AMERICAN HEALTH CONSULTANTS®

Providing Evidence-based Clinical Information for 20 Years

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

Inosine Promotes Stroke Recovery

ABSTRACT & COMMENTARY

Source: Chen P, et al. Inosine induces axonal rewiring and improves behavioral outcome after stroke. *Proc Natl Acad Sci.* 2002;99:9031-9036.

DESPITE RECENT ADVANCES, THERAPY FOR ACUTE STROKE remains minimal. Thrombolysis is hampered by damaging side effects and restrictive time windows. Neuroprotection has failed in every human trial despite promising animal data. Given these limits, the possibility of enhancing recovery through neuronal regeneration offers an enticing new avenue for stroke treatment.

In the present study, inosine, a naturally occurring purine nucleoside, was injected into the ventricular system of rats with experimentally induced right hemispheric strokes. Strokes were induced surgically. In the first study, conducted at Harvard, the middle cerebral artery (MCA) was occluded and inosine was injected into the cisterna magna. In the second, at the University of Lethbridge, Canada, both the MCA and the anterior cerebral arteries (ACA) were occluded with inosine injected into the lateral ventricle on the healthy side. Animals were studied behaviorally and histochemically.

Rats were tested for behaviors such as fore- and hindlimb placing or reaching for food. Treated animals performed significantly better than vehicle-treated rats on every modality. Remarkably, even when free to use either paw, treated animals used their paretic limb to retrieve food pellets. None of the vehicle-treated animals used their paretic limb to reach for food, even with their good limb constrained.

Infarct volumes showed no difference between treated and control patients, indicating that inosine had no neuroprotective effect. Any benefit of inosine, therefore, resulted from axonal reorganization rather than any reduction in the magnitude of the stroke itself. In histological studies, axons originating in the intact hemisphere were labeled with a tracer (BDA) that was transported to distal axon terminals. In both the corticorubral and corticospinal tracts, significantly increased axonal sprouting was observed into the damaged side. Treated animals showed increased levels of GAP-43—a marker of axonal growth not appreciably seen in controls. Inosine, acing

VOLUME 20 • NUMBER 12 • AUGUST 2002 • PAGES 89-96

INSIDE

through direct intracellular mechanisms, has been shown in cell culture to upregulate GAP-43 gene expression, and may thus do so in vivo as well.

COMMENTARY

It is well appreciated that a limited degree of rewiring occurs after stroke. Recovery can be enhanced with physical therapy, in particular, with the "constraint-induced" paradigm where patients are forced to use the paretic limb. Inosine appears to significantly augment this process. Unfortunately, prior pharmacological attempts at stimulating stroke recovery have failed. Drugs such as the myelin constituent CDP-choline (Citocoline) and bFGF, a neuronal growth factor, have shown positive results in animals and preliminary human studies, but failed in Phase III trials.

The present data are, therefore, viewed with some trepidation. As Chen and colleagues note, it will be important to clarify practical issues such as the eligible time window for this therapy. Inosine was dosed immediately in these rats, but previous studies by Chen et al have indicated benefits up to 24 hours after stroke. Further, in contrast to rats with intraventricular catheters, human subjects will require alternative dosing routes, such as intravenous infusions, which will achieve much lower CNS levels. Fortunately, since inosine is a naturally occurring substance, it will likely be tolerated by humans in fairly high doses. This differentiates it from glutamate antagonists, antioxidants, and other previously studied neuroprotective drugs that have been severely limited by toxicity. **—ALAN Z. SEGAL**

Neurology Alert, ISSN 0741-4234, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/
GROUP PUBLISHER: Donald R. Johnston.
EDITORIAL GROUP HEAD: Glen Harris.
MANAGING EDITOR: Robin Mason.
ASSOCIATE MANAGING EDITOR: Neill Larmore.
SENIOR COPY EDITOR: Robert Kimball.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail Address: customerservice@ahcpub.com
Editorial E-Mail Address: neill.larmore@ahcpub.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $287
Student/Resident rate: $145
Multiple Copies
2-9 additional copies: $213. 10-20 copies: $190.
Canada
Add 7% GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 20 hours of Category 1 credit toward the AMA Physician's Recognition Award.
Each physician should claim only those hours of credit that he/she actually spent in the educational activity.
This CME activity was planned and produced in accordance with the ACCME Essentials.
AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments
Please call **Neill Larmore**, Associate Managing Editor, at (404) 262-5480 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Apatoff is on the speaker's bureau of Biogen and Teva. Dr. Relkin is on the speaker's bureau of Pfizer, Eisai, and Athena Diagnostics and does research for Pfizer and Merck. Dr. Rubin does research for ASTA Medica and Eli Lilly. Dr. Plum, Dr. Frucht, Dr. Lado, Dr. Reich, Dr. Segal, and Dr. Trifiletti report no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.

