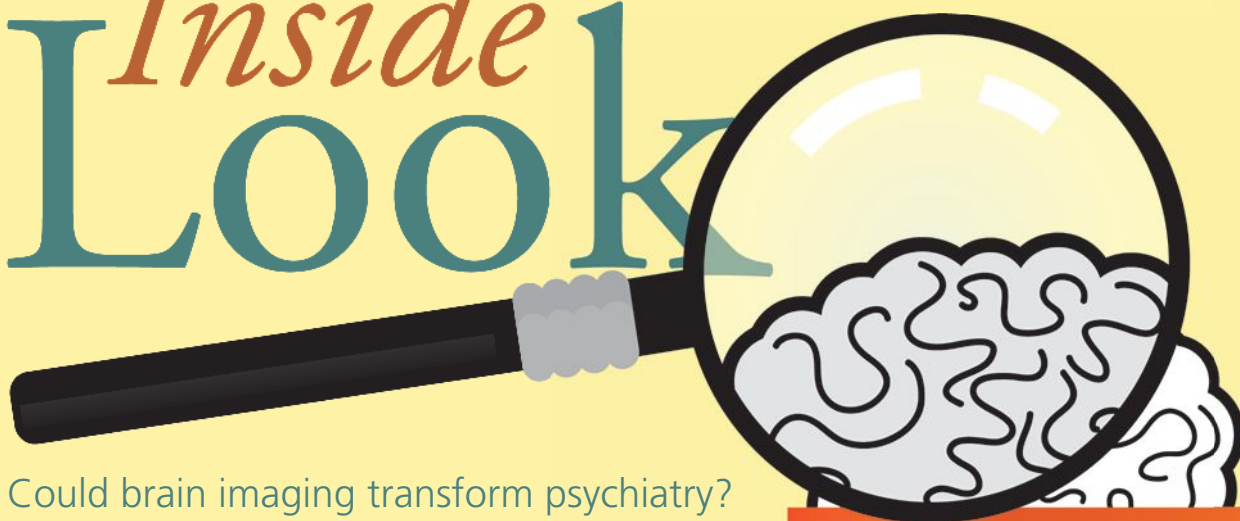


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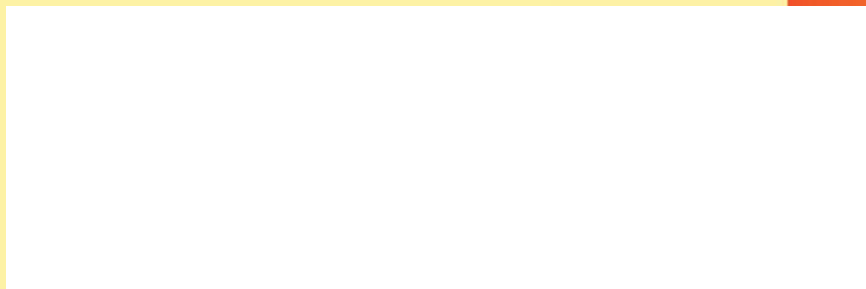
Could brain imaging transform psychiatry?

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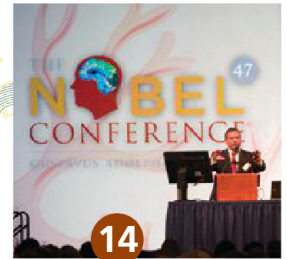
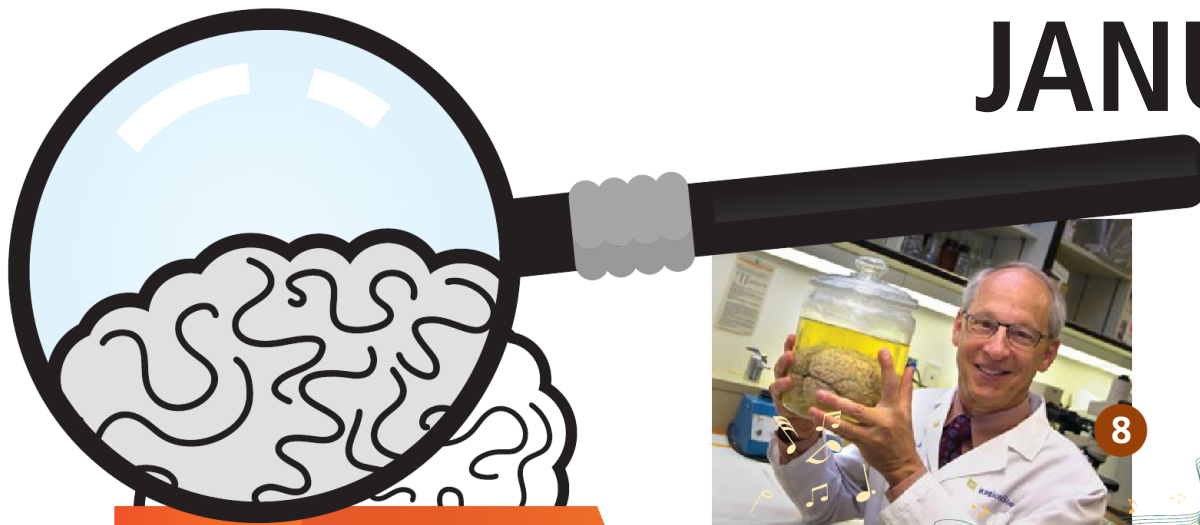
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in primary care

New criteria for diagnosing
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Photo by Scott Walker

For centuries,
man has struggled
to find out
what on earth
is going on inside
his own head.

Chipping Away at Mystery

The ancients used to drill holes to examine it. Phrenologists studied its bumps to figure it out. Psychiatrists before and after Freud have probed it with questioning and analysis. For centuries, man has struggled to find out what on earth is going on inside his own head.

As neuroanatomists traced pathways and mapped brain areas, it seemed as if it was all going to be a matter of electricity, and figuring it out was just a matter of drawing the right schematic. Indeed, some ailments and their neurological correlates seemed to follow electrical principles—cut a nerve and the muscle doesn't work or the skin doesn't feel, damage the anterior horn cells in polio and the innervated muscles don't move. Yet no matter how precise the explanations of neuroscience, there was the "soft" stuff of consciousness, love, hate, and joy that defied a mechanistic explanation and left a lot of room for mystery and speculation. Now, gradually, neuroscience is chipping away at that mystery.

The main tools doing that chipping are imaging techniques that show not only the anatomical details of the brain but that also track its function. Structural and functional magnetic resonance imaging, diffusion tensor imaging, magnetic resonance spectroscopy, and magnetoencephalography have moved us beyond diagnosing strokes and tumors to identifying physiological characteristics of illnesses such as schizophrenia, depression, and post-traumatic stress disorder, which previously were thought to be the business of psychiatrists. Using these techniques, we're seeing areas of the brain light up when thoughts stray, anger flares, or music plays. They're also enabling us to start to define the physiological underpinnings of Alzheimer's disease and perhaps in the future will allow us to make the diagnosis before the symptoms are obvious.

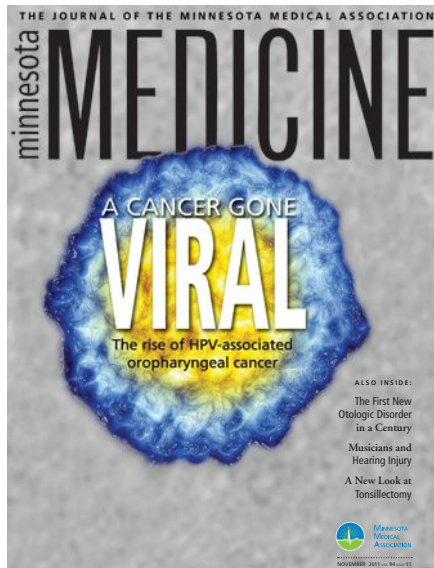
At the root of it all, still, is electricity.

The movement of sodium and potassium ions in neurons is well-studied, but the complexity of billions of neuronal connections in the brain and spinal cord beggar the intricacies of even the most sophisticated power grid or computer. Untangling that complexity will challenge neuroscience for decades to come.

The interface between the mysteries of human thought, emotion, and science has fueled a recent work of fiction. In his latest novel *The Lost Symbol*, uberbestselling author Dan Brown portrays a beautiful (of course), brilliant (naturally) heroine, Katherine Solomon, who is pursuing startling discoveries in noetic science, a discipline that attempts to apply scientific inquiry to such concepts as consciousness. Bankrolled by her billionaire brother, Peter, Katherine conducts her experiments in a super-secret cubicle hidden in an obscure region of the Smithsonian Institute. Katherine and Peter's nemesis is Mal'akh, a deranged Goliath of a man whose monomaniacal obsession is to acquire the secret pyramid of Masonic legend held by Peter, which is said to unlock ancient mysteries that will give its bearer untold powers. In addition, Mal'akh wants to destroy Katherine's research, viewing the potential scientific revelations about human consciousness and emotion to be a threat to the ancient truths held by the Masonic pyramid.

The Lost Symbol is classic Dan Brown, pseudoscience mixed with frantic action. Yet the kernels of truth in it speak to the conflict between mystery and science. Recent strides in neuroscience suggest that the future holds less mystery and more science, and that insights into the eternal mysteries of love, hate, and joy may be only a scan away.

.....
Charles R. Meyer, M.D., editor in chief, can be reached at cmeyer1@fairview.org



HPV Vaccine is Needed

I was pleased that you chose problems of the head and neck as the subject for the November issue. From 1962 until 1992, I operated in this area of the body and was involved in many procedures to remove cancers. During my fellowship at Roswell Park Cancer Institute, I interacted with approximately 150 patients who had oropharyngeal cancers, and only one of them did not use tobacco products. She had a tonsillar cancer (might it have been HPV-related?). During my years in Minneapolis, I saw a 28-year-old teacher with a carcinoma of the tonsil who also did not use tobacco; otherwise, all of the cancers were related to tobacco use and/or poor dental hygiene.

Now, as so aptly brought out in Jeanne Mettner’s article (“A Cancer Gone Viral,” p. 22), the epidemiological spectrum for oral cancer has shifted because of the rising incidence of HPV-related cancers. Fortunately, these relatively new tumors are more responsive to chemotherapy than those caused by tobacco. HPV doesn’t just affect the oral cavity; it’s also found in many anal cancers.

I hesitate to say this, but teleologically speaking, these cavities are not meant for cigarettes, cigars, or snuff, nor for the penis. However, I suspect a call for abstinence will go unanswered. Consequently, it is important that we make use of a workable vaccine—which is available although fraught with problems (such as

its cost and when to use it)—if we are to control these devastating cancers.

Harrison Farley, M.D.
Retired clinical professor of surgery
University of Minnesota

Neurologist Shortage “Critical”

Last spring, U.S. Senators Amy Klobuchar (D-Minnesota) and Susan Collins (R-Maine) introduced legislation (S. 597) to improve access to specialized care for Americans living with multiple sclerosis (MS) and other neurological disorders. Similar legislation was introduced in the House by Congressman Michael Grimm (R-NY) that also included funding for 1,000 new residents. If enacted, these bills would correct an omission in the Patient Protection and Affordable Care Act that led to the exclusion of neurology from the list of specialties eligible for Medicare payment incentives.

This effort recognizes a critical problem in the United States: a shortage of neurologists. This shortage is so widespread that it is now affecting the military as well. The Army issued a memorandum last March about the “critical shortage” of neurologists for our troops. More than 200,000 men and women who served in Iraq and Afghanistan have suffered head injuries ranging from minor concussions to more severe brain injuries.

One out of six people in the United States—nearly 52 million—has a neurological disorder. More than 400,000, including 10,000 in Minnesota, live with MS. Because of the complex and unpredictable nature of the disease, nearly 75 percent of people who have MS depend on a neurologist to coordinate their care. Often, neurologists serve as the primary care physician for patients with MS throughout their lives.

Today in Minnesota, there are simply not enough neurologists who specialize in the treatment of patients with MS to meet the need. It is not uncommon for a patient in the Twin Cities to wait up to six months to see an MS specialist. In addition, many of the state’s top MS specialists are reaching retirement age, and we are not seeing an influx of new physicians

to take their place.

The National Multiple Sclerosis Society and the American Academy of Neurology (AAN) are working to address this shortage by reaching out to medical students and medical schools to gain insight into what motivates students to choose a certain specialty, providing MS specialty fellowships to students, and educating providers at all levels about the shortage.

But there are no quick fixes. A number of factors influence a medical student’s choice of specialty, and compensation is clearly a major one. Our health care system provides significantly lower compensation to certain physicians, including primary care physicians and neurologists.

The majority of neurological care is offered through evaluation and management services. This type of “cognitive care” is time-intensive and is not reimbursed properly by our health care system. A recent AAN survey of 384 neurologists found that 19 percent have either stopped treating Medicare patients or are considering reducing the number they see because of the reimbursement situation. This is an alarming statistic, and it will only get worse as the baby boomers enter the Medicare system unless something changes.

We need to take the neurologist shortage seriously and find new, creative ways to encourage young people to specialize in this critically important area of medicine. We also need to address the systemic issues that inadvertently serve as disincentives to choosing certain specialties for medical students. We commend Senators Klobuchar and Collins and Congressman Grimm for addressing elements of the problem; but much more needs to be done.

Holly Anderson, president of the National Multiple Sclerosis Society, Upper Midwest Chapter, Minneapolis

Catherine M. Rydell, CAE, executive director and chief executive officer of the American Academy of Neurology, St. Paul



Photo by Erika Gratz, University of Minnesota

■ Intranasal Drug Delivery

Follow the Nose

Intranasal delivery may be the key to getting drugs to the brain. | BY TROUT LOWEN

Back in the 1980s, when William H. Frey II, Ph.D., first began investigating the use of natural therapeutic proteins such as insulin and nerve growth factor to treat Alzheimer's disease, his research kept hitting a wall. Frey, a biochemist, neuroscientist, and director of the Alzheimer's Research Center at what was then St. Paul-Ramsey Medical Center (now Regions Hospital), couldn't find a way to get a sufficient quantity of the therapeutic agent past the blood-brain barrier and into the brain.

"We started a clinical trial with a relatively small drug, and it became quite clear that even this molecule wasn't small enough or fat-soluble enough to get into the brain," he recalls. "It was quite frustrating."

Frey's brain must have been working overtime on the problem, however, because he came up with a solution one night while sleeping. In a dream, he was arguing with other scientists over the merits of treating Alzheimer's with growth factors. "I said it would work if we could find a way to get them into the brain. ... That was when this idea came to me," he recalls.

The idea was simple: Bypass the blood-brain barrier by going through the nose. Frey already knew that the olfactory and trigeminal nerves provide pathways from the nose to the brain for harmful substances such as heavy metals, viruses, bacteria, and even amoeba, so he wondered if the same pathways couldn't be used to deliver beneficial substances.

He felt so strongly about the idea that he began working on it. In 1989, he filed a patent application for the noninvasive intranasal delivery of targeted therapeutic proteins to the brain to treat neurodegenerative disorders such as Alzheimer's disease. The patent was finally granted in 1997. He later filed for a second patent specifically for intranasal treatment of Alzheimer's. It was granted in 2001.

Frey's patents cover the intranasal administration of a neurologic agent, either alone or in combination with a carrier agent, using a spray, gel, powder, infusion, ointment, injection, or drops to treat Alzheimer's disease, Parkinson's disease, depression, mania, stroke, and aging of the brain.

More than 30 years after Frey had his dream revelation, it's clear he was on to something. During the past five years, researchers working with Frey and independently elsewhere have conducted promising human and animal trials using the intranasal pathways to deliver treatments for Alzheimer's disease, Parkinson's

William Frey holds the patents for intranasal drug delivery, which allows the direct delivery of agents such as insulin to the brain.

disease, stroke, and other brain disorders. “We’re in the early stages but we’ve seen enough to make people very excited about it,” Frey says.

The Pathways

When a drug goes from the nose to the brain, it travels extracellularly along two nerve pathways. One follows the olfactory nerves, which are responsible for smell and are clustered in the upper third of the nasal cavity and connect to the olfactory bulb. The other follows the trigeminal nerves, which are distributed throughout the nasal cavity. Once in the brain, the drug is quickly disbursed into the perivascular spaces. Frey explains that as blood pumps through the brain, it creates a similar pumping mechanism in those spaces, transporting the drugs throughout the brain.

Frey says selecting which pathway to use for a particular agent is likely important, both in terms of maximizing the drug’s efficacy and avoiding side effects. However, researchers still have a lot of work to do to develop methods and devices that can direct substances along one pathway or the other.

Alzheimer’s Research

Thus far, the majority of research on intranasal drug delivery has focused on Alzheimer’s disease.

Researchers have known for some time that Alzheimer’s patients have reduced insulin levels in the brain and reduced glucose uptake in the hippocampal region, which controls memory. Some have suggested that this could contribute to the disease.

But increasing the amount of insulin in the brain was problematic. Administering insulin through the bloodstream puts patients at risk for hypoglycemia, increased insulin resistance, and other related problems. Frey provided another option.

In 2006, he, Suzanne Craft, Ph.D., a

Patients with Alzheimer’s disease and mild cognitive impairment who were given a single dose of intranasal insulin showed measurable improvement in memory.

professor of psychiatry and behavioral sciences at the University of Washington and director of the Memory Disorders Clinic at the VA Puget Sound Health Center, and her colleagues conducted the first trial of intranasal delivery of insulin looking at the effects on memory. In that trial, patients with Alzheimer’s disease and mild cognitive impairment who were given a single dose of intranasal insulin showed measurable improvement in memory within just 20 minutes. “So right away, we realized this was something,” Frey says, “because most of the drugs tested for Alzheimer’s don’t really improve memory. They slow down the cognitive decline of the patient over time compared to placebo, but you’re not really seeing significant memory improvement like this.”

