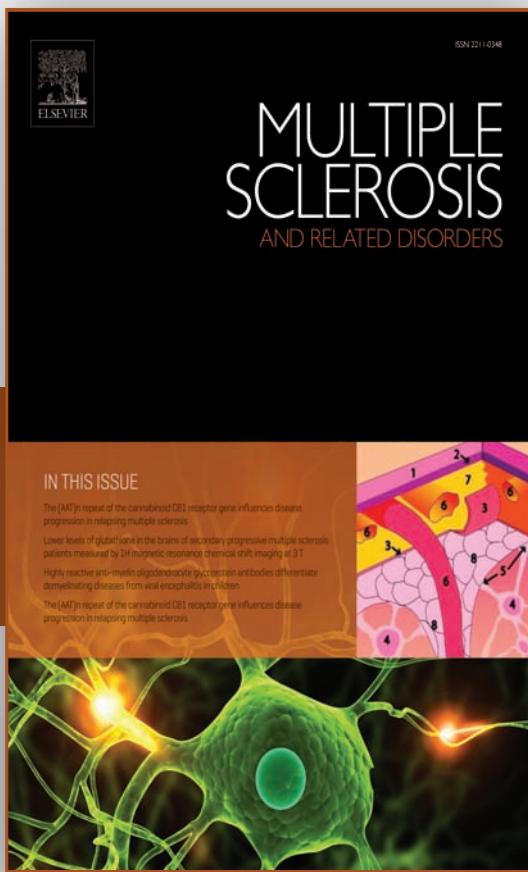
“The initial positive effects of subthalamic nucleus DBS on balance and postural stability ... in the first years from surgery seem to be mostly related to the improvement of rigidity and bradykinesia, rather than to a specific effect on balance and gait,” the authors noted.

At baseline, only one patient showed moderate dysphagia. During the follow-up period, the incidence of dysphagia increased, as did speech difficulties. After more than 7 years, 12 had dysphagia, 3 required a percutaneous gastrostomy, and 9 had speech disturbance.

Constipation and postural hypotension, as measured by the need for drug intervention, remained low for 3 years after surgery. For those who reached a follow-up observation longer than 7 years, half required a catheter or diaper.

Dementia, depression, and hallucinations also became increasingly common over the follow-up period. After more than 7 years of follow-up, six patients required medication for depression, nine required medication for hallucinations, and six developed dementia.

None of the authors had any relevant disclosures. ■



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FOCUS ON TRAINING – BASHKORTOSTAN, RUSSIA

Integrating Learning With Clinical Routine

BY LEYLA AKHMADEEVA, M.D.,
PH.D., AND RIM MAGZHANOV,
M.D., PH.D.

Continuing professional learning for neurologists is a priority in the Republic of Bashkortostan, central Russia – almost a tradition, some would argue. Neurologists have to confirm their qualifications every 5 years and we are eager to deliver the best possible training to our interns and residents, so we consider their professional education to be of paramount importance.

At our clinic at the Bashkir State Medical University in Ufa, the capital city (see sidebar), we have integrated professional education into our routine in a number of ways. Our daily practice includes seeing patients, doing research, and continuing our professional education in neurology. As in other parts of the country, a full-time hospital-based neurologist takes care of 20 inpatients, though we try to work as teams that include trainees so that they can learn from the more experienced team members.

Presently there are five interns (medical school graduates who are starting out in their specialty training), and one resident (the level after the 1-year internship).

We have weekly meetings for neurologists, neurology residents, and students that are carefully planned in advance and allow for the discussion of very spe-

cific neurological problems. Occasionally, we might invite colleagues from other medical specialties as guest speakers. For instance, we had a number of talks and hands-on training with a professor of psychology, at which we learned how to talk to patients with incurable disorders, how to talk to their families, and how to manage an aggressive patient.

But we also draw heavily on input from our colleagues overseas and elsewhere in Russia. Twice a year, we organize free international neurological conferences and invite well known experts from different fields of medicine to lecture for us on topics such as rehabilitation, nursing, sociology, HIV/AIDS, and



Prof. Leyla Akhmadeeva and Dr. Cyndi Robinson (center left and right, respectively) with trainees at Bashkir State Medical University.

psychiatry. In addition, the ability to teleconference has opened new opportunities for learning and cooperation. Among our most steadfast teleconferencing foreign partners are colleagues led by Prof. Leif Gjerstad from the Rikshospitalet in Oslo, Norway. Prof. Gjerstad has been a supporter of ours since 1993.

We have learned many new skills from our local and foreign neurology colleagues by holding master classes at the clinic. For example, Dr. Cyndi Robinson of the University of Washington (Seattle, USA) has given separate master classes on innovative approaches and techniques in neurorehabilitation and balance assessment in multiple sclerosis.