Cyclophosphamide for Severe Myasthenia Gravis

ABSTRACT & COMMENTARY

Source: Gustavo De Feo LC, et al. Use of intravenous pulsed cyclophosphamide in severe generalized myasthenia gravis. *Muscle Nerve.* 2002;26:31-36.

TWENTY-THREE PATIENTS, AGED 21-65 YEARS, WITH severe generalized myasthenia gravis inadequately controlled with steroids, or experiencing significant steroid side effects, were randomized into a prospective, double-blind, placebo-controlled trial of high-dose pulsed cyclophosphamide (CP) to determine its efficacy and safety. Diagnosis of myasthenia was confirmed by positive antibody titers, decremental response on repetitive motor nerve stimulation, or positive Tensilon test. All patients were steroid dependent for 6 months, unable to taper below 10 mg/d, or were experiencing side effects including hypertension, glaucoma, osteoporosis, diabetes, pseudotumor cerebri, or psychiatric difficulties. Inadequate control of myasthenia was defined as forced vital lung capacity < 60% of predicted, voice or swallowing impairment, or pronounced limb muscle weakness. CP, 500 mg/m^2 of body surface, or placebo, was administered monthly for 6 months and then bimonthly for an additional 6 months. Each subsequent CP dose was increased 25% by an unblinded investigator if no improvement was observed, no complications were experienced, and the white blood cell count and polymorphonuclear cell count exceeded 3000/mm^3 and 2000/mm^3, respectively. Study end points included changes in muscle strength, steroid or pyridostigmine requirements, frequency of ventilatory failure (forced vital lung capacity < 30%), or swallowing impairment requiring feeding tube placement. ANOVA, Student's t-test, Wilcoxon's rank sum, and chi-square or Fisher's exact test were used for statistical analysis.

Five of 12 CP-treated patients were able to discontinue steroid treatment by 12 months compared to none of the 11 placebo-treated patients. By 36 months following study completion, 4 CP patients required no steroids and 3 additional CP patients required no pyri-

dostigmine. Muscle strength was significantly improved at 12 months in the CP group compared to placebo, particularly in bulbar and extraocular muscles. Bronchopneumonia resulted in ventilatory failure in 1 CP patient whereas 2 placebo patients developed respiratory failure due to muscle weakness. Side effects were not significantly increased in the CP group, including hematological and infectious complications, nausea, vomiting, abdominal pain, diarrhea, akathisia, or fasciculations. One CP patient developed bladder cancer 2 years after study completion but had other risk factors associated with this complication (smoking, age > 65 years).

COMMENTARY

Intravenous pulsed CP can be used safely and effectively for refractory severe generalized myasthenia gravis.

Other recent offerings in the treatment of myasthenia include tacrolimus (FK-506), a calcium-calcineurin inhibitor, which was reported to be effective as the sole immunosuppressant in a patient who developed myasthenia during interferon alpha treatment for hepatitis C (*Muscle Nerve.* 2002;25:111-114).

Intravenous immunoglobulin (IVIG) therapy is another safe and effective adjunct for myasthenia gravis, although randomized trials are lacking (*Neurol Sci.* 2002;23(Suppl 1);S9-S24). IVIG results in rapid improvement, lacks any long-term toxicity, and may reduce the need for other immunosuppressive agents. Presently, IVIG is useful for the management of myasthenic crisis, particularly where plasma exchange is not feasible, including the elderly, the young, and the septic patient. IVIG may also be used for chronic maintenance therapy when other agents have failed. Monthly or bimonthly infusion may stabilize chronic refractory patients. **—MICHAEL RUBIN**

Chronic Infection May Contribute to Stroke Risk

ABSTRACT & COMMENTARY

Source: Pietroiusti A, et al. Cytotoxin-associated gene-a-positive *Helicobacter pylori* strains are associated with atherosclerotic stroke. *Circulation.* 2002;106:580-584.

It is well known that chronic inflammation is a significant contributor to atherosclerotic disease. Serologic positivity for *Chlamydia pneumoniae* and *Helicobacter pylori* have been associated with atherosclerosis independent of other vascular risk factors. These organisms have been linked to disease in the coronary arteries, carotid system, and peripheral vasculature. Although *H pylori* often presents as peptic ulcer disease and chlamydia rarely produces pneumonia, these chronic infections are usually entirely asymptomatic and thus are rarely treated.