In 2008, Craft conducted a second trial involving 33 adults with Alzheimer’s disease or mild cognitive impairment and 59 adults with normal cognitive function. Each was given five intranasal treatments over six weeks at varying dose levels from placebo to 60 IU. The participants rested for 15 minutes and then were given a battery of cognitive tests involving story recall, verbal learning, and psychomotor skills. The results of that study, published in the *Journal of Alzheimer’s Disease* in 2008, showed intranasal treatment had no effect on memory in the adults with normal cognition but improved memory for some of the Alzheimer’s and memory-impaired individuals. (Persons with apolipoprotein E-4, a genetic risk factor for late-onset Alzheimer’s disease, actually saw a decrease in memory function.) None of the participants showed an increase in blood glucose or insulin levels.

Another study out of the University

of Washington reported in *Neurology* in 2008 found that twice-daily intranasal insulin treatment for 21 days improved memory, attention, and functional status in 25 patients with early-stage Alzheimer’s disease or mild cognitive impairment.

In September 2011, Craft and colleagues published the results of another trial in which participants were given placebo or insulin through the nose over a period of four months. Those who received the intranasal insulin showed improved memory but also something else. While PET scans of the brain showed a decline in ability to take up glucose over the trial period among both groups, the decline was much more significant in patients who received the placebo. The results, published online in *Archives of Neurology*, indicate that intranasal insulin may actually do more than just treat the symptoms of Alzheimer’s disease.

“It looks like there’s a possibility—not proven yet—that if the treatment is started early enough, you might actually be able to delay progression or onset of the disease,” Frey says.

That’s because when insulin reaches the brain, he explains, it stimulates the formation of insulin-degrading enzyme, which is capable of degrading beta amyloid, one of the principal proteins known to accumulate in the brains of Alzheimer’s patients.

Furthermore, insulin seems to reduce the activity of glycogen-synthase kinase-3-beta, the enzyme that phosphorylates tau to create Alzheimer’s neurofibrillary tangles. Insulin also helps to maintain or increase synaptic density.

Other Applications

Other researchers are now studying whether Frey’s intranasal method might be used to deliver stem cells to patients with Parkinson’s disease, and deferoxamine, an iron-binding drug, to those who’ve had a stroke.

One study, involving Frey and an international research team led by Lusine Danielyan, M.D., of University Hospital of Tübingen and reported in *Rejuvenation Research*, used intranasal delivery of

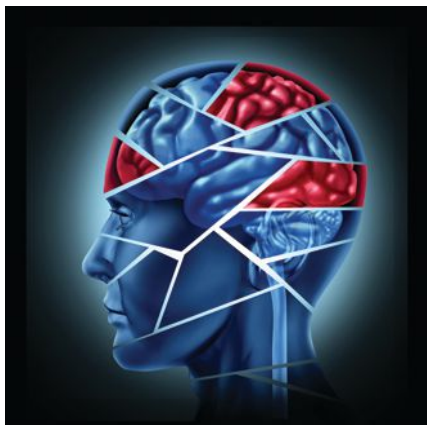
stem cells to treat Parkinson's disease in rats. Once in the brain, the stem cells were able to detect and migrate to the damaged areas. The result was a dramatic reduction in inflammation and a dramatic increase in mobility and motor function. Frey says the improvement lasted for the duration of the 110-day experiment. Another report out of the Netherlands published in *Pediatric Research* found that the same intranasal stem cell treatment induced func-

tional recovery and a reduction in brain damage in neonatal mice with ischemia.

In a study conducted by Frey and colleagues at the Alzheimer's Research Center and the San Francisco VA Medical Center, which was published in the *Journal of Pharmacology and Experimental Therapeutics* in September 2009, deferoxamine was administered to rats intranasally 48 hours before surgically induced stroke. Compared with the control group, the rats

that received the deferoxamine suffered 55 percent less brain damage. Rats given deferoxamine immediately after the surgery also showed similar protective results.

Additional studies exploring the use of intranasal treatments are underway around the world. Approximately 20 papers on intranasal treatment were presented at this year's annual meeting of the Society for Neuroscience. "And it all started in Minnesota," Frey says. ■



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■ **Head Injuries in Hockey**

Battered Brain

Minnesota Wild player Derek Boogaard, who died last May, was the focus of a recent *New York Times* story that raises questions about the safety of hockey. The story chronicled how researchers from a lab at the Veterans Affairs Medical Center in Bedford, Massachusetts, obtained Boogaard's brain following his death and found extensive evidence of chronic traumatic encephalopathy, which is believed to be caused by repeated blows to the head. The story notes that 20 former NFL players as well as many boxers have been found to have the condition, which can only be diagnosed posthumously. ■

Source: Branch J. Derek Boogaard: A Brain "Going Bad," *New York Times*, December 9, 2011.

■ **The Brain and Music**

Fascinating Field

With the advent of brain imaging in the last decade, there's been a surge of interest in the relationship between music and the brain. Universities have carved out space for the field, typically within their centers for cognitive science. Harvard University even has the Institute for Music and Brain Science.

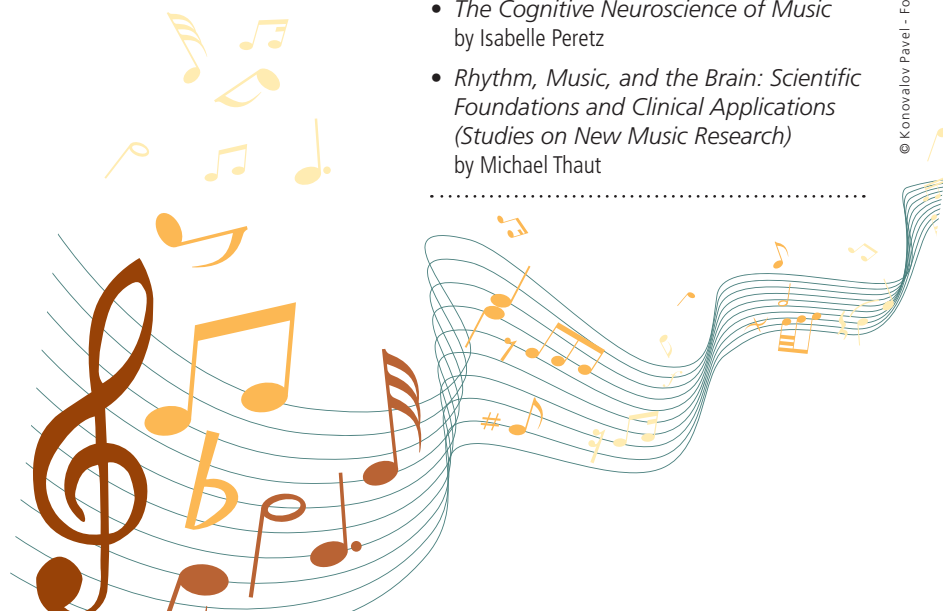
The fascination with the connection between music and the brain was evident this fall. Among the speakers at an annual symposium sponsored by the Center for Cognitive Science at the University of Minnesota was Roger Dumas of the Brain Sciences Center, who is using magnetoencephalography (MEG) to understand neural processing of melody. And at the Nobel Conference at Gustavus Adolphus College, Aniruddh Patel, Ph.D., of the the Neurosciences Institute in San Diego described, among other things, how he uses MEG to study how the auditory cortex processes sound sequences. ■

Want to Read More?

A number of books about music and the brain have been published or republished in recent years. Here are a few:

- *This Is Your Brain on Music: The Science of a Human Obsession* by Daniel J. Levitin
- *Music, Language, and the Brain* by Aniruddh D. Patel
- *Why We Like Music: Ear, Emotion, Evolution* by Silvia Bencivelli
- *Music, The Brain, and Ecstasy: How Music Captures Our Imagination* by Robert Jourdain
- *The Cognitive Neuroscience of Music* by Isabelle Peretz
- *Rhythm, Music, and the Brain: Scientific Foundations and Clinical Applications (Studies on New Music Research)* by Michael Thaut

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■ Traumatic Brain Injury

Blood Test for Brain Injury?

A small study published in *Annals of Emergency Medicine* suggests a blood test for traumatic brain injury might be in the offing. Researchers found a difference in the levels of glial fibrillary acidic protein (GFAP) in patients with a traumatic brain injury as compared with others. Those who were found to have significantly higher levels of GFAP also had positive findings for traumatic brain injury on CT scans. The researchers hope GFAP might serve as a biomarker that could be used to help emergency personnel either rule out the need for CT or ensure that those needing it get it. ■



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There is a high incidence of but little research on concussions in female athletes.

■ Concussions

Women Left Out of Concussion Research

Female athletes have higher concussion rates than males playing similar sports, and the research community needs to work harder to understand why. That's the main message of a video documentary produced by the University of Minnesota, the Tucker Center for Research on Girls and Women in Sport, and Twin Cities Public Television. The hour-long program was first broadcast in October to raise awareness about the high incidence of concussion in women and the dearth of research on female athletes and concussion.

In an interview in the video, Diane Wiese-Bjornstal, Ph.D., of the university's School of Kinesiology, notes that even though females sustain fewer concussions than males in terms of frequency, the rate of concussion (injury per activity time) among female athletes is actually higher than the rate among males who play comparable sports. In hockey, for example, the rate for women is more than two times that of men. She notes that this has raised red flags among researchers, who are now exploring why this is the case. University of Minnesota team physician Suzanne Hecht, M.D., says in the video that some speculate the high rate is because females are more likely than males to report their symptoms.

Last year, Minnesota Gov. Mark Dayton signed a bill into law that requires coaches to sideline any athlete who shows signs of concussion. Those athletes cannot return to practice or play until they get clearance by a state-licensed medical provider. ■

The video "Concussions and Female Athletes," is online at www.mnvideovault.org/index.php?id=22775&select_index=0&popup=yes.

■ Cognitive Rehabilitation Therapy

Too Little Evidence on TBI Treatment

An Institute of Medicine study of cognitive rehabilitation therapy (CRT) done at the request of the U.S. Department of Defense concluded that there's little evidence regarding use of the therapies now being used for people who have sustained a traumatic brain injury (TBI).

The researchers found that both the quality and volume of studies on CRT were insufficient for providing definitive guidance about CRT. They recommended that more research on CRT be done in order to better define which therapies are most effective for different types of injuries. However, they also recommended continued use of CRT for people who have had a TBI until better options are developed.

Each year, 1.7 million people in the United States sustain a TBI. TBI is considered the signature injury of the Iraq and Afghanistan conflicts. The number of military service members diagnosed with a TBI nearly tripled from 2000 to 2010. ■

Source: Institute of Medicine. Cognitive Rehabilitation Therapy for Traumatic Brain Injury: Evaluating the Evidence. Available at: www.iom.edu/Reports/2011/Cognitive-Rehabilitation-Therapy-for-Traumatic-Brain-Injury-Evaluating-the-Evidence.aspx. Accessed December 14, 2011.



■ Cancer and the Brain

The Chemobrain Controversy

No one disputes that many cancer patients experience cognitive difficulties during and even after treatment. But should we blame chemotherapy? | BY JEANNE METTNER

In Internet chat rooms for cancer patients, the personal accounts abound: A woman with breast cancer searches frantically for her keys, only to find them hours later when she opens the refrigerator and sees them perched on top of a container of leftovers. A patient with colon cancer drives to a destination and sits in the parking lot for several minutes trying to remember why she is there. A breast cancer survivor purchases several bags of groceries, wheels them to the car, then drives off before loading them in her trunk.

For years, cancer patients have swapped stories about the mental fog they experience before, during, and after chemotherapy. Somewhere around the mid to late 1990s, the mainstream media and breast cancer advocacy circles began referring to the phenomenon as “chemobrain.” More than a decade later, the term has stuck.

It's difficult to determine how many people experience cognitive impairment during or after treatment for cancer, although some have surmised that at least 25 percent of patients who undergo chemotherapy are affected by symptoms of mild cognitive impairment. One study conducted by University of Minnesota researchers in 2005 reported an 82 percent rate.

What's in a Name?

All told, the complaints about chemobrain are too common to be ignored. But is chemotherapy really the culprit? In 2006, researchers at the University of California, Los

Researchers say “chemobrain,” the term that describes the mental fogginess experienced by many cancer patients, is a misnomer.

rible word; it’s a garbage bucket term for something that is real for patients but may not be associated at all with what its name implies,” says Timothy Moynihan, M.D., a medical oncologist with Mayo Clinic. “We haven’t yet pinpointed the causes or mechanisms of these cognitive challenges.” Moynihan says that anecdotally, breast cancer patients seem to be reporting symptoms more often than patients with other cancers—but again, there is no evidence to substantiate that observation or to explain why that is the case.

What Causes the Haze?

Determining the cause of cancer-related mental fogginess has proved difficult because there are so many potential variables. For one thing, numerous conditions that may coexist with cancer—depression, anxiety, stress, hormonal changes (especially with breast or prostate cancer treatment), and low blood counts—can have an effect on a person’s memory and ability to focus. Second, because cancer exists in a person’s body for an undetermined amount of time before diagnosis, it’s tough to determine a baseline from which to measure cognitive decline. In addition, everyone’s ability to concentrate varies dramatically from day to day, depending on the stressors they experience, the quality of sleep they get, and other factors.

Given these factors, the exact cause of cancer-associated cognitive changes is not likely to be identified anytime soon, particularly with the precision required to yield definitive results. “To be honest, there is so much going on at one time ... that it’s very difficult to tease out exactly what’s going on,” explains Sadhna Kohli, Ph.D., an assistant professor of oncology at Mayo Clinic. “There are many things we need to look at it before we can confidently call it ‘chemobrain.’”

Further confounding the issue is the fact that objective measures of a patient’s cognitive function do not always corroborate their self-reported symptoms. Kohli has found this to be anecdotally evident

in the breast cancer patients she evaluates. “In many cases, women may be complaining of cognitive difficulties; but when they actually go in to do the neuropsychological tests, their results show that they are still functioning in the normal range. For some reason, the two sources of data just do not correlate,” she says.

Kohli will look at why that’s the case in a new study, for which she is recruiting 33 newly diagnosed breast cancer patients. Before the patients undergo chemotherapy, Kohli and her team will gather baseline data from three sources—self-reported surveys, in-office neuropsychological assessments, and magnetic resonance spectroscopy (which measures brain metabolites). The researchers will follow up with the patients four to eight weeks after they complete chemotherapy, then again one year later, to observe any changes that may have occurred. “What we are hoping to see is a correlation between the patient’s self-report, neuropsychological test results, and brain metabolite measures,” Kohli explains.

More Survivors, Better Understanding

With close to 80 percent of breast cancer patients surviving 10 years after their diagnosis, clinicians are increasingly addressing issues of survivorship, one of which is cognitive function after treatment. “A lot of the complaints of cognitive challenges first came from breast cancer advocacy groups; they’ve helped people speak up,” says Moynihan, “and, for the most part, that’s a good thing.”

He explains that as more resources are dedicated to meeting and understanding the needs of cancer survivors, clinicians will likely get better at helping people with cancer-associated cognitive problems. In the meantime, patients should be encouraged to talk about the issue. “The more we see and hear about their cognitive challenges,” Moynihan says, “the more we are able to determine what we can do to help.” ■

Angeles used positron emission tomography (PET) to assess brain function in 21 women who underwent treatment for breast cancer five to 10 years earlier. All of the women had surgery to remove their tumors, and 16 of the 21 underwent chemotherapy. PET scans revealed that the 16 women in the chemo group had a lower metabolism in the frontal cortex than the five women who did not receive chemotherapy, which, the researchers suggested, could explain the mental confusion afflicting many cancer survivors.

Other researchers have attempted to identify which agents are most neurotoxic—and potentially detrimental to mental alertness. In 2008, researchers at the University of Rochester’s School of Medicine and Dentistry in New York found that systemic 5-fluorouracil, a chemotherapy agent commonly used to treat colorectal, breast, pancreatic, and stomach cancers, causes a thinning of the myelin in the central nervous system that could lead to cognitive deficits resembling dementia.

For many physicians and researchers, however, the term “chemobrain” is a misnomer. “I think chemobrain is a hor-



■ Nobel Conference

Big Ideas on the Prairie

Gustavus Adolphus College hosts world-class neuroscientists. | BY CARMEN PEOTA

Gustavus Adolphus College, in the small southwestern Minnesota town of St. Peter, is home to one of the state's treasures—the Nobel Conference. Every fall, the liberal arts college brings in top scientists for the two-day event. The conference was launched in 1963, when the college's then-president approached the Nobel Foundation, asking for permission to hold a science conference using the Nobel name.

Attending the conference is an exhilarating and exhausting experience, as the first lecture of each day starts at 10 a.m. and the last at 8 p.m., and the metal folding chairs set in long rows in the college's field house feel less comfortable with each speaker. However, about 5,000 enthusiastic people attend the event each year, a

testament to the fortitude and curiosity of Minnesotans.

This year, eight speakers from disciplines ranging from biology to theology took on the theme “The Brain and Being Human.” Here's a sampling from Day 1.