Last year, one of the highlights of our training program was the European Federation of Neurological Societies' first regional teaching course at our institution. Experts from numerous countries presented lectures, seminars, and workshops on a range of topics: David Vodusek (Slovenia) on visceral pain and neurogenic bladder; Reinhold Schmidt (Austria), Wolf-Dieter Heiss (Germany), and Sergej Illarioschkin (Russia) on dementia, neurodegenerative diseases, and Parkinson's disease; Jozef Opara (Poland) and Alla Guekht (Russia) on rehabilitation, especially after stroke; Andrej Danilov (Russia) on diagnosis and management of neuropathic pain; and Hermann Stefan (Germany) on seizures, cognition, and epilepsies; and Ralf Baron (Germany) on pain. The 150 neurologists who attended this course had the opportunity to sit for the EFNS exam.

Such international cooperation gives us a broader perspective and a better understanding of neurology. The student research society members stand to benefit

from these education endeavors when they apply for international academic exchange programs or to attend or present at local and international meetings.

We are always open to news ways of collaborating with our colleagues, and increasingly, modern technologies are helping us build those bridges. ■

PROF. MAGZHANOV is chair of the department of neurology at Bashkir State Medical University, in Ufa, Russia, and PROF. AKHMADEEVA is the director of the neurology clinic and ward at the university.

About the Clinic

The Republic of Bashkortostan (population 4 million) has one medical university, Bashkir State Medical University. Its department of neurology was opened in 1936. In 2004, the university established its own hospital and clinic, and 2 years ago the hospital was reorganized into clinics consisting of a ward with in-patients and consultants who see outpatients. The neurology clinic is one of the largest of these entities: there are 60 beds in the ward and two full-time consultants who work with outpatients both from the region and the rest of Russia. The director of the clinic has weekly rounds and consultations with outpatients; sees all complicated cases daily and intensive care patients as needed; and leads the educational programs and research studies with specialists, residents, doctorate and medical students.

BOOK REVIEW

Electronic Atlas of Neuropathology Is Available

Digital Atlas of Basic Neuropathology

By John S. Woodard, M.D.

An e-book published by California Medical Publications, Temecula, Calif., USA

This e-book is a collection of interesting photographs and micrographs assembled from the author's collection. The pictures are accompanied by brief commentaries with some – but not extensive – references.

In the introduction, the author, who was a principal investigator in the Camarillo Brain Study Project, refers to another e-book of his, *Diagnosis and Prevention of Dementia*, published in 2006. A note on the downloading site of *Diagnosis and Prevention* says it is based on the Camarillo project, which was a study of brain morphology and mental disorders in California. The *Digital Atlas* site has a similar note about the Camarillo project, but it is not clear whether the two publications contain any of the same images.

The book is divided into units comprising developmental, neoplastic, anoxic, neuron storage, alcohol-related, infectious, degenerative, demyelinating, trauma, and cerebrovascular disorders. Overall, although it has some good pictures, the selections do not cover all areas of neuropathology and the book is spoiled by the poor quality of many of the slides.

Some of the pictures are very good, but many of them suffer from discolored edges to the brain slices with dark brown areas. Some have highlights that obscure the anatomical point, for example, the purulent exudate in the meningitis pictures (slide 675). A number of the micrographs are labeled Luxol fast blue but look more like Weigert or one of the other hematoxylin-based stains used for celloidin sections. This may be a result of poor color balance of

the pictures or poor reproduction. Yet other micrographs have a poorly placed condenser.

The references are old, and the commentaries in the neurodegenerative and neuron storage disorders are out of date. Most of the references in this volume predate 1990, although there is one from 2001 (slide 652). Slide 755 says that several pathologists have died from Creutzfeldt-Jacob disease, but a search of the literature reveals maybe two or three, which is no different from the rest of the population.

The e-book contains 857 slides and is available as a 43-megabyte PDF. It can be downloaded at www.drivehq.com/file/df.aspx/shareID8403974/fileID695316588/samples1.pdf for a nominal fee. ■



BY E. TESSA HEDLEY-WHYTE,
MD

Dr. Hedley-Whyte is professor of pathology at Massachusetts General Hospital, Boston, Mass., USA.

FROM THE WFN HISTORY GROUP

Subacute Combined Degeneration of the Spinal Cord

BY J.M.S. PEARCE, M.D., FRCP

Although international research and study in neurology dates back centuries, multicenter, collaborative trials were rare until after World War II. Before that time, researchers in different countries often worked independently of each other, as was the case with the early investigators of subacute combined degeneration of the cord (SACD)



PETER J. KOEHLER, MD, PHD, is the editor of this column. Dr. Koehler is a neurologist in the department of neurology at the Atrium Medical Centre, Heerlen, the Netherlands. Visit his website at www.neurohistory.nl.

in Britain, the United States, Switzerland, and Germany.

The spinal cord, brain, optic nerves, and peripheral nerves are all affected by vitamin B₁₂ (cobalamin) deficiency, the cord usually first. The association of anemia with abnormalities of the brain, spinal cord, and peripheral nerves was recognized in early 19th century clinical and postmortem reports. But it was not until 1849, when the English physician Thomas Addison (1793-1860) provided a clinicopathological description of pernicious anemia (which the French physician Armand Trousseau named Addisonian anemia), that was it recognized as an entity and subsequently became linked with SACD.