In the current report, Pietroiusti and colleagues present data linking a particularly virulent *H pylori* strain (bearing the cytotoxin-associated gene A [CagA]) with stroke due to atherosclerosis. Dividing stroke patients into etiologic subtypes, 138 patients with large vessel stroke were compared to 61 patients with cardioembolic infarcts and 151 healthy controls. *H pylori* infection in general was highly prevalent in all groups, occurring in approximately 70% of patients. The prevalence of CagA-positive strains, however, was much higher in patients with large vessel strokes (43%) than among patients with cardioembolism (20%) or controls (18%)—$P < 0.001$ for either comparison. C-reactive protein levels, indicating an inflammatory state, were also significantly higher in the presence of CagA.

COMMENTARY

By dividing infarcts into specific subtypes, rather than treating them as a lump sum, Pietroiusti et al were able to make significant insights into stroke pathophysiology. These data indicate that inflammation appears to play a role in strokes mediated by atherosclerosis, but not strokes related to cardiac thrombi. Similarly, stroke is not associated with all *H pylori* infections (an exceedingly common phenomenon), but rather with a specific more virulent (and less common) strain.

In a related article, Franceschi and colleagues (*Circulation.* 2002;106:430-434) further elucidate this interesting link. In an ex vivo, immunochemical model, they demonstrate that Anti-CagA antibodies specifically bind to epitopes on atherosclerotic blood vessels. *H pylori* may, therefore, promote atherosclerosis through a much more discrete process than merely nonspecific inflammation. Antibodies made against CagA may cross react with antigens expressed by cells involved in atherogenesis such as vascular smooth muscle, fibroblasts, or endothelial cells.

While mass treatments with antibiotics to prevent stroke and myocardial infarction are not yet justified, there is compelling evidence that particular chronic infections may significantly contribute to vascular disease. **—ALAN Z. SEGAL**

Sensory Training for Patients with Focal Hand Dystonia

ABSTRACT & COMMENTARY

Source: Zeuner KE, et al. Sensory training for patients with focal hand dystonia. *Ann Neurol.* 2002;51:593-598.

FOCAL TASK-SPECIFIC DYSTONIA (FTSD) IS ONE OF THE most unusual movement disorders. Far from rare, it affects a sizable portion of the adult population, typically taking the form of writer's cramp. By definition FTSD affects only one part of the body (typically the hand), and is triggered only by one specific activity. The task that triggers dystonic symptoms is usually a skilled motor activity requiring sustained attention, such as writing or playing a musical instrument. Aside from dystonia, the neurologic examination is entirely normal, and imaging studies and nerve conduction tests are normal as well.

Over the last decade, numerous studies have demonstrated disordered cortical topography of the hand area in the motor and sensory cortex in patients with FTSD. The normal rigid separation and strict ordering of the fingers in the homunculus is blurred in patients with FTSD. Along with their dystonic symptoms, patients have a deficit in fine sensory perception, which can be demonstrated with a simple technique designed to test the limits of 2-point discrimination.

In the present study, Zeuner and colleagues studied 10 patients with FTSD of the hand and 10 normal controls. They measured sensory perception in the affected hand using the JVP dome system, a series of plastic domes with gratings of different widths cut into their surface. The domes are placed gently against the skin, and the patient is asked to report the orientation of the grooves. The severity of dystonia was evaluated using standard clinical rating scales and by measuring the time needed to write a standard paragraph.

All patients were trained to learn to read Braille for 8 weeks, practicing 1 h/d for the first week and 30 minutes /d for the remaining 7 weeks. Patients practiced at home, and their compliance with the training program was measured by a series of test exercises. Patients practiced using the finger most affected by dystonic contractions. After 8 weeks of training, sensory perception of both patients and controls improved, and the change was statistically significant. Observer's ratings of the severity of dystonia improved in 5 of 10 patients, and 6 patients shortened the time needed to write a standard paragraph. There was, however, no statistically significant improvement in patients' rating of their disability. Several patients stopped practicing their Braille reading, only to see their symptoms of dystonia worsen. When they resumed practicing, dystonic symptoms improved.

COMMENTARY

This is an interesting and important study. Zeuner et al showed that daily practice of an attended, complex motor task (learning to read Braille) alters the sensory perception threshold of both normal and dystonic individuals. Further, learning to read Braille improved rating scale measures of dystonia, although patients did not feel that their functional disability improved. This study provides further evidence that the adult brain possesses remarkable plasticity when presented with a complex task requiring concentrated attention. It also suggests an avenue of further research for therapeutic trials in patients with focal and generalized dystonia. **—STEVEN FRUCHT**

NeuroUpdate: Disorders of Beta-Oxidation

ABSTRACT & COMMENTARY

Source: Vockley J, Whiteman DAH. Defects of mitochondrial beta-oxidation: A growing group of disorders. *Neuromuscul Disord.* 2002;12:235-246.