The opening speaker was Larry Young, Ph.D., a professor of psychiatry and behavioral sciences at Emory University in Atlanta. Young's interest is the neurobiology of social attachments, that is, the biochemicals and processes responsible for one being bonding with another. To learn more about how this works, Young has been studying the hamster-like prairie vole, the only vole species that mates for life. Among his discoveries is the fact that prairie voles, unlike other species of voles, have receptors in their brains for oxytocin,

the molecule that's produced in the hypothalamus and secreted into the blood stream in high amounts during pregnancy to promote contraction of the uterus and milk ejection. And he's shown that when the receptors for oxytocin are blocked, prairie voles become as disinterested in one another as other species of voles.

Young believes that what he's learning about the brain circuitry of prairie voles might have implications for people with autism spectrum disorders, which are characterized by deficits in social engagement. He speculates that a disruption in brain circuitry disables an autistic person's ability to form the attachments other people do.

The question is whether doses of oxytocin might help those with autism. In a few studies, oxytocin delivered intranasally has been shown to increase the length of time someone will spend looking at the eye region of a face, enhance the ability to infer emotions, enhance empathy, improve memory of faces, increase socially reinforced learning, and increase the gen-

This year's Nobel Conference brought attendees from throughout Minnesota.

eral saliency of social stimuli.

Vilayanur Ramachandran, M.D., Ph.D., director of the Center for Brain and Cognition at the University of California, San Diego, who has been described as a medical Sherlock Holmes, discussed his interest in finding brain-based explanations for unusual conditions. One is synesthesia, the phenomenon where one sensory experience triggers another. For example, someone might see a certain color when they encounter a certain number.

As Ramachandran explains it, the condition is common—about one in 30 people have it—and a matter of genetics and brain anatomy. People with the gene for synesthesia have a hyperconnectivity between certain brain regions, often ones that are adjacent to one another.

Helen Mayberg, M.D., professor of psychiatry and neurobiology at Emory University School of Medicine, who pioneered deep brain stimulation for depression in 2002, described how the advent of imaging enabled researchers to identify parts of the brain most affected in people with depression. She also explained the rationale that led her to think that electrical stimulation of the brain might alleviate depression.

Mayberg said treatment for depression ought to be viewed as an attempt to restore brain dynamics. And, she said, she sees psychiatry undergoing a conceptual evolution, moving from a focus on brain chemistry to a focus on brain circuitry.

If there is a main take-away from this year's Nobel Conference, it's that we are finding biological bases—neurons, pathways, regions, circuits—for things we've long relegated to the nonmaterial realm of mind, mood, and spirit. Yet with every gain in knowledge comes awareness of all that we do not yet know about the brain—and hence, ourselves. Still, this is an exciting time for neuroscience and those who follow it, and Gustavus gathered a set of fascinating speakers this year. ■

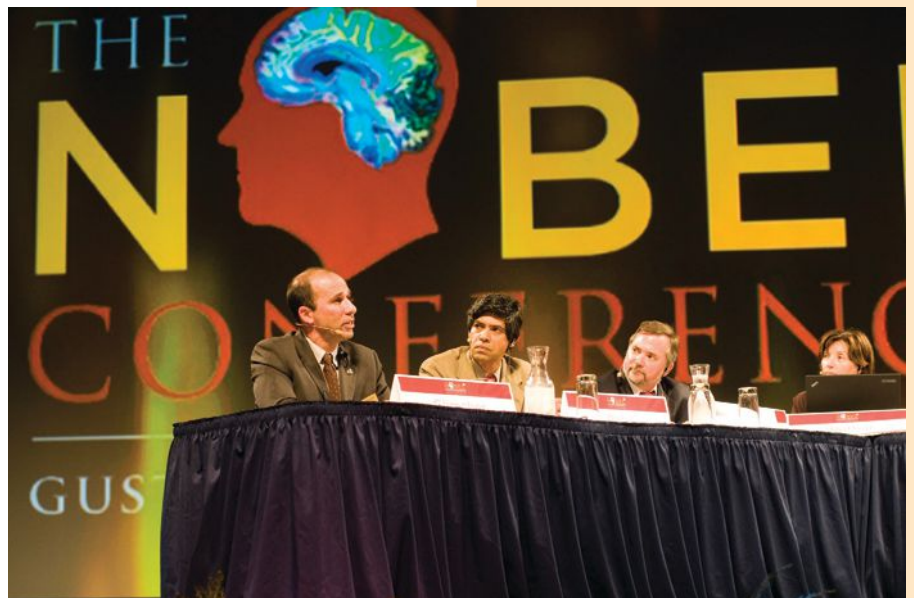
The Lectures

Missed this year's conference? You can watch videos of the main lectures online at <https://gustavus.edu/events/nobelconference/2011/>.

- "The Monogomas Brain: Implications for Novel Therapies for Autism" by Larry J. Young, Ph.D.
- "The Neurology of Human Nature" by Vilayanur Ramachandran, M.D., Ph.D.
- "Mapping Depression Circuits: Foundation for New Treatment Strategies Using Direct Brain Stimulation" by Helen Mayberg, M.D.
- "Music and Biological Evolution" by Aniruddh D. Patel, Ph.D.
- "Merging Mind to Machines: Brain Computer Interfaces to Restore Lost Function" by John Donoghue, Ph.D.
- "The Neurobiology of Decision-Making" by Paul W. Glimcher, Ph.D.
- "21st Century Neuroscience: From Lab and Clinic to Home, School, and Office" by Martha J. Farah, Ph.D.
- "Did My Neurons Make Me Do It? A Philosophical and Cognitive Science Analysis of Moral Responsibility" by Nancey Murphy, Ph.D., Th.D.



Above: Larry Young describes why prairie voles might hold clues to understanding autism spectrum disorders. Below: The conference speakers discussing ideas and asking questions following a presentation.



Take in the Nobel Conference

You can plan now to attend next year's conference, the theme of which is "Our Global Ocean." The 48th Nobel Conference will be held October 2 and 3, 2012. For more information, go to www.gustavus.edu/nobelconference.

Tumor Fighter

By Kim Kiser

John Ohlfest, Ph.D., is on a quest to find less toxic, more effective treatments for brain cancers.

John Ohlfest's eyes light up when he picks up a piece of paper showing six images of a brain. The MR images—three sets of two views—show four tumors including a large one above a ventricle slowly disappearing over five months. They belong to one of the nine patients who are participating in a Phase 1 clinical trial of a vaccine Ohlfest and his staff have developed to fight gliomas—aggressive brain tumors that are known for their ability to outsmart conventional treatment. For Ohlfest, an associate professor of pediatrics and neurosurgery at the University of Minnesota and a McKnight Land-Grant professor, this accomplishment trumps all other honors he has received in his short-but-prolific career. “I’ve had papers published, received grants, and had press coverage. But never anything like this,” he says of the patient’s response.

For Ohlfest, who directs the Ohlfest Brain Tumor Lab, this is what being a cancer researcher is all about: coming up with treatments that can save lives and help patients avoid the devastating side effects of radiation and chemotherapy. “Our goal is to make sure that no cancer patient has to undergo chemotherapy,” he says during an interview in his office—an orderly cubicle that guards the entry to the lab where researchers quietly attend to their work. “Patients

like the sound of that. Oncologists tell me I’m crazy.”

But Ohlfest is proving that the idea isn’t so crazy. Since his lab opened in 2005, he and a team of 15 or so researchers have been collaborating with staff from the veterinary school to engineer a vaccine from brain tumor tissue that can direct the immune system to kill those very tumors. Working with Elizabeth Pluhar, DVM, a veterinary surgeon, Ohlfest began testing the vaccine in dogs with gliomas and menin-

gliomas in 2008. In November 2010, he began testing a similar vaccine in humans whose gliomas had recurred despite surgery, radiation, and chemotherapy. “This is their last chance,” he explains.

Some of the dogs that have undergone treatment have shown no recurrence of the tumor; some are still alive two years after treatment. As for the human patients, Ohlfest is cautiously optimistic. “We have a functional vaccine that appears to be safe and has

some effect preliminarily,” he says.

For patients with brain tumors, this is reason for hope. “We haven’t made a significant impact on the outcome of many brain tumors in four decades,” says Christopher Mordetel, M.D., a pediatric neuro-oncologist and director of the pediatric brain tumor program at the University of Minnesota. “But when you compare this with other Phase 1 trials that we’ve run, we’re very pleased that patients’ qual-





Photo courtesy of John Ohlfest

John Ohlfest has been developing cancer vaccines from brain tumor tissue for dogs and humans. His goal is to one day eliminate the need for chemotherapy.

ity of life has been preserved or enhanced ... and that we are getting hints that we may be helping the immune system have an impact on brain tumors.”

Research Renegade

The fact that Ohlfest and his staff began developing and testing a vaccine in humans just two years after they first tested one on dogs reflects his philosophy about research—one that challenges the status

quo. “I’ve been very frustrated by a culture that seems to do what I call research for research’s sake. There are a lot of brilliant minds that get so focused on answering a question that they lose sight of the fact that the reason the taxpayers are paying the NCI [National Cancer Institute] to fund our jobs is to cure cancer, period,” he says.

One of the biggest problems in his opinion is that research often starts and ends with mice. “We keep testing things

in mice, and they always work. Then we take them into humans and they almost never work. If that were a business model, the business would go bankrupt, yet this is the model we have,” he says. When he got his lab up and running, he vowed that his work wouldn’t end with animals. “I love dogs; I have one, but it can’t end there,” he says.

Ohlfest’s determination to find a cure stems from having watched his grandmother

suffer. During his sophomore year at Iowa State University in Ames, she developed ovarian cancer that quickly spread to her lung, kidney, and liver. She was told she had only three months to live. After multiple surgeries and chemotherapy, she appeared to have beaten the disease. But her cancer returned, and she died while Ohlfest was still an undergraduate student.

What made an impression on Ohlfest wasn’t so much

Creating and Administering the Vaccine

In dogs

In most cases, the tumor is surgically removed. If it is determined to be a glioma or meningioma, it is sent to the lab, where the remainder of the tissue is placed in growth medium and incubated in a low-oxygen environment (5 percent). The cells are then frozen with liquid nitrogen so they immediately crystalize and explode. The remains are mixed with an adjuvant and frozen as a sterile solution. Dogs receive a topical immunostimulant before the vaccine is injected subcutaneously. Altogether, they receive a total of six treatments given three weeks apart.



In humans

The process of creating the vaccine is nearly identical to the one used for dogs, except for the fact that the cells come from a line called GBM6 and not the patient's tumor. Another difference is the delivery mechanism. With human patients, the tumor cells are mixed with dendritic cells that have been extracted from their blood, creating a "personalized" vaccine. Those cells are then returned to the body. Patients receive a treatment monthly for up to one year.



the effects of the disease as it was those of the treatments. "I specifically remember one time when she took interferon. She was very ill, and she was just sitting there shaking. It gives you the worst fever you've ever had for days," he says. "I remember thinking, 'This is crazy.'" Ohlfest, who didn't have a direction when he started college, suddenly found his calling: to develop cancer therapies that didn't have devastating side effects. From that point on, he aced his undergraduate classes. He went straight to the Ph.D. program at the University of Minnesota, finishing in a record three years and earning his

doctorate in molecular cellular developmental biology and genetics in 2004. When another institution tried to hire him, the University of Minnesota countered and let him start his own research program in 2005—a coup for the researcher who was only 28 years old at the time.

"Everyone across the country and around the world knows that this guy is really smart. He knows the field, he knows where he's going," Mortel says. "For someone his age, he's a star."

Dynamic Duo

As he was establishing his lab, Ohlfest attended a seminar by

a veterinary oncologist who talked about the fact that cancer is the No. 1 cause of death in adult dogs. He learned that an estimated 14,000 dogs get brain cancer each year and that most of them are euthanized. (Ohlfest's own dog, Tillie, a Staffordshire terrier, recently went through surgery to remove a mast cell tumor from her leg. He plans to create a vaccine for her as a follow-up treatment.) "It was a no-brainer," he says of his next step. "I wanted to do studies where you took out the tumor and used it to make a vaccine."

Ohlfest found a partner who was "willing to do something risky that hadn't been done before" in Pluhar. Together, they began recruiting dogs with brain tumors for a study. Pluhar would remove the tumor. If it proved to be a glioma, the tissue was sent to Ohlfest's lab, where cells would be cultivated, killed, and turned into a vaccine.

Making the vaccine wasn't as simple as it sounds. Ohlfest and his team needed to find a medium in which the cells would grow and a substrate to which they would attach. "We went through painstaking failure with growth media," he says. Then there was the issue of the environment. Most labs grow cells in an incubator that is perfused with air that has a 20 to 21 percent oxygen concentration, the amount in the air we breathe. Tissue in tumor cells has an oxygen concentration of 1 percent or less. "So it's very unnatural for a tumor cell to grow when exposed to that level of oxygen," he says of the 20 percent environment. They found that growing tumor cells in a low-oxygen

environment results in a vaccine that's much more likely to provoke an immune response.

When Ohlfest and Pluhar treated the first dog in 2008, a shepherd mix named Batman, they grew cells from his tumor at 5 percent oxygen. But Batman's case took an unexpected turn. Even in those optimal conditions, the tumor cells didn't grow quickly enough. So they used cells from another dog's tumor to produce enough vaccine to finish his treatments. They didn't know if this approach would work; but the vaccine produced the hoped-for immune response, killing Batman's remaining glioma cells and preventing a recurrence. (Batman died of other causes in January 2010; he was cancer-free at the time.)

From Dogs to Humans

With that finding, Ohlfest began thinking about extending the concept to humans. He wondered whether glioma cells from one patient could be used to treat another patient who was inoperable. And could another patient's tumor cells be used if a patient's own cells didn't grow fast enough, as was the case with Batman? "These are practical issues that companies trying to make cancer vaccines from tumors are facing," he explains. His team began an initiative to characterize a panel of primary human glioma samples to try to identify markers that were present on the majority of those tumors, then develop a cell line that had the most common markers. The theory was that those cells could be used to evoke an immune response in patients whose tumors had

the same markers. And if they could make cells that were renewable, they could create a product that would be readily available.

After looking through a number of cell lines, they came upon one that had every marker they sought and then some. They named the line GBM6 for the protein component of the vaccine. (Ohlfest says this cell line, along with their efforts to grow cells in a low-oxygen environment, sets their work apart from other efforts to create vaccines for cancers.) Just over a year ago, they began testing a vaccine created from those cells in humans. He and Moertel recently enrolled the ninth and final patient in the first phase of that trial. (The university is looking for an industry partner to produce larger quantities of the vaccine

for a Phase 2 trial.)

Unlike the dogs, who received the vaccine as a first-line treatment, all of the human patients in the Phase 1 trial had undergone conventional treatment without success. This inspired Ohlfest and Pluhar to do additional studies to find out whether exposure to other treatments could make the vaccine more or less effective in dogs. So far, they are finding the effects of chemotherapy on a person's ability to mount an immune response to the vaccine are much worse than they imagined. "It's very devastating what chemotherapy does," Ohlfest says. He and his team are also developing and testing new adjuvants for the vaccine that can trick the immune system into thinking the tumor is a virus and generate an immune response. "It's been ef-

fective with things like measles and smallpox," he says.

In addition, researchers in his lab have sequenced tumor cells to identify all mutations, not just the ones they're trying to attack with the vaccine. They're also trying to make a new synthetic version of the vaccine using the genetic information they extract from a patient's tumor cells. "We call it a personalized genomic vaccine," he says. They are currently trying to prove the concept in mice, then will begin testing it in humans. "We don't want to stop or even get side tracked," he says.

In early 2012, Ohlfest and Moertel plan on opening another clinical trial in which they will use cells from the GBM6 line to create a vaccine for pediatric patients with diffuse intrinsic pontine gliomas,

a cancer of the brainstem that is aggressive and difficult to treat. They plan to test it in combination with radiation therapy in children who have never received chemotherapy. "We think the radiation and vaccine are more likely to work together than the chemo and the vaccine, which we know can work against each other," he says.

Ohlfest hopes those children will respond like the patient in the glioma trial whose tumors appear to have regressed and who is doing well. "I want to see more people walking out of here feeling like he feels," Ohlfest says of that patient. Again, he picks up the images of that man's brain and reflects on them. "Seeing that is addicting," he says. "I want more, I want more."

MM

Kim Kiser is associate editor of *Minnesota Medicine*.



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Inside Look

By Howard Bell

Could brain imaging transform psychiatry?

Apostolos Georgopoulos, M.D., Ph.D., dreams of a day when everyone will go to the doctor for a brain check-up. Our brains will be scanned much like our bones are scanned, and those scans will help diagnose psychiatric disorders by visualizing abnormal brain structure and function. Follow-up scans will show whether treatment leads to beneficial changes in the brain. “We have the imaging techniques,” Georgopoulos says, referring to structural magnetic resonance imaging (sMRI), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and magnetoencephalography (MEG). “In a few years, we’ll have an image database for what’s healthy and unhealthy.”

Human brains have at least 100 billion neurons, and those neurons are capable of an immense number of interactions, according to Georgopoulos, who directs the Brain Sciences Center at the Veteran’s Affairs Medical Center in Minneapolis. And, he says, the information we’re now able to get from very few of those interactions is enough to let us see the difference between healthy brains and unhealthy brains and tell which of the unhealthy brains have schizophrenia, dementia, post-traumatic stress disorder (PTSD), multiple sclerosis, or chronic pain.

Brain imaging could potentially transform many areas of medicine, and it is already being used to help diagnose Alzheimer’s disease (see p. 24). But the implications for psychiatry, where diagnoses have been based primarily on patient interviews, are perhaps greatest, as brain imaging has the potential to render diagnosis and treatment a more measurable science. A number of researchers in Minnesota are currently hard at work trying to realize that potential.