The German physician Otto Leichtenstern (1845-1900) reported the first clear association of pernicious anemia with cord disease in 1884, but attributed it to tabes dorsalis. In 1887, the German neuropsychiatrist Ludwig Lichtheim (1845-1928), first pointed out that the histology of the cord in tabes dorsalis

(syphilitic myelopathy) was distinct from that found in pernicious anemia. He later described two patients with pernicious anemia who had clinical cord signs. At autopsy, he showed changes, especially in the posterior columns of the spinal cord.

In 1890, Charles L. Dana (1852-1935), of the Cornell Medical School, N.Y., USA, and James Jackson Putnam (1846-1918), first professor of neurology at Harvard University in Cambridge, Mass., USA, reported subacute combined degeneration of the cord simultaneously, but as a result of separate exploration. Putnam described eight “enfeebled patients” with combined

sclerosis of the corticospinal tracts and posterior columns, and neuritis; in addition they suffered from anemia and exhaustion. “A group of cases of systemic sclerosis of the spinal cord, associated with diffuse collateral degeneration; occurring in enfeebled persons past middle life, and especially in women,” he noted, and he observed that “the progressive impairment of both the sensory and the motor functions of all four extremities.”

William Gowers (1845-1915), the English neurologist, described “ataxic paraplegia – combined lateral and posterior sclerosis,” which he distinguished from tabes, but did not mention anemia.

By the beginning of the 20th century, pernicious anemia and SACD were considered to result from infections. William Hunter (1861-1937), pathologist at Charing Cross Hospital in London, recorded several distinctive cases of subacute combined degeneration of the cord in pernicious anemia in 1900; his



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In 1884, Otto Leichtenstern (left) reported the first clear association of pernicious anemia with cord disease, and in 1887, Ludwig Lichtheim first pointed out that the histology of the cord in tabes dorsalis was distinct from that found in pernicious anemia.

conceptions were dominated by the causal role of oral infections.

In 1900, three physicians from the National Hospital for the Paralyzed and Epileptic in London – Risien Russell (1863-1939), Frederick Batten (1865-1918), and James Collier (1870-1935) – reported a definitive clinical analysis that has not been bettered. They coined the term “subacute combined degeneration of the spinal cord,” reporting that some of their “most typical cases presented no anaemia throughout the course ... others only late in the disease, while in other cases, anaemia preceded the nervous symptoms by many months.”

PUTNAM DESCRIBED EIGHT PATIENTS WITH ANEMIA, NEURITIS, AND SCLEROSIS OF THE CORTICO-SPINAL TRACTS AND POSTERIOR COLUMNS.

It is interesting to note that S.A. Kinier Wilson later debated the nomenclature, arguing that “the lesions are neither confined to the dorsal and lateral columns nor systematized; the term conveys no hint of the connexion with anaemia; the epithet ‘subacute’ is not only awkward to define, but inapplicable at least to some instances ...” – but clearly to no avail.

Subsequent History

In the 1920s, the Americans George Whipple, George Minot, and William Murphy experimented with liver supplements as a possible therapy for pernicious anemia. They treated 45 patients over a 2-year period, all of whom responded. Their discovery won them the 1934 Nobel Prize in Physiology or Medicine.

Twenty-two years later, the American Karl Folkers and E. Lester Smith (England), and their respective colleagues reported within weeks of each other that they had isolated vitamin B₁₂ (renamed cobalamin).

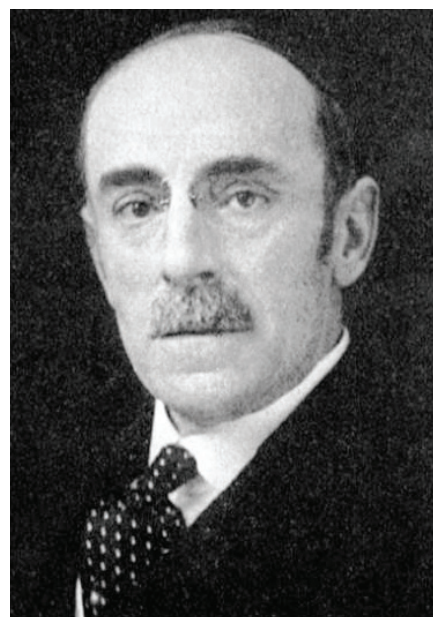
Dorothy Hodgkin, a British chemist and crystallographer, described crystallized cobalamin in 1956, for which she won the Nobel Prize for Chemistry in 1964. Five years later, an American organic chemist and 1965 Nobel laureate, Robert Woodward, and his Swiss collaborator, Albert Eschenmoser, reported on the synthesis of the vitamin.



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ALASTAIR COMPSTON, "FROM THE ARCHIVES," BRAIN, 2005, 128, 12, 2757-59, BY PERMISSION OF OXFORD UNIVERSITY PRESS

Risien Russell (left), Frederick Batten (middle), and James Collier (right), three physicians from the National Hospital for the Paralyzed and Epileptic in London, coined the phrase subacute combined degeneration of the cord after reporting a definitive clinical analysis that said some of the most typical cases presented no anemia throughout the course of the disease.

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