FIRST DESCRIBED IN 1973, AT LEAST 22 INBORN DISORders of fatty acid metabolism are currently recognized, many of which produce myopathy or neuropathy, and are, thus, of interest to the neurologist. Beta-oxidation denotes the process by which free fatty acids (FFAs) lose 2 carbon units at a time, with the end result being generation of ATP by hydrogen ion transfer down the electron transport chain. FFAs, derived from the diet or fat stores, are metabolized in peroxisomes if carbon length is more than 20, and in mitochondria if carbon length is 20 or less.

FFAs enter the cell cytoplasm from blood by a poorly characterized specific transport process and must be transformed into acyl-CoA thioesters, by acyl-CoA synthase, prior to entering the mitochondria. Carnitine palmitoyl transferase I (CPT I), located on the inner aspect of the outer mitochondrial membrane, conjugates carnitine with the acyl-CoA thioester forming acylcarnitine and, by carnitine-acylcarnitine translocase (CAT), passes it onto CPT II, located in the inner mitochondrial membrane, allowing acylcarnitine to enter the mito-

chondrial matrix. Importantly, carnitine itself must be transported into the cell from blood by a specific transporter protein. Once inside the mitochondria, 2 carbon acetyl-CoA units are sequentially cleaved from acylcarnitine via beta-oxidation. ACDs (acyl-CoA dehydrogenases) catalyze the removal of the 2 carbon fragments, with 4 specific enzymes being involved: VLCAD, LCAD, MCAD, and SCAD responsible for very long chain, long chain, medium chain, and short chain acyl-CoA dehydrogenation, respectively. Energy (ATP) is ultimately generated when acetyl-CoA is oxidized to carbon dioxide and water in the citric acid cycle. This releases hydrogen ions which are transported down the respiratory chain to generate ATP. Defects at all these levels have been described and those of potential interest to neurologists are synopsized.

Defective Cellular FFA Uptake. Acute liver failure and impaired FFA uptake in fibroblasts has been described in 2 patients, supporting a likely defect of cellular FFA uptake. Efforts to identify the gene defect are ongoing.

Cellular Carnitine Deficiency Due to Defective Uptake. Progressive muscle weakness, hypertrophic cardiomyopathy, and muscle lipid storage in the first year of life have been reported with deficiency of the plasma membrane carnitine transport protein, precluding carnitine entry into the cell. Plasma carnitine is low but supplementation is therapeutic.

CPT II Deficiency. Recurrent myoglobinuria from rhabdomyolysis precipitated by exercise, fasting, high fat intake, viral illness, or stress is the hallmark of this disorder, the most common of the group. It presents in late childhood or early adulthood and may be severe enough to result in acute renal failure. Characteristically, plasma carnitine is low with elevated acylcarnitine. Carnitine supplementation is of no benefit. CPT I deficiency rarely causes muscle symptoms.

ACD Defects. Myopathy, cardiomyopathy, or recurrent rhabdomyolysis beginning in adolescence may be seen in VLCAD deficiency. A variety of genetic defects have been described but genotype/phenotype correlation remains questionable. MCAD deficiency may present as Reye syndrome, sudden infant death syndrome, isolated hypoglycemia, or episodic muscle weakness with lipid excess in muscle and is one of the most common inborn errors of metabolism in some northern European populations. SCAD deficiency has been described in multicore myopathy, hypotonia, and developmental delay.

Mitochondrial Matrix Beta-oxidation Enzyme Defects. Myopathy, recurrent myoglobinuria, or peripheral neuropathy may be seen with deficiency of long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD). Short chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD) deficiency is rare and may result in acute liver failure and sudden death. Further studies are needed to confirm this relationship. Developmental delay and muscle weakness is described in 3 patients with 3-ketoacyl-CoA thiolase deficiency but definitive enzyme studies were not performed. Multiple acyl-CoA dehydrogenation disorder (MADD) causes a potpourri of clinical abnormalities including, among others, severe hypotonia, lipid storage myopathy, and structural brain abnormalities (cerebellar vermis agenesis, hypoplastic temporal lobes, focal cerebral cortical dysplasia). Mutational analysis has revealed a variety of abnormalities but with no clear correlation between gene defect and clinical severity.

Pregnancy and Beta-oxidation Defects. Twenty-one pregnancies complicated by acute fatty liver of pregnancy (AFLP) or hypertension, elevated liver enzymes, low platelets (HELLP) have been reported where the child subsequently born was found to have a defect of FFA metabolism, supporting the notion that AFLP or HELLP should trigger a work-up for a beta-oxidation defect.