Mapping the Brain

The University of Minnesota Center for Magnetic Resonance Research along with Washington University in St. Louis are leading a nine-center consortium in an ambitious effort to learn how the human brain is wired.

The Human Connectome Project (HCP) is a five-year National Institutes of Health-funded program that began in the fall of 2010 and will end in the summer of 2015. Similar in scope to the Human Genome Project, the HCP will map the brain's structural and functional neural pathways and make the data available free to the world's scientific community.

The plan is to scan the brains of 1,200 healthy adults, including twins and their nontwin siblings, using diffusion tensor imaging and functional magnetic resonance imaging. They will image participants at rest and while performing various tasks. One hundred participants also will be scanned using magnetoencephalography.

The goal is show in unprecedented detail how white matter axons connect different parts of the brain. That information will then be correlated with behavioral testing and genotyping.

The project is predicted to be a leap forward in the emerging field of human connectomics, the measurement of connections between distant regions in the brain, and will set the stage for future studies of abnormal brain circuits in neurological and psychological disorders.—H.B.

Schizophrenia

Neuroimaging for schizophrenia has been studied more and longer than neuroimaging for any other psychiatric illness, according to Charles Schulz, M.D., head of the University of Minnesota's department of psychiatry. Thirty years ago, he used computed tomography (CT) to show that adolescents with early-stage schizophrenia had structural abnormalities in their brains.

Other types of imaging have revealed more details. For example, sMRI has shown that people with schizophrenia have a thinner cortical layer, primarily in the frontal and temporal areas that are important to memory, attention, and decision-making. Their hippocampal volume is smaller, too. Functional MRI shows less-efficient neural processing when people with schizophrenia perform memory tasks. And DTI has shown that white-matter fibers are more disorganized in people with schizophrenia than in people without it.

Psychiatrist Kelvin Lim, M.D., a professor of psychiatry at the University of Minnesota, was one of the first to show that white-matter connectivity is abnormal in people with schizophrenia. Lim has found that people with schizophrenia have lower fractional anisotropy values (a measure of white-matter health), particularly in the cingulate, a region of the brain responsible for higher thought processes and emotional control, than people who don't have the disorder. Other studies have shown decreased fractional anisotropy values in the corpus callosum, which allows

the brain's two hemispheres to communicate and enables sustained attention during complex cognitive tasks. "In schizophrenia, white-matter bundles of axons are not as structurally well-organized as they are in healthy brains," Lim says. "We believe different brain regions aren't as well-connected to each other." No conclusive studies have been done on how or whether medications favorably alter white-matter connectivity.

MR spectroscopy shows abnormally low glutamate levels in many people with schizophrenia, according to Schulz. Glutamate is the brain's most abundant excitatory neurotransmitter. Low levels may be the reason people with schizophrenia lack motivation, affect, and interest in life in general, even though they are not necessarily depressed. "We also find it interesting," adds Schulz, "that street drugs like PCP are glutamate-blocking agents that can produce psychotic symptoms that look like schizophrenia."

Researchers from the university and the VA are using what they've learned from imaging to find a biomarker that confirms a diagnosis of schizophrenia earlier so patients can begin treatment sooner rather than later. Starting treatment close to or before the first episode improves long-term outcomes. They also are looking at combining the results of imaging tests with current diagnostic methods. "We already know that combining sMR measures of brain volume with neuropsychological tests is a more accurate way to confirm a diagnosis of first-episode schizophrenia than testing alone," Schulz says. Including sMR images also helps distinguish between schizophrenia and bipolar disorder, which can be hard to do in the early stages when symptoms are similar, according to Georgopoulos.

Mood Disorders

Brain imaging is revealing fascinating new information about mood disorders, which

The Next Step: Treatment

Brain imaging will hopefully lead to numerous new treatments for psychiatric disorders. One of the first to attract attention is deep brain stimulation (DBS), a procedure that was used first to alleviate tremor in Parkinson's patients and is now being studied for obsessive compulsive disorder, Tourette syndrome, and depression, among other things.

In February, Medtronic received approval from the U.S. Food and Drug Administration for a humanitarian device exemption for its Reclai Deep Brain Stimulation Therapy for chronic, severe obsessive-compulsive disorder. The company is now involved in a clinical trial of the device for depression.

Deep brain stimulation for depression was pioneered by neuroscientist Helen Mayberg, M.D., of Emory University in 2002. Using positron emission tomography (PET), Mayberg identified the region of the brain that appeared to be most involved in depression and then delivered electrical impulses to that area. Some of her patients reported immediate relief.

The University of Minnesota's Aviva Abosch, M.D., Ph.D., is among the researchers worldwide who are optimistic about the prospects for DBS for depression. "PET imaging shows that a specific part of the subgenual cingulate white matter has increased metabolic activity in patients with major depression, which treatment normalizes," she says. She also knows DBS needs further study. "We're not sure how it works."



"As scanner performance and our interpretation of results improve, we hope to have a powerful diagnostic tool that can be used on individuals. And when we do, it will have significant benefit for public health."

—John Port, M.D., Ph.D.

include depression, bipolar disorder, anxiety disorders, and borderline personality disorder. "We're a long way from being able to take a picture and diagnose depression," says Kathryn Cullen, M.D., a University of Minnesota psychiatrist who studies adolescents with major depressive disorder. "But we're learning a great deal that will one day have practical uses."

Using fMRI, she and her colleagues have found reduced connectivity along the fronto-limbic network of neurons connected to the subgenual anterior cingulate in adolescents who are depressed. When intact, this connection prevents excessive emotional reactivity and stress response. She also has used DTI to show impaired connectivity within this circuit. "We believe that disruption of this regulatory circuit underlies adolescent depression and probably adult depression," Cullen says.

Lim's DTI studies confirm that the white-matter "hard wiring" between the frontal lobe and limbic regions is not as well-organized in people with depression. "Once we better understand how patterns of white-matter connectivity relate to psychiatric disorders, we can create a diagnostic imaging test for schizophrenia and distinguish between it and depression," he says.

Whether depression causes abnormalities in the brain or whether the abnormalities cause the depression "is the question that always gets asked," according to Cullen. Regardless, she believes that

brain circuit wiring "went awry" during brain development in adolescents with depression. "Now we need to study the effects medications have on connectivity within this network," she says. (Thus far, no conclusive research involving imaging the brain before and after medications are given has been done.) "Since adolescent brains are still developing, neuroplasticity may lead to treatments that prevent abnormal neurodevelopment of these circuits," she explains.

Using fMRI, researchers have found that the brains of people with borderline personality disorder, are characterized by areas of hyperactivity, according to Schulz. "When we show these patients a series of faces expressing a variety of emotions, their limbic areas just light up. We always thought this happened for purely psychological reasons," Schulz says. "Imaging shows us that parts of these patients' brains are amazingly over-reactive."

There isn't yet a reliable imaging test for bipolar disorder. Measuring the excitatory neurotransmitter glutamate with MR spectroscopy "is currently our best hope for coming up with an objective diagnostic marker for the disease," says John Port, M.D., Ph.D., a Mayo neuroradiologist, associate professor of radiology, and assistant professor of psychiatry. "So far, we've found that people with bipolar disorder have significantly different glutamate levels compared to normal controls. In some areas of the brain, it's lower and in

other areas it's higher."

Port is also using MR spectroscopy to measure brain lithium levels in bipolar patients taking lithium, the primary treatment for the disorder. "Half of patients get better with lithium therapy and half don't," Port says. "If my new technique pans out, we should be able to tell within a couple days of starting lithium if it will work for a given patient."

Port hopes that MR spectroscopy will soon help tell whether a patient has bipolar disorder or major depression, which can be difficult to distinguish because depression is a main feature of bipolar disorder. The two conditions are treated with entirely different drugs. "If you put a bipolar patient on antidepressants, they can get worse," Port says. "So we hope spectroscopy will help us make the right diagnosis so we can prescribe the right medication."

Glutamate spectroscopy is not yet precise enough to diagnose bipolar disorder in the clinic partly, Port says, because there is considerable similarity in glutamate levels in bipolar brains and in healthy brains. "As scanner performance and our interpretation of results improve," he says, "we hope to have a powerful diagnostic tool that can be used on individuals. And when we do, it will have significant benefit for public health."

Post-Traumatic Stress Disorder

Brain imaging using MEG has shown that PTSD changes how the brain works. "We used to debate whether PTSD was real," says Georgopoulos. "Now we know that it is a brain disease that produces abnormalities in the brain that we can see."

Georgopoulos and Brian Engdahl, Ph.D., a clinical psychologist and PTSD expert, found that the superior temporal gyrus of the right hemisphere, which is involved in causing us to relive past experiences, interacts with other parts of the brain very differently in people with PTSD than in healthy people.

Pinpointing the area of the brain that is hyperactive in persons with PTSD is one step toward finding a diagnostic biomarker for it, according to Jose Pardo, M.D., Ph.D., director of the VA's Cognitive

Neuroimaging Unit. "Once you have your biomarker, you can test the effectiveness of treatments," he says.

Engdahl and Georgopoulos are in the early stages of using MEG to study the brains of people with Gulf War syndrome, which has a variety of unexplained physical and psychological symptoms, and of those who have suffered mild traumatic brain injury (TBI). "You can see the difference between someone who has TBI

and someone who doesn't," Georgopoulos says. "We've even identified a subgroup of veterans who were pronounced cured of TBI whose brains are not normal whatsoever."

As for Gulf War syndrome, Georgopoulos says, "we're going to find out the neural basis of the symptoms using MEG. If we can image it, then we can test the effectiveness of therapy by imaging before and after treatment."

Brain Imaging Techniques

Most brain imaging techniques have been around for decades; but during the last 10 years we've seen an explosion of refinements that make these technologies more useful for visualizing the difference between healthy and unhealthy brains.

Structural magnetic resonance imaging (sMRI) – Available since the mid-1980s, this technology uses powerful magnets to produce two- or three-dimensional images of brain structures. It does not show brain activity.

Functional magnetic resonance imaging (fMRI) – Provides a snapshot of brain activity by measuring change in oxygenated blood flow, which increases in regions of the brain where there is increased activity. (Oxygenated and de-oxygenated hemoglobin have different magnetic properties that can be visualized.) fMRI is done while the person is at rest (resting state-fMRI) or doing a mental task (task-fMRI). It has been used in brain mapping since the early 1990s.

Diffusion tensor imaging (DTI) – This type of magnetic resonance imaging measures the health of white matter and identifies disrupted or abnormal white-matter connectivity in different brain regions. The non-invasive technique was developed more than 10 years ago. Whereas fMRI indirectly measures brain activity using a metabolic signal, DTI visualizes white-matter connectivity by measuring the diffusion of magnetically aligned water molecules along axon nerve fibers.

Positron emission tomography (PET) – Measures the location of small radioactively labeled molecules (radioisotope-tagged sugar molecules) in the brain. Areas of higher radioactivity are associated with greater brain activity. In Alzheimer's disease, PET is used to image decreased metabolism of glucose in areas of the brain affected by the condition. When a molecule that attaches to beta-amyloid protein is used, PET visualizes fibrillar amyloid.

Magnetoencephalography (MEG) – Measures the magnetic fields created when message-carrying sodium and potassium ions speed across synapses between nerve cells. It collects information on brain activity at the same speed as the brain itself operates. Developed in the 1970s to track submarines, the technology is still rare. Only a few MEG machines are available worldwide.—H.B.

Drug Addiction

Brain imaging could have profound implications for those working with people with drug addictions or babies born with fetal alcohol syndrome. Using DTI, Jeff Wozniak, Ph.D., a pediatric neuropsychologist at the university, has found that adolescents exposed to alcohol in utero have significantly disrupted white-matter connectivity, especially in the corpus callosum. Using MEG, Georgopoulos has found that the brain activity of chronic alcoholics undergoes rapid changes after the person goes through detox. “Within seven days of sobriety, the brain activity flipped with a dramatic shift toward normal,” he says. Likewise, using DTI, Lim has found decreased connectivity in frontal areas and in the corpus callosum of cocaine addicts, a finding he thinks helps explain their impulsivity. “We know cocaine constricts

blood vessels,” Lim says. “We believe reduced blood supply alters white matter and reduces connectivity.”

Still a Basic Science

Whether these imaging techniques make their way into psychiatrists’ offices any time soon remains to be seen. For now, says Georgopoulos, all the work being done is still at that basic science level, providing researchers greater understanding of the areas involved in specific psychiatric disorders. “One thing we have learned,” Pardo says, “is that terms like depression, schizophrenia, and dementia are gross descriptions that include many subtypes.”

In order to better understand those subtypes, imaging technology and the methods used to analyze the images they produce need to become even better than they are now. “As they do,” Lim says, “we’ll

more precisely locate microstructural abnormalities associated with specific psychiatric disorders. For now, there’s considerable overlap in findings that makes differential diagnosis difficult.”

Even if neuroimaging does improve to the point where it is ready to be used in the clinic, cost and access become factors. A PET scan, for example, costs around \$3,000. And the VA’s MEG imager, which cost \$3 million, is the only one in Minnesota with 248 sensors.

“It’s not practical to scan millions of people for depression,” Cullen says, “especially since we’re already pretty good at diagnosing it.” Instead, she says, scanning might be used selectively for questionable cases where symptoms overlap different diagnoses. And sometimes it will be useful for prescribing the right medication the first time, which can be difficult now,

It Started with Alzheimer’s Disease

Clinicians have been using structural magnetic resonance imaging (sMRI) in the diagnosis of Alzheimer’s disease (AD) since the late 1980s. According to David Knopman, M.D., a Mayo Clinic neurologist and investigator in Mayo’s Alzheimer’s Disease Research Center, when a patient is being evaluated for dementia, sMRI can rule out abnormalities such as tumors, subdural hematomas, and cerebrovascular disease. It also can show localized brain atrophy that is typical of AD. He explains that while a diagnosis of AD by sMRI is not possible with certainty, sMRI can diagnose frontotemporal degeneration (FTD) with confidence.

Positron emission tomography (PET) also can help distinguish between AD and FTD, both of which are characterized by atrophy of the brain. If the radiolabelled sugar used in PET shows decreased activity in the frontotemporal region, the cause of the person’s dementia is FTD. If it shows decreased activity in the posterior temporal, lateral parietal, and medial parietal regions, it is quite likely to be AD. Telling the difference is critical because managing these conditions is quite different, according to Knopman. “For FTD there is no treatment, whereas we have medications such as cholinesterase inhibitors that sometimes

slow AD progression but can make FTD worse.”

A breakthrough technique that could revolutionize diagnosis of AD, according to Knopman, is using PET to image fibrillar beta-amyloid protein in the brain. Mayo Clinic’s Val Lowe, M.D., and Clifford Jack, M.D., are using a radioisotope called Pittsburgh compound B that attaches to the beta-amyloid, which can begin to accumulate in the brain as early as 15 to 20 years before the person develops cognitive symptoms of Alzheimer’s.

Brain amyloid accumulation will eventually lead to death of neurons followed by clinical symptoms. Thirty

percent of people older than 70 years of age have positive amyloid imaging and, thus, are at greater risk for dementia, according to Knopman. “We’re now trying to determine what percent of those 30 percent go on to develop Alzheimer’s.”

It is believed that people who are not amyloid-positive do not get AD, which makes beta-amyloid a good biomarker for AD, Knopman says.

He and others may one day use amyloid imaging to select patients for AD drug trials. Knopman is currently studying several drugs that would alter or stop the progression of amyloid accumulation at its earliest stages. “Once drugs are developed for treating the mildly impaired or those at risk but with no symptoms, imaging biomarkers like amyloid will be essential. But for now, he says, “we’ve advanced imaging for AD beyond our ability to treat the disease.”—H.B.

“For now, there is considerable overlap in findings that makes differential diagnosis difficult.”

—Kelvin Lim, M.D.



according to Cullen, because “each of the antidepressants we have works for only 60 percent of patients.”

Cullen is trying to develop imaging “neuroprofiles,” subtypes of depression based on the areas of the brain that are affected correlated with results from traditional clinic evaluations. The profiles would guide treatment choices by iden-

tifying a more precise treatment target in the brain. “That way, we get patients on the right medication for them without wasting time on several drug trials,” she says.

But translating such basic research findings into clinical tools requires more and bigger studies, and getting grants to perform them is a challenge, according

to Pardo. “The grant people ask us, why image if you can’t treat it? We tell them we can’t develop treatments if we don’t image. Mental diseases are not what people like to fund.”

Clearly, more work needs to be done before we will be able to use brain imaging to diagnose and treat psychiatric disorders. But with each study, we are moving closer toward that capacity. “Right now, everybody is investigating their own small piece with their favorite technique,” Georgopoulos says. “Each gives additional information and each has its advantages and disadvantages. But psychiatry is like the rest of medicine. You don’t look at just one thing. You look at everything you’ve got.” **MM**

Howard Bell is a medical writer and frequent contributor to *Minnesota Medicine*.



Transparency improves quality.

Statewide Health Care Quality Reporting is here, and it’s time to report your clinic’s information.

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- CHECK OUT the MMA’s online measurement and reporting toolkit for physicians and clinics: www.mnmed.org/measure
- ATTEND a webinar January 12. Visit www.mnmed.org/measure to register



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Nursing Home Rounds

A simple conversation can yield important clues about the health of a patient with dementia.