Treatment of mitochondrial beta-oxidation disorders centers on the avoidance of fasting thereby avoiding the need for fat metabolism to generate energy. Healthy individuals should restrict fat intake to 25% or less of total caloric intake, and during illness carbohydrate intake should be increased by intravenous or nasogastric means if necessary. Dietary supplementation is generally of little benefit in these disorders but carnitine, 300 mg/kg/d or 100 mg/kg/d, is warranted in carnitine transporter deficiency and secondary carnitine deficiency, respectively. Glycine has been suggested for multiple dehydrogenase deficiency but may be toxic. Riboflavin, 200 mg/kg/d, may be helpful in MADD.

COMMENTARY

Muscle, given its high energy requirement, is often affected in mitochondrial disorders. Several mitochondrial cytopathies have been described, which do not involve beta-oxidation, and myopathy is prominent in most. Progressive external ophthalmoplegia (PEO) is extremely suggestive of a mitochondrial disorder, as is dysfunction of the central nervous system including ataxia, seizures, and sensorineural deafness. Short stature, diabetes, and cardiomyopathy are common expressions of mitochondrial dysfunction, and pigmentary retinopathy ("salt and pepper" pigmentation with normal vision) may be seen in up to one third of such patients. Exertional headache and nausea, with weakness or myalgia, are particularly suggestive. Other clues include unexplained lactic acidosis and myopathy in

association with peripheral neuropathy. Colorful abbreviations incorporating each abnormality have been appended to these disorders and include, among others, myoclonus epilepsy with ragged-red fibers (MERFF), mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), and neuropathy, ataxia, and retinitis pigmentosa (NARP). MNGIE has also been referred to as polyneuropathy, ophthalmoplegia, leucoencephalopathy, and intestinal-pseudo-obsruction (POLIP) and mitochondrial encephalomyopathy, sensorimotor polyneuropathy, ophthalmoplegia, and pseudo-obsruction (MEPOP). Muscle biopsy is helpful in most instances, demonstrating ragged red fibers, subsarcolemmal accumulations of mitochondria, on modified Gomori trichrome stain. Recently, molecular genetics has identified numerous mitochondrial mutations providing specific genetic diagnoses, indeed creating a new classification system for mitochondrial myopathies. **—MICHAEL RUBIN**

Brief Alert

Don't Crack the Back? No Benefit of Chiropractic for Low Back Pain

Source: Hsieh CY, et al. Effectiveness of four conservative treatments for subacute low back pain. *Spine.* 2002;27: 1142-1148.

THIS RANDOMIZED, ASSESSOR-BLINDED CLINICAL trial was designed to investigate the effectiveness of 3 manual treatment regimens (joint manipulation, myofascial therapy, or a combination of these 2) vs. a back education program. Two hundred patients were assigned to 1 of the 4 groups, with assessments at baseline, every 3 weeks, and at 6 months after the completion of therapy. The primary outcome measures used visual analog scales and Roland-Morris activity scales.

COMMENTARY

All 4 groups showed equal improvement in pain and activity scores after 3 weeks of treatment, and had no further benefit at the 6-month folllow-up assessment. There was no significant difference between outcomes using chiropractic treatments as compared to the back education school. Given that back pain is such a large issue in neurology, costing hundreds of millions for the health economy, it is hoped that such well-designed studies will provide evidence-based medicine to guide rational health care and eliminate unhelpful chiropractic methods. **—BRIAN R. APATOFF**

Special Feature

Decade of the Brain Gives Birth to New Neuroethics

Conference Focuses on Ethics of Treating Brain Disorders

A LITTLE MORE THAN 10 YEARS AGO, IN 1990, THE federal government launched the Decade of the Brain initiative, a focused effort to encourage research into the diseases of the brain and potential of the human mind.

The result has been stunning progress in the field of neuroscience, researchers and ethicists say. But now more effort must be made to understand the social and ethical implications these advances will have on our society.

"I think we are starting to be able to ask questions about individuals that we were not ever able to ask or probe before," says Judith Illes, PhD, senior research scholar in the department of radiology at Stanford University in Palo Alto, CA. "We need to look at how we do that responsibly and what are the ethical implications of doing that."

For example, Illes notes, new neuroimaging technology is allowing researchers to examine not only traditional concepts such as memory and language, but also allowing them to examine how changes in a person's brain activity may indicate other things—whether the person is angry or upset, aroused, or being untruthful, for example.

"That really brings to the foreground new issues: How do we use that data in a research environment? How do we communicate that data to the public? How might such information get used—in the courtroom, for instance—not just in the medical field," she says.

To begin looking at these issues, Stanford and the University of California at San Francisco held a conference May 13-14 in San Francisco to map this new field of study, which many are calling neuroethics.

At the conference, neuroscience researchers, bioethicists, and public policy experts came together to determine what initial questions needed to be asked about the impact new knowledge about the brain will have on society, says conference chair Zach Hall, MD, former director of the National Institute for Neurologic Diseases and Stroke (NINDS), now president and CEO of EnVivo Pharmaceuticals Inc. in Redwood City, CA.

"It is more to map a new terrain than to come up with any answers right now," Hall says. "We are not going to solve the question of when is the use of stem cells appropriate or when should you use electrical stimulation of the brain in two days. But, [we wanted to] simply question and think and start the discourse—that was the goal of the conference." Attendees had plenty to discuss, he adds.

Use of Stem Cells on the Horizon

One of the key topics discussed at the conference was the use of embryonic stem-cell transplants to treat neurologic diseases, notes Barbara Koenig, PhD, associate professor of medicine and the executive director of the Stanford University Center for Biomedical Ethics.

Although stem cells are thought to have the potential to treat numerous diseases of the body, neuroscientists already are discovering practical applications to treat problems of the brain and the impact that these treatments may have needs to be studied now, she says.

"We are probably likely to see more of an immediate impact," she explains. "It will be a long time before you can take a bunch of stem cells and grow a heart. But it might not be long before you can say, 'Here are two nerves that are no longer connected. Here are some growth factors that will get them to reconnect.' Those kinds of experiments are already going on."

It's important that the ethical implications of such technology are examined now, adds Illes. "One of the things we want to do is promote proactive bioethics. Very often, ethics comes into play once the research has been done and somebody says, 'Uh oh.' The results get reported in Newsweek, and the public is calling."

What if You Can Predict Aberrant Behavior?

As the field of neurology advances, scientists increasingly also are finding biological bases for or factors that affect human behavior. For example, advanced magnetic resonance imaging may be used in research to examine different sites of brain activation for people who abuse drugs, for children who have attention-deficit disorder, or people who are lying, says Hall.

This research has significant implications for people who experience substance addiction or exhibit antisocial or criminal behavior, explains Koenig. "We might have the potential for predicting different kinds of behavior. And if we can, should we do this? What effect will that have on different parts of our society?"

A new understanding of biological factors related to human behavior may drastically alter the criminal justice system, for example, she says. If there is some basis for criminal behavior in biology, how much responsibility should one bear?

"We are not just studying how many numbers people can remember anymore," says Illes. "We are now actually looking into their brain and seeing if some brain centers light up to fear-evoking stimuli or not, or sadness, for example."

Another area that needs more discussion is the use of enhancements to improve brain function, says Illes.

Researchers already are examining how electrical stimulation of certain centers of the brain can be used to treat degenerative neurologic disorders and chronic pain. But healthy people could also potentially use this technology.

"We need to look at patterns of the use of mental enhancers, from traditional things like use of amphetamines—which some people have used to stay up all night to study for exams—to new technology like transcranial magnetic stimulation, a single pulse to the brain, to boost your energy with your morning coffee."

Such questions have already come up with the increased use of mood-altering drugs such as Prozac and the increased use of Ritalin in children, say Hall and Koenig.

"How much should we allow? Should we allow it? Maybe we shouldn't [use] any kind of manipulation that could change people's personal characteristics," Hall says. "If we have a pill that makes you feel better, should everyone have access to it? Who will pay for that? What if we have a pill that will make you less shy at a party or better able to concentrate while working?"

Enhancements have the potential to alter our concept of a normal personality, says Koenig, and that will have implications for people who may be denied access to the enhancements.

"We have drugs that may improve cognitive function in patients with Alzheimer's," she says. "But if we do develop drugs to enhance memory, will there be justice issues about who gets them? Will there then be a new version of normal memory? There are a lot of issues surrounding that."

As research goes forward into degenerative illnesses of the brain, methods of protecting patients who suffer from these illnesses and who need to be included in clinical trials will also become an issue.

"Many neurological and psychological conditions involved reductions in cognitive ability, so our whole ability to conduct research and intervene is more complicated," says Koenig.

And, because the brain contains so much of what our society considers to be the self, a decision to deliberately alter a person's brain, even to heal a deadly disease, should be carefully examined, says Hall.

"The brain is responsible for many of the things that make us individuals," he notes. "If I do something to

treat your liver, I am not going to change your personality. But if I do something to treat your brain, I may."

These questions should not just be answered by medical researchers and academic ethicists, but also must be addressed by society, he says.

"These are not questions that physicians or scientists should answer alone. They have to do with the core values of our society and we need to engage a broad spectrum of people," he says.

The San Francisco conference was limited to 50 participants carefully selected to balance representation from the fields of neuroscience, bioethics, and public policy, says Hall.

In addition, the sessions and breakout groups were scheduled to be two hours long, to allow an hour for discussion following each presentation.

Conference organizers plan to develop a consensus of what the attendees felt were the key neuroethics issues that require immediate attention.