By William Amundson

Joyce* wasn't in her room when we went to see her in the nursing home. We found her sitting in her wheelchair between the nursing station and the cafeteria, watching the other residents and staff. Dr. Johnson knelt down beside her and said, "Hello! It's good to see you today." Joyce didn't recognize him, despite his many previous visits. We asked her if we could go back to her room so we could talk to her and examine her. She told us the room was occupied because "they were doing something in the classroom." Dr. Johnson didn't seem concerned and started walking toward her room. I followed, pushing Joyce in her wheelchair.

This was my first experience with nursing home rounds. I had spent the morning in the clinic and saw a dozen patients with problems ranging from depression to upper respiratory tract infection. In the clinic, medicine is fast-paced and to-the-point. You ask questions, patients answer them, and your exam is focused. Often, it feels as if the patient is working for you. However, the nursing home is not the clinic.

Like most of the patients we saw that afternoon, Joyce was just getting a checkup. We knew of no particular complaints, and she probably couldn't have told us otherwise. Once we got to her room, we again told her who we were and what we were doing. She seemed comfortable with us examining her and asking her questions, but I am not sure she ever really grasped who we were or what we wanted to know. Dr. Johnson didn't seem fazed by this.

He proceeded by taking pictures from the walls of Joyce's room and asking her who was in them. She was able to answer, for the most part, and then started telling stories about her husband, children, other family members, and friends. At one point, she sneezed and asked Dr. Johnson to hand her a Kleenex "from over there," pointing across the room to a Kleenex box that was out of her view. Dr. Johnson gave her a tissue, and under his breath said, "Oriented times one." Seconds later, Joyce remarked

Joyce remarked that Fridays were always hard for her, earning an "oriented times two" from Dr. Johnson.

that Fridays were always hard for her, earning an "oriented times two" from Dr. Johnson since it was, indeed, a Friday. For almost our entire 15-minute visit, we sat next to Joyce's wheelchair, chatting about life and listening to her reminisce. The conversation was free-flowing and unguided. Never once did we ask her about a specific medical problem. I found myself wondering

when the actual exam was going to start.

When we left the room, Dr. Johnson turned to me and talked about how well she was doing. He has known Joyce for a long time, and although she didn't remember who he was, he was able to use her behaviors and stories as surrogates for answers to questions he would have asked in the clinic. This nontraditional approach to examining a patient revealed that Joyce was still alert and oriented to her surroundings, still able to recount important moments in her life and tell us about her family, and still functioning in a nursing home setting. We did listen to Joyce's heart and lungs and examine her feet. However, Dr. Johnson was able to get most of the information he needed just by having the conversation about her life.

The interaction was simple and so different from the regimented interview techniques we learn in medical school. This was truly medicine on the patient's terms. And it was a reminder that care should be about the patient, not the physician. Unfortunately, clinic medicine is not nursing home medicine. Focused questions have a place, as physicians must do the necessary detective work to uncover and treat problems during a short office visit. We should not, however, disregard the more humanistic conversations that can provide clues regarding concerns a patient may not tell us about. Instead of focusing on how to make patient interactions productive for us, we need to focus on what makes them most productive for our patients. **MM**

William Amundson is a fourth-year medical student at the University of Minnesota.

*Names of the patient and doctor have been changed.



THE PHYSICIAN ADVOCATE

News about Policy, People, and Politics

Legislative Preview: The Big Issues for 2012

Lawmakers will start the 2012 legislative session January 24 with a budget surplus, something they haven't seen since 2007.

At the end of November, officials from Minnesota Management and Budget forecasted a surplus of \$876 million for the second year of the state's biennium.

Having a surplus means health care programs should get a break from cuts this year. "The better-than-expected forecast has made additional cuts to state health care programs less of a concern," says Dave Renner, the MMA's director of state and federal legislation. He explains that the MMA will be at the Capitol educating lawmakers about the fact that the poor reimbursements that resulted from recent cuts may force some clinics to see fewer Minnesotans on public health insurance programs.

The surplus hopefully creates the opportunity for lawmakers and Gov. Mark Dayton to avoid gridlock, quickly pass a bonding bill, and end the session by the May 21 constitutional deadline.

Health Insurance Exchange

One of the issues lawmakers are expected to address this session is the establishment of a health insurance exchange. The Affordable Care Act requires each state to set up its own health insurance exchange by 2013 or participate in one created by



the federal government. The MMA would support a bill that would create an exchange framework for Minnesota. "We believe the Legislature should pass something this year in order to provide Minnesota residents with the best exchange possible instead one from the federal government," Renner says.

Some of the questions lawmakers need to answer about an exchange include who should run it (a state agency or a newly created organization), what cost and quality information about health plans and providers it should provide to consumers, and how it should be funded.

Provider Tax

The provider tax may become part of this discussion, since lawmakers will be looking for revenue to help pay for the exchange.

"During the upcoming session, we will continue to watch to make sure that people don't find new uses for the pro-

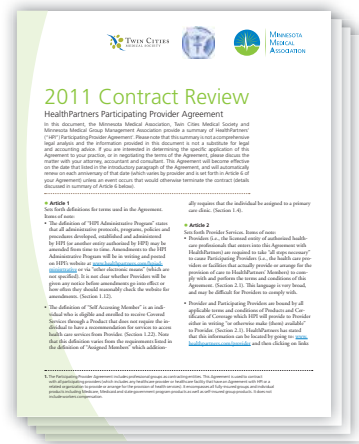
vider tax," Renner says. The Health and Human Services budget bill that passed in July of 2011 included a repeal of the 2 percent provider tax in 2019. The tax will gradually be phased out starting in 2013. "Finally, the Legislature heard our message that the provider tax must go. Now we must make sure they follow through on their commitment," Renner says, adding that the tax repeal may be targeted if deficits return.

The MMA is also developing legislative strategies for reducing administrative burdens related to prior authorization and bolstering the state's primary care workforce. "These are going to be high priorities for the MMA over the next three to five years, and we want to start educating lawmakers about the added costs of prior authorizations and the need for Minnesota to have an adequate supply of primary care physicians," Renner explains.

Scope of Practice

One issue that the MMA may have to play defense on is attempts by chiropractors to expand their scope of practice by allowing them to do more imaging studies and use the term "chiropractic physician."

"Our hope is that we can work out a compromise that addresses some of the chiropractors' legitimate issues, while still protecting patient safety and the physician's scope of practice," Renner says.



HealthPartners Contract Review Available

For the first time, the MMA, along with the Twin Cities Medical Society (TCMS) and the Minnesota Medical Group Management Association (MMGMA), is providing members with a legal review of the HealthPartners Participating Provider Agreement.

Providers are required to sign the agreement to be part of HealthPartners' network. There are several provisions that the MMA, TCMS, and MMGMA found noteworthy. They include having to have a designated "provider's liaison" to interact with HealthPartners; yearly reporting requirements including a summary of the

provider's quality assurance and improvement activities; required implementation of a continuous quality improvement system and establishment of a committee to monitor it; and establishment of one or more peer-review organizations to review medical errors and complaints from members and share the results with HealthPartners.

Another noteworthy provision says providers will not make any changes to medical staff, administrative staff, their organization, or their facilities that would prevent them from carrying out their obligations under the agreement.

In addition, the agreement says HealthPartners may unilaterally change, combine, or recode any procedure or billing codes in accordance with industry coding standards.

The MMA is providing this review as an exclusive benefit to members. To see the review in its entirety go to mmed.org/HPcontract.

Smoke-Free Workplaces Reduce Cardiac Deaths

Smoke-free workplaces have dramatically reduced the risk for heart attacks and cardiac deaths, according to a study by Mayo Clinic researchers that was presented at an American Heart Association conference in November.

The Mayo team studied the incidence of heart attacks and sudden cardiac deaths among residents of Olmsted County, Minnesota, before and after ordinances banning smoking in workplaces took effect. Eighteen months before Olmsted County passed its first smoke-free law in 2002, which banned smoking in restaurants, the regional incidence of heart attack was 212.3 cases per 100,000 residents. In the 18 months following the implementation of a more comprehensive ordinance in 2007 banning smoking in all workplaces, the rate dropped to 102.9 per 100,000 residents—a decrease of about 45 percent. Additionally, during the two study periods, the incidence of sudden cardiac death fell by 50 percent from 152.5 to 76.6 per 100,000 residents.

At the same time, the number of adults who smoked fell by 23 percent. The rates for other risk factors for heart



A Mayo team found a reduction in heart attacks among Olmsted County residents after the county implemented a smoking ban.

disease such as high blood pressure, high cholesterol, diabetes, and obesity remained steady or increased, according to the study.

"The study shows that everyone, especially people with known coronary artery disease, should avoid contact with secondhand smoke," Richard Hurt, M.D., director of Mayo Clinic's Nicotine Dependence Center, said in a press release.

The MMA was a strong proponent

of Minnesota's Freedom to Breathe Act, which became law in 2007 and prohibits smoking in indoor workplaces, including bars and restaurants, and on public transportation. In the United States, 23 states plus Washington, D.C., and Puerto Rico have banned smoking in all public indoor facilities, according to the American Cancer Society.

MEET A MEMBER

Rebecca Hafner-Fogarty, M.D.



Rebecca Hafner-Fogarty, M.D.

Rebecca Hafner-Fogarty, M.D., is a leader, both in the delivery of health care and in organized medicine.

Now as chief medical officer of Zipnosis, a service that allows patients to receive an online diagnosis of and treatment for simple acute medical conditions, she is helping harness technology in a way that makes evidence-based care more convenient and less expensive for patients. “As we enter the age of ACOs [accountable care organizations] and face a shortage of primary care physicians, the ability to ‘right site’ becomes increasingly important,” she says of the development of Zipnosis and similar services that provide an alternative to the traditional office visit for patients with straightforward conditions. “Health care reform is moving us from encounter-based medicine, and technology improvements are making high-quality virtual visits feasible.”

Hafner-Fogarty made the transition from practice to administration after earning an MBA in health care management from the University of St. Thomas in 1992. She honed her leadership skills

serving and as president of the Minnesota Board of Medical Practice (BMP) and as vice president, vice speaker, and speaker of the MMA House of Delegates. “The MMA gave me leadership opportunities that I did not have as a rural physician who was not part of a large clinic system,” she says.

Hafner-Fogarty went on to become medical director and later chief clinical officer of MinuteClinic, which operates clinics in retail centers across the United States. Under her watch, the number of retail-based clinics grew from 137 in five states to more 400 in 20 states in just three years. She joined Zipnosis in 2010.

Hafner-Fogarty, who also works in urgent care centers for Whitesell Medical Staffing and Northwest Family Physicians, was appointed to the BMP in 1998 after being endorsed by the MMA. She served on the board until 2010.

During that time, she represented the board on a task force that collaborated with MMA leaders and others to develop an online profiling system to provide consumers with accurate, timely, and appro-

priate information about Minnesota physicians. She also was involved in the board’s efforts to maintain physician competence and led the development of guidelines for physicians wanting to re-enter medicine after taking time off from clinical practice because of illness, or to raise a family or return to school. Minnesota’s board was one of the first in the country to address this issue.

Her experience on the BMP gave her a unique perspective, as she saw how stress could contribute to errors and unprofessional behaviors on the part of physicians. This insight prompted her to serve on the MMA’s task force on physician well-being, which addressed physician burnout and other work-life issues.

“As a profession and as employers, we need to do more to address the stresses that cause burnout,” she says.

Few Tobacco Dollars Used for Prevention

Minnesota is spending just 3 cents of every dollar it receives from the tobacco settlement and tobacco taxes to fight smoking and other forms of tobacco use.

Even with this low level of investment, Minnesota ranks 10th in the nation in terms of funding programs to prevent kids from smoking and help smokers quit.

The information comes from a report, “A Broken Promise to Our Children: The 1998 State Tobacco Settlement 13 Years Later,” released by the Campaign for Tobacco-Free Kids, American Heart Association, American Cancer Society Cancer Action Network, American Lung Association, Robert Wood Johnson Foundation, and Americans for Nonsmokers’ Rights.

Tobacco Facts

- **In Minnesota, 19.1 percent of high school students smoke, and 6,800 more kids become regular smokers each year.**
- **Tobacco claims 5,500 lives and costs the state \$2.06 billion in health care costs annually.**
- **States will collect a total of \$25.6 billion in revenue from the tobacco settlement and tobacco taxes in 2012, but will spend only 1.8 percent of that on prevention and cessation programs.**
- **Tobacco companies spend nearly \$23 to market tobacco products for every \$1 states spend on fighting tobacco use.**

“At a time when tobacco use is still the No. 1 preventable cause of death and disease in the United States, it is shameful that Minnesota is only spending only 3 cents of every tobacco revenue dollar to fight tobacco use,” says MMA President Lyle Swenson, M.D. MMA policy supports using tobacco settlement funds only

AT A GLANCE**CURRENT PRACTICE:**

Chief medical officer, Zipnosis
Urgent Care Physician,
Whitesell Medical Staffing and
Northwest Family Physicians,
Crystal

MEDICAL SCHOOL: University of
North Dakota, Grand Forks, 1978

INTERNSHIP: Family medicine,
University of North Dakota, 1979

MMA INVOLVEMENT: Joined
the MMA in 1979. Member
of Committee on Ethics and
Legal Affairs since 2010 and
from 1995-2003 (chair, 1998-
2000). Served as vice president
(1999), speaker (2002-2003),
and vice speaker (2000-2001)
of the House of Delegates. "The
MMA allows me to support the
profession on a larger scale that
has value. As physicians, we have
an obligation to assure that our
profession grows and remains
vital and has the best leaders
involved."

for health care programs.

Minnesota collects \$633 million from the 1998 tobacco settlement and tobacco taxes each year but spent just 3.1 percent (\$19.6 million) on tobacco-prevention and cessation programs in fiscal year 2011, according to the report. That amount is 33.4 percent of what the Centers for Disease Control and Prevention recommends spending on such programs.

MMA IN ACTION

Happenings around the state.

Janet Silversmith, MMA director of health policy, represented the MMA on the MN Community Measurement Cost Measure



Janet Silversmith

Data Specifications Subcommittee in November. The group has been tasked with exploring options for a standardized, community-wide total-cost-of-care measure. She also gave a presentation at Essentia Health St. Mary's Medical Center in Duluth on changes in Medicaid enrollment and physician payments related to the Affordable Care Act.

Dave Renner, MMA director of state and federal legislation, and Eric Dick, MMA manager



Dave Renner

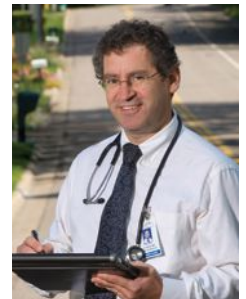
of legislative affairs, met with Rep. Bob Barrett (R-Lindstrom) in November to discuss health the insurance exchange and indoor tanning. Dick also spoke at a joint meeting of the Minnesota Rural Health Advisory Caucus and the Health Education-Industry Partnership in December about the challenges of provid-

ing health care in a rural setting.

The MMA's Resident and Fellow and Young Physician sections hosted "You're a Doctor...Now What? Surviving Life and Practice" at the Mall of America in December. More than 40 residents, fellows, and young physicians attended the event to get up to speed on managing personal finances, buying a home, and negotiating employment contracts.

Karolyn Stirewalt, J.D., MMA policy counsel, met with representatives from the state-run Health Professionals Services Program (HPSP), the Physicians Serving Physicians program, and Hazelden regarding the current eligibility requirements for licensed health care employees to be admitted to the HPSP program more than once.

MMA member Ed Ratner, M.D., worked with MMA staff to secure an \$1,800 grant to promote the physician orders for life



Ed Ratner, M.D.

sustaining treatment (POLST) form in Minnesota. The grant was from the Oregon Health & Science University's Center for Ethics in Health Care and the Retirement Research Foundation.

MMA President Lyle Swenson, M.D., was interviewed on Fox 9 News in December about Medicare's proposed 27 percent cut to physician payments and the deadline for Medicare enrollees to sign up for Medicare Advantage or supplemental insurance and drug benefit program.

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Industry Gifts: Dos and Don'ts

| by Karolyn Stirewalt, J.D.

In her role as the MMA's policy counsel, Karolyn Stirewalt, J.D., staffs the MMA's Ethics and Medical-Legal Affairs Committee, which is charged with promoting professionalism in medicine. She also takes questions from member physicians about ethical and legal issues. Here she shares answers to a few of the questions she's recently received about accepting gifts from industry.

Q: I have been asked to serve on the faculty for a professional or educational conference of a drug distributor. Is it O.K. for me to be compensated for it?

Yes. Minnesota Statute 151.461 allows practitioners to accept reasonable compensation for their expenses as well as honoraria from manufacturers or drug distributors for serving on the faculty of a professional or educational conference.

Q: Are the meals provided at a conference sponsored by a drug manufacturer or distributor considered "gifts" under Minnesota law, even if they are modest?

It depends on whether you are attending the conference or are on the faculty. While attendees may accept a modest meal at this type of conference, the meal would be considered a gift, and it would apply toward the \$50 per year limit on items they may accept from drug distributors or manufacturers. Practitioners serving as faculty members of a conference or educational event may accept modest meals without counting them toward the \$50 limit.

Q: If I participate in a drug survey, would it be considered a research project and, therefore, be compensable?

No. Those types of surveys are conducted by independent research organizations and are considered commercial marketing activities (not market research) of the drug company. Compensation may only be rendered by drug companies for the substantial professional or consulting services in connection with a genuine research project.



Karolyn Stirewalt, J.D.

Photo by Janna Nettland Lovar

Q: Are professional samples of a drug provided to a prescriber for free distribution to patients considered a gift? What about drugs that are distributed by a medical device manufacturer as an incidental part of its business?