They are planning to publish a summary of the conference to inform the public and other interested parties, Hall reports.

"One of the things we hope to end up with is something that is accessible to the public," he says. "If someone asked, 'What is neuroethics?' they could sit down and read our document in a couple of hours and have a sense of what happened at the conference and what the main problems are." **—CATHI HARRIS**

Cathi Harris is the Editor of Medical Ethics Advisor.

CME Questions

4. Agents potentially useful for the treatment of myasthenia include:

a. intravenous immunoglobulin.
b. tacrolimus (FK-506).
c. high-dose pulsed cyclophosphamide.
d. cyclosporine.
e. All of the above

5. Which of the following is true regarding chronic infection and stroke risk?

a. Infection is related to strokes of any subtype.
b. Any *H Pylori* seropositivity increases stroke risk.
c. C-reactive protein is elevated in all patients with *H Pylori.*
d. Antibodies against *H Pylori* may cross react with blood vessel walls.
e. Mass antibiotic campaigns should be waged to eradicate *H Pylori*.

In Future Issues:

NPH: A Valid Concept in 2002?

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

Reader Survey

Please fax your completed form to 1-800-850-1232. Thank you.

1. What could *Neurology Alert* do differently or better to increase its value to you?

2. What work-related problems keep you awake at night?

3. What unique benefits of *Neurology Alert* induce you to renew your subscription?

4. What topic(s) would you like to read more of?

5. What topic(s) would you like to read less of?

6. What other two publications do you find most useful for obtaining specialty medical information?

   Publication No. 1

   What I like

   What I would improve

   Do you use this publication for CME/CE credit?

   Publication No. 2

   What I like

   What I would improve

   Do you use this publication for CME/CE credit?

7. Do you regularly use the Internet to access neurology information? ❒ Yes ❒ No

8. What are the top five features of a web site that compel you to use it on a regular basis?

9. What is your specialty?

10. What is your work setting? ❒ Private practice ❒ Hospital ❒ University

11. Please describe your typical caseload:

12. Please add any comments that you think will improve *Neurology Alert:*

PHARMACOLOGY WATCH

No Shortage in Sight for Tetanus-Diphtheria Vaccine

The number of vaccine shortages has been unprecedented in the last year, but at least one vaccine, tetanus-diphtheria (Td), is back in full production. The Centers for Disease Control and Prevention (CDC) has announced that they are removing restrictions on the Td booster. Despite the fact that there is only one manufacturer of the vaccine, supplies are large enough to resume routine vaccination. The news is also good for childhood vaccines that have been in short supply, including MMR, varicella, and PCV-7 (pneumococcal) vaccine. All are expected to be in full supply by the end of the year.

Cholesterol-Lowering Therapy OK for Seniors

What to do with the 75-year-old patient with a cholesterol of 300, but no history of heart disease? Primary prevention studies have shown a benefit for treatment of younger patients, but there have been few studies of primary prevention studies in the elderly. Now data from the Cardiovascular Health Study of patients age 65 or older suggest that cholesterol-lowering therapy is useful in older patients as well. After nearly 7.5 years of follow-up, elderly patients with elevated cholesterol levels clearly benefited from cholesterol-lowering treatment. Compared with no drug therapy, statin use was associated with a decreased risk of cardiovascular events (multivariate hazard ratio [HR], 0.44; 95% CI, 0.27-0.71) and all-cause mortality (HR, 0.56; 95% CI, 0.36-0.8). This translates into a relative risk reduction of 56% of incident cardiovascular events and a 44% reduction in all-cause mortality. This was a prospective study, as pointed out in an accompanying editorial; however, it does add to the body of medical literature that suggests that the recent National Cholesterol Education Program (NCEP) guidelines should apply to those aged 65 or older (*Arch Intern Med*. 2002;162:1395-1400; editorial 1329-1331).

Beta-Blockers and CABG Patients

Preoperative beta-blockers have been shown to reduce operative complications and mortality in noncardiac surgery, and now 2 studies confirm the importance of beta blockade in patients undergoing coronary artery bypass grafting (CABG). In a large observational analysis of more than 600,000 patients undergoing CABG, preoperative beta-blocker therapy was associated with a small but consistent survival benefit in all patients except those with a preoperative left ventricular ejection fraction of less than 30% (*JAMA*. 2002;287:2221-2227). The most common postoperative complication of CABG is atrial fibrillation. A recent meta-analysis compares beta-blockers, sotalol, amiodarone, and biatrial pacing to prevent atrial fibrillation after heart surgery. All 4 modalities were effective (odds ratio compared to placebo—beta-blockers 0.39, sotalol 0.35, amiodarone 0.48, biatrial pacing 0.46). Each of the 4 drug modalities also significantly reduced length of stay. Significantly, beta-blockers, which are safe and easily administered were as effective as other treatment modalities (*Circulation*. 2002;106:75-80).

Asthma Sufferers: Use Clarithromycin

Asthmatics with evidence of infection with *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* ben-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

efit from a 6-week course of the macrolide antibiotic clarithromycin, according to a new study. In 55 patients with stable asthma in the Denver community, 31 were found to have evidence of mycoplasma or chlamydia infections by PCR and culture. All 55 patients were randomly assigned to treatment with either placebo or clarithromycin 500 mg p.o. b.i.d. 6 weeks. Patients who were PCR-positive and received clarithromycin were found to have a significant improvement in FEV_1 (2.50 pretreatment, 2.69 post-treatment; $P = 0.05$), while those who were PCR negative and those who did not receive antibiotic showed no change (*Chest*. 2002; 121:1782-1788). In a related study, Turkish researchers administered azithromycin 250 mg twice weekly to a group of 11 asthmatics for 8 weeks. No change in FEV_1 was noted, but patients had a marked reduction in bronchial hyperresponsiveness as measured by histamine challenge tests. These patients were not evaluated for evidence of infection prior to initiating therapy (*J Asthma*. 2002;39:181-185).

Good News: Antibiotic Use in Children Down

Meanwhile, efforts by the CDC and others to curb the use of antibiotics in children seem to have paid off. Researchers compared antibiotic prescription rates from 1999-2000 to data from 1989-1990. The number of prescriptions per 1000 individuals age 15 and younger decreased from 838 to 503 a decade later ($P < 0.001$). Prescriptions per 1000 office visits also fell during the same period of time (*JAMA*. 2002;287:3096-3102).

Linezolid Successful in Treatment of MRSA

Methicillin-resistant *Staphylococcus aureus* (MRSA), the bane of hospitals coast-to-coast, is effectively treated with linezolid. Previously vancomycin has been the standard of care for treating MRSA. A new study compares linezolid with vancomycin in 460 patients with known or suspected MRSA infections. Patients were treated with either linezolid 600 mg twice daily (n= 240) or vancomycin 1 g twice daily (n = 220) for 7-28 days. Clinical cure rates and microbiological success rates were similar for both groups, and both regiments were well tolerated with similar rates of adverse events. It is suggestive that linezolid is a reasonable alternative to vancomycin for MRSA infections and adds the additional option of oral therapy (*Clin Infect Dis*. 2002;34:1481-1490). The study is timely, as the CDC has reported the first isolate of fully vancomycin resistant *S aureus* in a Michigan man. Several cases of intermediate vancomycin-resistant staph have been reported, but this represents the first case of full resistance (*Morb Mortal Wkly Rep MMWR*. 2002;51:565-567).

SSRIs Relieve Dizziness in Psychiatric Patients

General internists and family practitioners will be delighted to learn that selective serotonin reuptake inhibitors (SSRIs) have been shown to effectively relieve dizziness in patients with psychiatric symptoms, a common office complaint. A group of 60 patients at University of Pennsylvania with psychogenic dizziness, dizziness due to a neurotologic condition (with psychiatric symptoms), or idiopathic dizziness were treated with an SSRI for at least 20 weeks. Two thirds of patients had been treated previously with either meclizine or a benzodiazepine. Twenty-five percent of the patients did not tolerate SSRIs. Of those who finished at least 20 weeks of therapy, 84% improved substantially with no difference between patients with major psychiatric disorders and those with lesser psychiatric symptoms. Patients with peripheral vestibular conditions and migraine also improved with SSRIs (*Arch Otolaryngol Head Neck Surg*. 2002;128:554-560).

DEET-Based Mosquito Repellents Just in Time for Vacation

Just in time for summer vacation, the *New England Journal of Medicine* has published a report showing that DEET-based mosquito repellents are superior to non-DEET-based repellants. DEET is the most common compound found in commercial insect repellents. Recently, several botanical repellents have come on the market as well as 3 repellant-impregnated wristbands. These were tested against DEET containing repellents as well as one other chemical repellent containing IR3535. The worst performers were the wristbands, which offered no protection. The IR 3535-based repellents offer minimal protection while the soybean oil-based botanical repellents work for an average of 95 minutes. In comparison, the formulation containing 23.8% DEET offers complete protection for more than 300 minutes (*N Engl J Med*. 2002;347:13-18).

FDA Actions

Risedronate (Actonel), P&G Pharmaceuticals' bisphosphonate for the treatment of osteoporosis, has been approved in a 35 mg once-a-week form. The drug has been available as a 5-mg daily tablet. As with other bisphosphonates, the drug needs to be taken 30 minutes before meals, and patients must remain upright for at least 30 minutes following administration. ■