No. Drug samples that are distributed by drug manufacturers, distributors, or agents for use by patients free of charge are not considered gifts and would not count toward practitioners' \$50 annual limit. Drugs distributed as an incidental part of a medical device manufacturer's business are not considered gifts under the statute, either.

Q: What is the MMA's policy on physicians accepting gifts from industry?

MMA policy states: "In the interest of professional ethics, good medical practice, and responsible stewardship, physicians should not accept any gift from pharmaceutical, medical device, or medical equipment manufacturers and distributors."



New Quality Measures Take Effect

Starting this month, Minnesota clinics will be required to report three new measures—patient satisfaction, total knee replacement, and maternity care—as part of the Minnesota Statewide Quality Reporting and Measurement System.

The measures will be added to the ones for which the state has been collecting data since 2010—optimal diabetes care, vascular care, asthma care, use of health information technology, depression remission, and colorectal cancer screening.

In September, the MMA sent comments to the Minnesota Department of Health highlighting physicians' concerns about one of the asthma measure's requirements—having an asthma action plan for all patients with asthma. MN Community Measurement, which administers the quality reporting system, convened a group to consider the matter. They concluded that asthma action plans can be beneficial even for patients with mild asthma and that it

would be difficult to define which subsets of patients should and should not have the plans. The Department of Health kept the asthma action plan requirement.

The MMA will host webinars about

the new reporting requirements in January, February, and March. For more information, visit mnmed.org/measure or contact Becky Schierman, at 612-362-3766 or rschierman@mnmed.org.

New Measures for 2012

Maternity Care. Efficacy of maternity care will be measured by primary cesarean-section rates (the percentage of cesarean deliveries for first births) and early elective induction rates (the percentage of elective inductions between 37 and 39 weeks' gestational age). Family medicine, internal medicine, obstetrics and gynecology, and perinatology physicians, certified nurse midwives, and certified professional midwives will be required to report this information.

Total Knee Replacement. The quality of a total knee replacement will be measured by the postoperative functional status according to the Oxford Knee Score and the patient's quality of life at one year postop measured using the EQ-5D survey. Reporting will start in 2014 for procedures performed in 2012.

Patient Experience. Clinics will be required to use the CAHPS Clinician and Group survey to evaluate patient experience. Clinics will need to hire a CMS-approved vendor to survey patients between September and November 2012 (actual reporting will happen in 2013). The survey will be required every other year.

Minnesota Sees Jump in Number of Uninsured Kids

Minnesota had the biggest increase in the nation in the percentage of children who were uninsured between 2008 and 2010, according to a study by the Georgetown University Health Policy Institute's Center for Children and Families. During that period, the percentage of children without insurance increased from 5.9 percent to 6.6 percent.

Although Minnesota's rate remains better than the national average of 8 per-

cent, 26 states and the District of Columbia have a lower percentage of children who are uninsured than Minnesota, according to the report, which was released in November.

The MMA supported legislation in 2009 to reduce the number of children without insurance by increasing the MinnesotaCare program's income limit for families with children.

Nationally, 34 states experienced a

decrease in the rate of uninsured children since 2008. Researchers found that although the number of children living in poverty increased significantly during that time period, the number of uninsured children in the United States fell from 6.9 million in 2008 to 5.9 million in 2010.

The progress in most states is attributed to more children enrolling in Medicaid and the Children's Health Insurance Program, which have filled a void created by a decline in employer-sponsored health insurance, a high unemployment rate (and loss of insurance), and the increasing cost of private health insurance.

The report is based on data from the U.S. Census American Community Surveys for 2008 and 2010.



VIEWPOINT

| by Lyle Swenson, M.D.

An Unfortunate Tradition

In the United States, payment for care by a physician is not usually made by the patient receiving the care but by a third party, typically a health insurance company.

Before this method of payment became the norm, the value of the care given by physicians was established, to a large extent, by the fee set by the physician. When Medicare was established in 1964, physician reimbursement was set according to what was “usual and customary” in the locale where the care was given. Today, reimbursement bears little relationship to what physicians charge or the true value of the care they deliver.

Since 1998, the Centers for Medicare and Medicaid Services have used the sustainable growth rate (SGR) formula to determine the amount physicians should be paid for providing care to Medicare beneficiaries. This formula ties reimbursement to the nation’s gross domestic product and does not take into consideration increases in the cost of providing care. As a result, reimbursement rates for physicians have decreased in each of the last eight years. When Congress has considered the possible effects of such decreases, especially the effect on access to care, legislators have passed stop-gap measures that slightly increase or freeze the reimbursement rates for a temporary period. Thus, SGR remains in effect, and a 27.5 percent cut in physician reimbursement is projected for 2012.

This year, as in years past, a hue and cry lamenting the damaging effects of such a cut in reimbursement has gone out, and the annual pilgrimage of physician organizations to the halls of Congress has begun. In previous years,



Lyle Swenson, MD
MMA President

Photo by Steve Wewerka

despite calls for repeal of the SGR and the creation of a more reasonable, sustainable formula for determining reimbursement, Congress has put off any long-term solution. This yearly debate on the SGR, with its perverse effects on the valuation of physician services, is terribly demoralizing for physicians. It is no surprise that this has led to anger, disgust, resentment, and a lack of faith in Congress’s ability to correct an obviously flawed and unsustainable program.

Congress’s unwillingness to fix the SGR formula has led many physicians to make heart-wrenching decisions. A number of physicians in Minnesota have left independent practice and have become employed, in part, to be protected from payment issues such as the SGR problem. Some have stopped seeing new Medicare patients. More are opting out of Medicare.

By the time this issue has gone to press, there will undoubtedly be more to the story. What we can say now, however, is that SGR will have to be scrapped sooner or later. For now, Medicare will continue to underfund physician services. Whether other financing strategies such as those embedded in the accountable care organization concept will value physician services more fairly and lead to a sustainable method for determining adequate reimbursement remains to be seen.

SGR will have to be scrapped sooner or later.

Minnesota’s Health Ranking Holds Steady

For the third year in a row, Minnesota ranked sixth in the America’s Health Rankings report published by the United Health Foundation.

The report, which measures how well states perform on a number of health indicators, noted low rates of public health funding, high rates of binge drinking, and a high incidence of infectious disease as areas of concern for Minnesota. The report also noted health disparities among racial groups in the state. For example, Hispanics and African Americans in Minnesota have higher rates of smoking and diabetes than non-Hispanic whites.

Minnesota continues to do well in several areas: having a low uninsured rate, good cardiovascular outcomes, and solid high school graduation rates. Minnesota also reduced its rate of preventable hospitalizations from 55.1 to 52.9 discharges per 1,000 Medicare enrollees during the last year.

In the 2011 report, Vermont ranked first, followed by New Hampshire, Connecticut, Hawaii, and Massachusetts. The report is available at www.americashealthrankings.org/.

Minnesota’s Fall from No. 1

Year	Rank
2006	1
2007	2
2008	3
2009	6
2010	6
2011	6

Screening for Dementia in a Primary Care Practice

By Susan McPherson, Ph.D., A.B.P.P., L.P., and George Schoepfoerster, M.D.

■ Dementia is a common condition of the elderly; yet it often is unrecognized by primary care providers. This article presents a compelling argument for screening for dementia in a primary care setting. It also provides a protocol for effective screening, instructions on how to use it, and steps to follow if the screening indicates the patient may have dementia.

Approximately 5.3 million people in the United States are living with Alzheimer's disease (AD).¹ Alzheimer's disease occurs in almost 50% of individuals older than 85 years of age, making it one of the most common conditions in the elderly. By 2050, an estimated 11 million to 16 million people 65 years of age and older in the United States will have the disease unless science finds a way to prevent or treat it.¹ Although many forms of dementia exist (Table), AD is the No. 1 cause of dementia in the elderly.

Recognizing that Minnesota's population is aging, the Legislature passed a bill in 2009 charging the Minnesota Department of Health with assessing the state's capacity for dealing with the anticipated onslaught of people who will be affected by Alzheimer's disease. Department of Health officials convened the Alzheimer's Disease Working Group (ADWG), which met during 2009 and 2010 to study the issue. As members of that group began looking at the state's health care resources, it became clear that primary care needed to be one area of focus. A subgroup of the ADWG was formed to explore screening for dementia in primary care. Members of that

group, which included neurologists, primary care physicians, neuropsychologists, nurses, and representatives from the Alzheimer's Association-Minnesota and North Dakota Chapter, considered evidence that early identification of dementia led to higher-quality care and better outcomes. They also reviewed studies that showed that primary care providers often fail to detect dementia.

This article presents the work of that subgroup. It discusses the rationale for early dementia screening and introduces a protocol designed to help busy primary care physicians detect early signs of cognitive change in their patients.

What is Dementia?

Dementia is a constellation of symptoms related to a decline in cognitive functioning. It has a number of causes. Dementia can manifest as deficiencies in multiple areas of mental functioning including language, memory, perception, emotional behavior or personality, and cognitive processing (ie, performing calculations, abstract thinking, or judgment). A diagnosis of dementia is made when the following DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition) criteria are met:

1. The patient *must* have memory im-



Screening for Dementia in Primary Care Practice

Date of release: January 6, 2012

Estimated time of completion: 30 minutes

Educational objectives:

- 1) To understand the importance of screening for dementia in a primary care setting.
- 2) To be able to use the new protocol for screening for early stage dementia.

Target audience: Primary care physicians

Authors

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Disclosures

Faculty have indicated they have no relationship which, in the context of their presentations, could be perceived as a potential conflict of interest.

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pairment. Specifically, a person must have lost his or her ability to make new memories. That loss is often measured in cognitive screening tests by the lack of ability to recall three items in five minutes or in a formal neuropsychological evaluation.

2. In addition, the patient must have one or more of the following cognitive disturbances:
 - Agnosia—difficulty recognizing or identifying familiar objects or other sensory cues, despite intact sensory function. In the case of AD, agnosia refers to an inability to provide the correct name of a familiar object;
 - Aphasia—disturbance of comprehension or expression of language. Patients with AD have difficulty primarily with word-finding;
 - Apraxia—difficulty performing familiar motor activities, despite a desire to do so, while still having intact motor function. Persons with AD often have a construction apraxia marked by difficulty copying drawings or putting together puzzles; and
 - Disturbance in executive functioning, which includes planning, organizing, sequencing, and abstracting.
3. Finally, the patient's loss of mental function must be severe enough to affect daily life, and their mental functioning must have declined since the last screening.

The symptoms of dementia also can be caused by treatable conditions such as thyroid disorders, nutritional deficiencies, side effects of anticholinergic medications, and normal-pressure hydrocephalus. Identifying and treating those causes should be the initial task of any primary care physician. When no other treatable cause is present, dementia becomes the primary concern.

Why Screen for Dementia?

Screening is the first step toward providing high-quality care for people with Alzheimer's disease and other forms of dementia.

Identifying dementia early in its course is critical for a number of reasons. Having a formal diagnosis helps explain

Table
Types of Dementia

Type of Dementia	Distinguishing Characteristics
Mild cognitive impairment (MCI)	Associated with memory difficulties or one of the other four cognitive disturbances that are part of a dementia diagnosis. These symptoms do not affect daily life. They may or may not indicate an early stage of dementia.
Alzheimer's disease	Most common type of dementia; it accounts for an estimated 60% to 80% of cases. Difficulty remembering names and recent events is often an early clinical symptom; apathy and depression also may be early symptoms. Later symptoms include impaired judgment, disorientation, confusion, behavior changes, and difficulty speaking, swallowing, and walking. Hallmark abnormalities are deposits of the protein fragment beta-amyloid (plaques) and twisted strands of the protein tau (tangles).
Vascular dementia	Impairment is caused by decreased blood flow to parts of the brain, often due to a series of small strokes that block arteries. This is relatively rare and accounts for only 6% to 10% of dementias of old age. Symptoms often overlap with those of Alzheimer's, although memory may not be as seriously affected.
Dementia with Lewy bodies/ Parkinson's dementia	The second most common type of dementia, accounting for 30% of dementias. Hallmark symptoms include two of the following: 1) visual hallucinations, 2) frequent fluctuations in cognition, 3) parkinsonism. Pattern of decline is more rapid than in Alzheimer's. Hallmarks include Lewy bodies (abnormal deposits of the protein alpha-synuclein) that form inside nerve cells in the brain. Many people who have Parkinson's disease also develop dementia. Lewy Bodies dementia may exist with or without Parkinson's disease. If it accompanies Parkinson's, it may occur in either the early or late stage of the disease.
Frontotemporal dementia	The third most common form of dementia primarily affects individuals in their 50s and 60s. Nerve cells in the front and side regions of the brain are especially affected. Previously known as Pick's disease, although Pick bodies are only present in 25% of cases. Distinguishing symptoms include EITHER 1) marked changes in personality and behavior, or 2) a language variant marked by difficulty in speech production (stuttering) or difficulty finding the right words when speaking (semantic dementia).
Creutzfeldt-Jakob disease	Fatal disorder that impairs memory and coordination and causes behavior changes. Caused by the misfolding of prion protein throughout the brain. A variant of Creutzfeldt-Jakob disease is believed to be caused by consumption of products from cattle affected by mad cow disease.
Normal-pressure hydrocephalus	Caused by the buildup of fluid in the brain. Symptoms include difficulty walking, memory loss, and urinary incontinence. Can sometimes be corrected with surgical installation of a shunt in the brain to drain excess fluid, particularly when discovered early.
Dementia with Huntington's disease	Part of an autosomal dominant inherited disorder associated with twitches, muscle spasms, difficulty with balance/coordination, and personality changes.
Cognitive decline from Korsakoff's syndrome and traumatic brain injury	Variable manifestations. May not meet criteria of a dementia. Best assessed with neuropsychological testing.

Source: Adapted from 2011 Alzheimer's Disease Facts and Figures

symptoms and cognitive problems that were distressing because the cause was unknown.^{2,3} It also enables patients to plan for their future before cognitive decline begins to interfere with their judgment and reasoning.

In addition, early identification leads to earlier treatment. Research suggests that some of the medications currently available for AD (in particular, cholinesterase inhibitors) are most beneficial when given during the early stages when the patient exhibits only mild symptoms.⁵ Studies show that placing patients on such medications can slow the rate of functional decline by approximately one year.⁶ Sustained cognition is not the only benefit to using medication. A study by Holmes and colleagues found that patients with AD who were treated with donepezil exhibited improvement in neuropsychiatric symptoms as compared with patients on placebo.⁷ Lopez and colleagues observed patients on both a cholinesterase inhibitor and memantine (n-methyl-d-aspartate receptor modulator) and found those patients were more than seven times less likely to go to a nursing home than patients on a cholinesterase inhibitor alone.⁸ These authors noted that although these medications do not delay mortality, their use does increase functional ability.

Early identification also helps patients avoid situations that can cause harm such as not taking medications on time or in the right quantity, which can lead to an exacerbation of other medical conditions; making poor financial decisions; falling; or getting lost while driving. It also helps providers make sure the patient is getting the treatment they need for their other conditions.

Finally, early identification may be cost-effective. Alzheimer's disease is the third most costly disease in the United States, following cardiac disease and cancer.⁹ Medicare beneficiaries with AD incur costs that are approximately 60% higher than those of persons without AD, possibly because of higher costs associated with caregiving.^{10,11} Early identification and use of both medical and nonmedical treatments to slow the course of the disease

coupled with interventions that support caregivers will reduce the risk of nursing home placement, thereby lowering costs.¹² In addition, use of cholinesterase inhibitors has been shown to decrease the overall cost of treatment by improving cognition and daily functioning.¹³

A Simple Way to Screen for Dementia

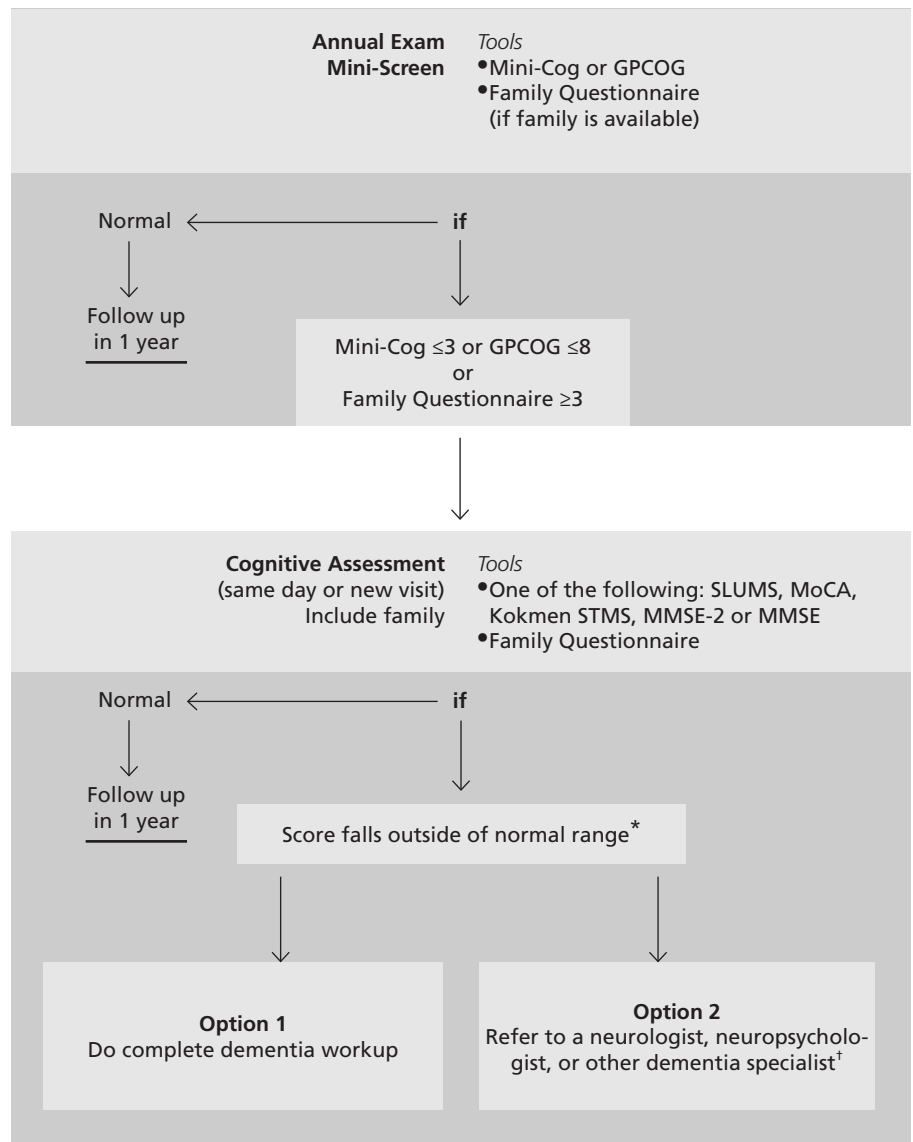
Although the reasons for early identification of dementia are compelling, research

has shown that primary care physicians fail to diagnose mild to moderate dementia at least 50% of the time.^{14,15} This may be because the majority of people in the early stages of AD are conversant and socially appropriate. Unless a formal mental status examination is conducted, the disease easily can go undetected during a routine office visit.

Another issue encountered by primary care physicians is the lack of guidance for assessing cognition. Physicians

Figure 1

Protocol for Cognitive Impairment Screening



* Normal Ranges: SLUMS = 27-30 (HS education); MoCA = 26-30 (HS education); Kokmen STMS = 29-38; MMSE/MMSE-2 = 27-30; Family Questionnaire ≤2

† Neuropsychological evaluation is most helpful for differential diagnosis, determining nature and severity of cognitive functioning, and the development of an appropriate treatment plan. Testing is typically maximally beneficial in the following score ranges: SLUMS = 19-27; MoCA = 19-27; Kokmen STMS = 19-33; MMSE/MMSE-2 = 18-28

have typically relied on either direct observation or information provided by family members when assessing a person's cognitive function. Given these considerations, the Minnesota Working Group decided to develop an algorithm that could help physicians detect the early signs of cognitive changes associated with dementia. One of the goals was to create a method for screening that could be done in a primary care office that would place minimal burden on physicians and other staff. (Dementia screening should become even more routine in the future, given that Medicare now pays for an annual wellness visit and requires that patients be screened for cognitive changes.)

The group reviewed a number of dementia screening tools and chose several to include in the protocol. The tools selected were based on sound psychometric properties. All are easily administered, with training, by a nurse or medical assistant. The screening algorithm is presented in Figure 1.

Because a dementia diagnosis requires a decline from a previous level of functioning, screening for a measurable and reproducible baseline level of cognitive function should be done during the patient's annual wellness visit. As cognitive screening is now a required portion of the annual Medicare exam, we recommend that it begin at age 65. It should be repeated annually. In addition, screening should occur whenever concerns about cognitive function are raised by the patient or his or her family members.

■ The Screening Protocol

The first step is to perform a preliminary screening. The Working Group recommended using either the Mini-Cog¹⁶ or the General Practitioner Assessment of Cognition (www.gpcog.com.au).¹⁷ Both are rapid screening tools for memory loss that can be administered by a nurse or medical assistant while taking the patient's vital signs.

The Mini-Cog asks the patient to remember three words. Immediately following the presentation of the words, the patient is asked to draw the face of a clock

and set the hands at "11:10." After they draw the clock, the patient is asked to recall the three words. One point is awarded for each word recalled. The patient receives two points if all the numbers on the clock are present and evenly spaced and the hands are set at the 11 and 2 positions. No points are awarded if neither hand is set correctly or if numbers are missing or unevenly spaced.

If the patient brings a family member to the visit, the physician may want to ask for their input as well. The National Chronic Care Consortium and the Alzheimer's Association's Family Questionnaire is one tool that can be used to get the caregiver's take on a patient's cognitive functioning (Figure 2). The questionnaire asks six questions of caregivers who have regular contact with the patient. Questions are scored as follows:

- Not at all = 0
- Sometimes = 1
- Frequently = 2

A score greater than 3 suggests the need for additional evaluation. If any of the initial screening tools (the Mini-Cog, GPCOG, or Family Questionnaire) indi-

cates that the patient may have memory loss, a second cognitive assessment that increases the testing specificity should be performed at the end of the visit. Physicians can introduce the need for a second screening by telling the patient that the first one suggested possible memory changes and that it would be helpful to ask a few more questions.

A number of tools can be used for this additional assessment. All tests chosen for the protocol take 10 to 15 minutes to administer, and all have similar psychometric properties as. None are meant to replace a thorough evaluation. The tools chosen include the Mini Mental State Examination (MMSE), available through Psychological Assessment Resources (www.parinc.com);¹⁸ the Montreal Cognitive Assessment (MoCA), www.mocatest.org;¹⁹ the Kokmen Short Test of Mental Status;²⁰ and the St. Louis University Mental Status (SLUMS) (http://medschool.slu.edu/agingsuccessfully/pdfsurveys/slumsexam_05.pdf).²¹

If the second screen is positive, the next step is to do a complete dementia workup or refer the patient to a demen-

Figure 2

The Family Questionnaire

In your opinion does _____ have problems with any of the following?

Please circle the answer:

1. Repeating or asking the same thing over and over?
Not at all Sometimes Frequently Does not apply
2. Remembering appointments, family occasions, holidays?
Not at all Sometimes Frequently Does not apply
3. Writing checks, paying bills, balancing the checkbook?
Not at all Sometimes Frequently Does not apply
4. Shopping independently (e.g. for clothing or groceries)?
Not at all Sometimes Frequently Does not apply
5. Taking medications according to the instructions?
Not at all Sometimes Frequently Does not apply
6. Getting lost while walking or driving in familiar places?
Not at all Sometimes Frequently Does not apply

What is your relationship to the older adult? _____
(spouse, son, daughter, brother, sister, grandchild, friend, etc.)

Source: Alzheimer's Association and the National Chronic Care Consortium.

tia specialist (a neurologist, geriatric psychiatrist, or geriatrician, for example). Additional testing by the primary care physician might include laboratory tests (CBC, B12, folate, thyroid), screening for substance abuse or medication mismanagement, and assessment for depression or other forms of mental illness. Referral to a neuropsychologist may be warranted for additional cognitive testing, and a CT or MRI scan of the brain might be ordered. Regardless of who completes the evaluation, it is important that an accurate diagnosis is made and that the type of dementia is identified.

Once the Diagnosis is Made

As with any other degenerative disease, the first thing to do is to inform the patient and his or her family of the diagnosis. Knowing that the patient has memory loss or difficulties with cognition can help the patient, the family, and the physician make important care decisions such as having a family member attend appointments and having a family member or visiting nurse assist with medication management and compliance. A referral to the Alzheimer's Association (800-272-3900 or www.alz.org) can be helpful for both the patient and caregiver, no matter the type of dementia the patient has. The Alzheimer's Association offers free information on many aspects of dementia including the most common types, advice for dealing with behavioral changes, support groups for caregivers, as well as information about respite services, adult day care, legal and financial planning services, and programs to keep people safe. For individuals with young-onset disease (onset before age 65) the association has "meet-up" groups and a mentoring program, which can help the patient better navigate the disease.

Summary

Dementia is a common condition in the elderly. Early detection allows for early treatment as well as better control of comorbid conditions; it also ensures that patients and their families have time to make plans and adjust to the inevitable changes that will accompany the disease. Being

diagnosed with dementia changes everything—for the patient, the patient's family, and their health care providers. Screening for the disease in its early stage can be the first step in making a difference in the care patients receive and in their quality of life.

MM

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New Clinical Criteria for the Alzheimer's Disease Spectrum

By Ronald C. Petersen, Ph.D, M.D.

■ New criteria for diagnosing Alzheimer's disease (AD) were recently published. These criteria cover the entire spectrum of AD including dementia due to AD, mild cognitive impairment due to AD, and preclinical AD. A major feature of the new criteria is that they distinguish between the clinical characteristics of the disorder and the pathological features. Earlier criteria were based on clinical features alone. The new criteria include the use of imaging and other biomarkers to aid in diagnosis. The criteria regarding clinical features are currently being used in practice; the criteria regarding biomarkers still need to be validated.

In 1984, a landmark paper was published by McKhann and colleagues outlining criteria for diagnosing Alzheimer's disease (AD).¹ About the same time, the National Institute on Aging established its AD program, and research centers around the country began embracing the diagnostic criteria. The criteria were readily adopted in clinical practice as well and have been used to diagnose Alzheimer's disease for the past 25 years.

The original criteria focused on the patient's history and the results of cognitive testing. Imaging was used primarily to rule out other disorders such as tumors, cerebral infarcts, and normal pressure hydrocephalus. Although seemingly simplistic at this point in time, these criteria have served the research and clinical communities very well. In fact, there has been a strong correlation between diagnoses made using these criteria and neuropathological evidence at autopsy in patients who have been followed longi-

tudinally.² The criteria (or variations of them) have been used in many clinical trials for AD and have contributed to the approval of five drugs for the disorder by the Food and Drug Administration.³ They also have influenced thinking about dementia and AD. For example, the characterization of dementia in the last several iterations of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III, DSM-III-R, DSM-IV, and DSM-IV-TR) has been strongly influenced by the McKhann criteria. In fact, some have suggested the construct of dementia has been "Alzheimer-ized" over the years.⁴ Nevertheless, the McKhann criteria for AD have dominated our approach to research involving large cohorts of subjects.⁵

During the last three decades, we have learned a great deal about the pathophysiology of AD.⁶ Research, including studies involving Mayo Clinic investigators, has yielded information that led some to call for a revision of the

criteria. In 2009, the National Institute on Aging and the Alzheimer's Association formed international work groups to revise the diagnostic criteria for AD, and in 2011, new criteria and guidelines that update, refine, and broaden the ones published in 1984 were issued. This article presents the rationale for issuing the new guidelines and discusses some of the key differences between the new and old approaches to diagnosing this disease.

The Old Versus the New Criteria

The most notable features of the new diagnostic criteria and guidelines are that they add criteria from existing guidelines for diagnosing mild cognitive impairment (MCI) and expand the conceptual framework for thinking about Alzheimer's disease to include a "preclinical" stage characterized by biological changes (biomarkers) that occur years before any disruptions in memory, thinking, or behavior can be detected. The new guidelines do not yet specify which

biomarkers should be considered signatures of preclinical Alzheimer's disease. Instead, they propose a research agenda and a framework for eventually adding biomarker benchmarks to the diagnosis of Alzheimer's disease in all of its stages.

Using the old criteria and guidelines, a person had to have clinical symptoms such as progressive memory impairment and other cognitive difficulties that are severe enough to affect daily functioning and harbor pathological features commensurate with AD before they could be diagnosed with the disease. This is similar to requiring a cardiac patient to have a symptom such as angina before a diagnosis of coronary artery disease can be made. As researchers began to learn more about what was occurring in the brains of people with AD, they discovered that the clinical symptoms of AD emerged after a preclinical period, during which a specific disease process was taking place. Consequently, the revised criteria refer to a clinical spectrum (Alzheimer's disease-clinical or AD-C) and a pathological spectrum (AD-pathophysiology or AD-P).

The new criteria and guidelines also allow for a more definitive diagnosis. In 1984, diagnosing AD was largely a matter of exclusion. That is, if the person had progressive cognitive impairment, an evaluation was undertaken to be certain that the cause was not related to factors such as vascular disease, normal-pressure hydrocephalus, tumors, or other medical comorbidities. Only if no other cause was found was a diagnosis of AD made. Now, making a diagnosis is an exercise of inclusion, in which the clinician looks for a clinical course fulfilling positive criteria for the diagnosis.⁷ Eventually, clinicians will also look for specific biomarkers of the pathological process.⁸

The new criteria and guidelines also better reflect distinctions between AD and other forms of dementia. In addition to the knowledge about the underlying pathophysiology of AD that has amassed in recent years, there is a great deal of new information regarding other types of dementia as well. For example, we now know more about vascular cognitive impairment,

and several attempts have been made to refine the criteria for this diagnosis.⁹ We also have a better understanding of dementia with Lewy bodies, and sophisticated criteria have been published and revised allowing for the rather precise characterization of this disorder.¹⁰ In addition, the overlap of dementia with Lewy bodies with Parkinson's disease-dementia and the more recently described Parkinson's disease-mild cognitive impairment (MCI) with coexisting AD pathophysiology have been studied.¹¹ And, recently, frontotemporal lobar degeneration has been characterized and subtyped.¹² Although the diagnostic criteria for these conditions are still evolving, the behavioral and language variants have been carefully characterized. The distinguishing clinical features and biomarkers of these entities are being investigated to allow further differentiation of these disorders from AD.

..... The New Model

We now understand that a sequence of events occurs prior to clinical manifestations of AD, which include cognitive and functional impairment. A major advance has been the development of a hypothetical model of those events.¹³

The model presumes that the deposition of amyloid in the brain initiates development of the disease. Numerous theories explain how amyloid gets deposited, but most consider fibrillization an early event. The deposition of amyloid can be detected in the cerebrospinal fluid (CSF) as low A β 42 or with positron emission tomography (PET) imaging using a radiolabeled ligand for amyloid.¹⁴ After the amyloid is deposited extracellularly, neuronal injury results. The first manifestation of this can be detected as an increase in CSF tau. Tau is an intracellular protein that becomes hyperphosphorylated in AD; its release during neurodegeneration can be detected in the CSF. Later, metabolic abnormalities occur that can be detected by fluorodeoxyglucose positron emission tomography; subsequent structural volumetric changes, which can be measured on MRI, then take place. It is only after these events have occurred that clinical symptoms begin to

manifest first in cognition and, later, in daily functioning.

It should be emphasized that, although it is based on an increasing number of studies of the biomarkers of AD, this is still a theoretical model. Yet it serves as the foundation for the new criteria and guidelines, which propose that clinical criteria be augmented with testing for biomarkers.¹⁵

The new criteria and guidelines divide the AD spectrum into three phases. The phase of greatest clinical impairment is "dementia due to AD." The intermediate stage is "mild cognitive impairment due to AD." And the stage designated "preclinical AD" refers to the point at which the patient is clinically asymptomatic but harbors biomarkers suggestive of a developing AD-P.¹⁶

■ Dementia Due to AD

This is the phase that most closely resembles AD as it was diagnosed using the 1984 criteria.⁷ It should be noted, however, that memory impairment is no longer an absolute requirement for a diagnosis of probable AD and, thus, there are subtle differences between the old and new criteria regarding the clinical presentations. Although having memory impairment represents the most common presentation of clinical dementia, there can be atypical presentations such as a prominent visuospatial deficit seen in posterior cortical atrophy or the logopenic form of aphasia.¹⁷ These uncommon, but well-recognized, clinical phenotypes often have AD-P as the underlying cause, and the new criteria accommodate them.

The core criteria for a dementia diagnosis include a cognitive impairment in two or more domains including memory, language, executive function, or visuospatial skills accompanied by a disruption of daily function. If these criteria are met and insidious onset and gradual progression of the symptoms are corroborated by someone who knows the person well, a diagnosis of probable AD dementia is made. The amnesic presentation often prevails; but nonamnesic presentations can occur.

The novel features of the new criteria

Table 1

Diagnostic Criteria for Alzheimer’s Disease Dementia

Diagnosis	Likelihood of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG PET, sMRI)
Probable AD Dementia			
Clinical evidence only	Uninformative	Conflicting/indeterminant/unavailable	
With biomarker evidence	Intermediate	Unknown	Positive
	Intermediate	Positive	Unknown
	High	Positive	Positive
Possible AD Dementia			
Clinical evidence only	Uninformative	Conflicting/indeterminant/unavailable	
Atypical clinical presentation with biomarkers for AD	High	Positive	Positive
Dementia unlikely due to AD	Low	Negative	Negative

Source: Adapted from McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement*. 2011;7(3):263-9.

Definitions

AD: Alzheimer’s disease • Aβ: amyloid beta • PET: positron emission tomography
 CSF: cerebrospinal fluid • FDG PET: fluorodeoxyglucose positron emission tomography
 sMRI: structural MRI

are outlined in Table 1. Initially, a clinical diagnosis of probable AD is made if the criteria for dementia are met and information from imaging or fluid biomarkers is unavailable or uninformative. The next level of certainty for a probable AD diagnosis is evidence of either amyloid deposition (detected on PET or in CSF) or neuronal injury (CSF tau levels, FDG PET, or MRI atrophy patterns). This evidence increases the likelihood that the clinical syndrome of dementia is the result of underlying AD-P. The highest level of certainty is achieved when there is evidence for both amyloid deposition and neuronal injury in the presence of clinical evidence. There is also the category “possible AD,” which is an appropriate diagnosis if the patient presents with an atypical clinical course but has both types of biomarkers—amyloid deposition and neuronal injury. Finally, with the wealth of available information on non-AD dementias, there is the category “unlikely due to AD,” which is appropriate if the person has a clinical syndrome accompanied by negative biomarkers for amyloid deposition and neuronal injury.

It should be noted that at this point, only the diagnosis of probable AD dementia should be used in practice. All of the other criteria listed in Table 1 need to be corroborated with physiologic evidence before they can be used.

■ Mild Cognitive Impairment Due to AD

The criteria for diagnosing MCI caused by AD follow a similar hierarchy.¹⁵ Initially, a patient must meet the following criteria: 1) concern raised by the patient, someone who knows the patient well, or by an examining clinician about cognitive function; 2) evidence of cognitive decline and impairment in at least one domain such as memory, language, executive function, or visuospatial skills; 3) preservation of functional independence, meaning the person does not need help with activities of daily living; and 4) not meeting the criteria for dementia.

As shown in Table 2, the first level of diagnostic certainty for MCI involves having the clinical evidence alone. The next level of certainty requires positive evidence of either amyloid deposition

or neuronal injury. The highest level of confidence that MCI is caused by AD is derived when the clinical syndrome is accompanied by positive evidence for both amyloid deposition and neuronal injury. As with dementia, the likelihood of a clinical syndrome not being caused by AD-P is low if the biomarkers are negative. At this point, only the diagnosis of MCI should be used in practice.

■ Preclinical AD

What may be the most exciting but least supported aspect of the new criteria pertains to a condition called “preclinical AD.”¹⁶ None of the diagnostic recommendations are ready for use in clinical practice; but these criteria outline a rich research agenda. Stage 1 refers to the presence of amyloid deposition without evidence of neuronal injury or subtle cognitive change (Table 3). Stage 2 refers to the presence of amyloid deposition and neuronal injury but without cognitive changes. Stage 3 uses the same biomarker criteria as Stage 2 but also includes subtle cognitive signals representing a change. A recent Mayo Clinic study applying the preclinical criteria to a population-based sample of subjects 70 to 89 years of age in Olmsted County, Minnesota, found that approximately 30% fulfilled the criteria for Stages 1-3.¹⁸ Another 43% had no evidence of amyloid deposition, neuronal injury, or subtle cognitive changes; these individuals are considered to be aging normally. Interestingly, many individuals showed evidence of either neuronal injury and/or cognitive changes but were negative with regard to amyloid deposition. These participants were designated as having a suspected nonamyloid pathway or SNAP.

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Conclusion

The new criteria issued in 2011 for diagnosing the AD spectrum were designed to advance the field from both a research and clinical perspective. The recommendations incorporate the dominant theoretical model of AD-C and AD-P and delineate criteria to reflect this. These new criteria are designed to help clinicians

Table 2

Diagnostic Criteria for Mild Cognitive Impairment

Diagnosis	Likelihood of AD etiology	AB (PET or CSF)	Neuronal injury (tau, FDG PET, sMRI)
MCI	Uninformative	Conflicting/indeterminant/untested	
MCI due to AD – intermediate likelihood	Intermediate	Positive	Untested
	Intermediate	Untested	Positive
MCI due to AD – high likelihood	High	Positive	Positive
MCI – unlikely due to AD	Low	Negative	Negative

Source: Adapted from Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement.* 2011;7(3):270-9.

Definitions

MIC: Mild cognitive impairment • AD: Alzheimer’s disease • AB: amyloid beta • PET: positron emission tomography CSF: cerebrospinal fluid • FDG PET: fluorodeoxyglucose positron emission tomography sMRI: structural MRI

Table 3

Staging of Preclinical Alzheimer’s Disease

Category	AB (PET or CSF)	Neuronal injury (tau, FDG PET, sMRI)	Clinical signs of cognitive change
Stage 1	Positive	Negative	Negative
Stage 2	Positive	Positive	Negative
Stage 3	Positive	Positive	Positive

Source: Adapted from Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer’s disease: recommendations from the National Institute on Aging-Alzheimer’s Association workgroups on diagnostic guidelines for Alzheimer’s disease. *Alzheimers Dement.* 2011;7(3):280-92.

Definitions

AB: amyloid beta • PET: positron emission tomography • CSF: cerebrospinal fluid • FDG PET: fluorodeoxyglucose positron emission tomography • sMRI: structural MRI

characterize individuals as early as possible in the course of their disease to allow for early intervention and prevention of subsequent neuronal damage. The criteria are also necessary for designing clinical trials for new therapies to prevent neuronal destruction. A great deal of research will be needed to validate these criteria, and numerous studies are currently underway throughout the world. **MM**

Ronald Petersen is director of the Mayo Alzheimer’s Disease Research Center.

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New Approaches to Neurorehabilitation

The Increasing Evidence Base

By Karl J. Sandin, M.D., M.P.H.

■ Recent advances in neuroscience have led to newer, more scientific approaches to rehabilitation for patients who have had a stroke or sustained a brain or spinal cord injury. Specifically, the pendulum in rehabilitation has swung away from a focus on compensatory techniques and toward impairment-mitigating therapies. In addition, there is a new push to base therapies on scientific evidence. This article explores these changes and the developments that led to them, including discoveries in basic science that have enhanced our understanding of neuroplasticity. It also describes new research directions in neurorehabilitation.

The International Classification of Functioning, Disability, and Health (ICF) is the World Health Organization's framework for measuring disability at both the individual and population levels

The ICF has three domains: body structure and function, activity, and participation. Loss of body structure and function refers to an impairment such as paralysis; activity limitation refers to inability to perform daily tasks or activities such as walking; and participation restriction refers to the inability to work or take part in social activities. A person who has had a stroke may have disability in all three domains, for example, left-sided weakness, inability to walk or dress themselves without help, and inability to work full-time.

Traditionally, neurorehabilitation for stroke would have focused on preventing the impairment from becoming worse through passive range-of-motion, stretching, and positioning exercises to prevent contracture and maximizing activity through compensatory strategies (eg, using a wheelchair to get around rather than walking). Regaining neural structure and function was not the goal.

The approach to rehabilitation for patients who have had a stroke or sustained a brain or spinal cord injury was empiric; determining which therapies to use, how often to use them, and for what duration they should be used was based more on what was feasible rather than on what had been shown to be effective through scientific research. As a result, there has been a lack of specificity about what is required in terms of neurorehabilitation for optimal recovery.

In recent years, the field has begun to change. Advances in neuroscience that shed light on neuroplasticity have led to changes in thinking about the goals of and our approaches to

neurorehabilitation. This knowledge has been the catalyst for scientific research into the efficacy of treatments. This article explores this shift in neurorehabilitation.

A New Look at Rehabilitation

Actor Christopher Reeve, who in 1995 sustained a C4 spinal cord injury after falling from a horse that resulted in tetraplegia, inspired many to begin to think differently about rehabilitation. Reeve insisted that the goal of his rehabilitation be recovery of ability. Although many individuals enter rehabilitation saying their goal is to “walk out of here,” Reeve had both the personal determination and economic resources to insist that his rehabilitation regimen include therapies that did more than help him accommodate his disabilities. Reeve received stem cell treatment and participated in robust locomotor training, both of which are not part of traditional rehabilitation. His findings on neurological examination did improve over time to an exceptional degree: He regained sensibility through C6 and some left index finger extension. Although Reeve did not achieve meaningful recovery of movement or enough sensibility to regain “normal” activity, his case prompted many to take a new look at rehabilitation following neurologic injuries. Since then, many rehabilitation clinicians have added improvement in body structure and function as a primary goal of rehabilitation.

During the same time that Reeve was challenging the traditional paradigm in rehabilitation, scientists were making tremendous strides in understanding the brain and nervous system. Especially relevant to rehabilitation medicine was new information about neuroplasticity. The concept of neuroplasticity is not a new one—American psychologist William James

first introduced the idea in 1890—and a century of research has confirmed it is a fundamental, evolutionarily conserved property of all nervous tissue. However, we have not been able to truly understand what is occurring at the cellular level until recently.

Neuroplasticity refers to any change in neuron structure or function in response to input from the environment. For example, individual neurons might enlarge their dendritic or axonal arbors, or populations of neurons may become denser. Changes in behavior are not on their own measures of neuroplasticity.

Also relevant to rehabilitation has been new information about the brain itself. With imaging and other technologies, we observed that humans have structural redundancies, several areas of the brain that can do the same thing, that allow for both neural recovery (restoring the function of injured brain tissue) and compensation (residual neural tissue takes over a lost function).

As imaging and other technologies provided evidence of brain remodeling in response to changes in input, the rehabilitation community began reconsidering its focus on adaptation. If exercise and training could change neural structure and function, which in turn would abrogate the need for accommodation, wouldn't such an approach be superior?

Rehabilitation Research

With that in mind, researchers began trying to better understand which therapies worked best and why. They also started better describing therapies to allow their replication in other settings. In 2006, the first article on neurorehabilitation for stroke patients that met standards used elsewhere in medical research was published. Here is a look at that and some other scientifically sound trials that have enlightened the medical community about new approaches to neurorehabilitation.

■ Forced-Use Therapy

The EXCITE trial conducted by Wolf and colleagues was the first clinical trial of its kind in rehabilitation therapy.¹ It looked at the effect of two weeks of constraint-induced movement therapy (CIMT), a forced-used paradigm, on upper-extremity (UE) function. The researchers randomized stroke survivors who had some UE movement three months to nine months after stroke into two groups. One group wore a restraining mitt on the less-affected hand while they practiced doing various tasks with their weak hand; the other group received usual care. Patients were involved in training up to six hours a day. Efficacy was assessed using the Wolf Motor Function Test, which measures movement speed and facility, and the Motor Activity Log, which assesses ability to perform 30 common activities. The CIMT group experienced statistically significant improvement in paretic arm motor ability and use as compared with the group that received usual care. Pointing to their desire to improve their paretic limb, adherence to the program was high, according to the participants' self-reports.

In process now is the Accelerated Skill Acquisition Program (ASAP) trial, which will compare the results of 30 hours of traditional rehabilitation with a combination of forced-use/constraint-

induced therapy and skill-based/impairment-mitigating motor learning training for people with arm weakness after stroke.² Additionally, the study aims to describe the frequency, duration, and content of traditional outpatient treatment, since "usual care" in neurorehabilitation has not been well-defined or described in the past.

Other studies of neurorehabilitation following stroke are using more clear definitions for the frequency, duration, and type of therapeutic exercise used. Questions, of course, remain: One is whether delay of forced-use therapies is harmful or helpful.

■ Medications

Several pharmacological approaches have been tried for improving outcomes after stroke. Some studies have looked at use of medications alone, and others at medicines in combination with rehabilitation. Most studied is treatment with amphetamines, typically dextroamphetamine, which stimulate the central and peripheral nervous systems. Walker-Batson used dextroamphetamine 10 mg in a promising double-blind placebo-controlled study of stroke survivors with aphasia.³ Using the Porch Index of Communicative Ability as the primary outcome measure, they concluded that administration of dextroamphetamine facilitated recovery from aphasia when paired with 10 one-hour sessions of speech/language therapy in a group of 21 patients during the sub-acute period after stroke. Small sample sizes have been a problem with research into the use of stimulants for neurorehabilitation; thus, a recent Cochrane review concluded there is not enough evidence to support the routine use of amphetamines to promote recovery after stroke.⁴

Determining the effect of selective serotonin reuptake inhibitors (SSRIs) in stroke patients has proved more complicated. Some studies have shown functional outcomes are worse for people who are taking SSRIs at the time of stroke;⁵ others point to potential benefits of SSRIs on functional outcomes because of increased levels of brain-derived neurotropic factors.⁶ Most studies support the efficacy of SSRIs in treating depression after stroke. Patients may be more motivated to participate in rehabilitation when their depression is under control and, as a result, see improvements in their mobility and ability to care for themselves.

In the recent FLAME study, a randomized placebo-controlled trial, 113 ischemic stroke survivors who had moderate to severe hemiplegia were treated with either fluoxetine 20 mg daily or placebo, beginning five to 10 days after stroke.⁷ Both groups received physical therapy. The main outcome measure was the Fugl-Mayer motor scale, which measures impairment on a scale of 0 to 100 points; secondary measures were the National Institutes of Health Stroke Scale, a measure of activity limitation, and a measure of mood. Although scores on the Fugl-Mayer scale showed a statistically significant difference between the groups, scores on the other outcome measures showed no difference. A Cochrane review is in process to address SSRI use in stroke patients.⁸



Figure
Rehabilitation Therapies that Aim to Restore Function



Photos courtesy Sister Kenny Rehabilitation Institute

A physical therapist helps a patient use her affected arm to maximize restoration of function.

■ **Physical Agents**

Noninvasive brain stimulation (NIBS) methods such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) show promise for inducing neuroplasticity in patients with brain lesions.⁹ The general idea is that physical forces cause changes in cortical excitability leading to recovery or reorganization of the brain network. In preclinical work, both TMS and tDCS may facilitate motor, perceptual, and cognitive performance in patients with brain lesions. As with other aspects of neurorehabilitation, there is a lack of specificity with regard to the duration, location, and frequency of stimulation. There also is uncertainty about how NIBS should be combined with other therapy protocols, medications, and rehabilitation interventions. Research continues in this promising area.

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Conclusion

We are on the cusp of more accurately identifying the type, duration, and frequency of physical, occupational, and speech therapies that lead to the best outcomes for patients who have experienced brain or neurologic injuries. Researchers are also exploring potential interactions of those therapies with medications as well as the efficacy of magnetic or electrical stimulation and other treatments. For now, it would appear that new approaches to neurorehabilitation such as trying to minimize impairment through forced use of the affected body part (Figure) should trump old approaches that focus on preventing contracture and compensating for disability. Although regaining neural structure and function is now a goal of neurorehabilitation, a truly effective rehabilitation program should ensure that the patient not only improves his or her physical body but also is able to fully engage in daily activities and participate in social functions.

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Karl Sandin is physician-in-chief of Sister Kenny Rehabilitation Institute.

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A robot-assisted treadmill supports the patient in an upright position while moving the legs through a normal walking pattern.

The Minnesota Women Healthy Aging Project

By Apostolos P. Georgopoulos, M.D., Ph.D.

■ The Minnesota Women Healthy Aging Project is an effort to understand how the brain changes with age and why some brains are more resilient than others. Using a unique methodology, researchers are evaluating the brain status of a number of women by taking multiple, multimodal measurements and relating those measures to cognitive abilities, language skills, and genetic information. The goal is to create a comprehensive databank that will provide information by which to characterize brain status, assess changes over time, and associate them with genomic makeup, cognitive function, and language ability. The project was initiated in 2010 and is being conducted through the University of Minnesota and the Minneapolis Veterans Affairs Health Care System. This article describes the project, which is the first of its kind, and its progress thus far.

The brain is the most complex organ in the body. It consists of more than 100 billion cells. (Compare that with the human population, which is only 7 billion.) Unlike the cells of any other organ, brain cells interact extensively with each other every millisecond. The brain's nature as a dynamic, massively interconnected network is the basis for its ability to process information. It is also the basis for learning, memory, and plasticity. These latter properties are formalized as changes in brain function, and they take place throughout our lives. These changes are cumulative, as illustrated by how our education, memories, habits, and injuries build on each other, whether we like it or not. Our understanding of the brain's cumulative nature forms the basis for all sorts of interventions, giving us hope that they will have a lasting effect.

The changes that take place in our brains are highly individualized and are influenced by our genetic/genomic makeup, environmental influences, and disease processes. We know that the manifestation and impact of brain disease vary from one individual to another. For example, acute brain infection or the formation of Alzheimer's plaques can affect different people quite differently. However, we do not understand the underlying mechanisms behind these changes.

One thing we do know, however, is that the effect of environmental insults can vary according to the age of the individual. Aged brains are more vulnerable to these insults, as are the developing brains of infants and adolescents. In fact, the con-

cept of brain vulnerability now has a prominent place in our thinking about susceptibility to disease and disease prevention.

The \$64,000 question is how to assess brain vulnerability for specific insults and diseases at given points in the lifespan. Such knowledge would allow for potential intervention—either preventing the occurrence of insults, protecting brain function (eg, by pharmacotherapy), or changing lifestyle and the social milieu.

Understanding how the brain changes with age and why some brains are much more resilient than others is one of the primary goals of the Minnesota Women Healthy Aging Project (www.brain.umn.edu/mnwomen.html). The project is the first attempt to comprehensively evaluate the status of the brains of a number of individuals over time using multiple, multimodal measurements and relate those measures to cognitive, language, and genetic information. The goal is to create a comprehensive databank containing information that can be used to characterize brain status over time.

About the Project

The project was initiated in 2010 with the support of a group of women from Minnesota and various foundations as well as the University of Minnesota and the Minneapolis Veterans Affairs Health Care System. It has a cross-sectional and a longitudinal component. One hundred new women ages 30 to 100-plus years of age will be studied each year; those women

will be re-evaluated annually. More than 100 women have been studied to date.

Participants are recruited from the Women Veterans Comprehensive Health Center of the Minneapolis VAHCS. Upon arrival at the Brain Sciences Center at the Minneapolis VAHCS, all are asked to provide informed consent. The women then go through a number of tests including a cognitive assessment, a speech evaluation, resting-state magnetoencephalography (MEG), and MR imaging. In addition, blood is drawn for DNA analysis. The cognition and language assessments and the MEG test are repeated every year; the MR tests are taken from subjects younger than 70 years old and are repeated every five years; blood is drawn only once. The protocol has been approved by the appropriate institutional review boards.

Cognitive function is assessed using the Montreal Cognitive Assessment (MoCA). It consists of 30 questions that test visuo-spatial/executive functioning, ability to name objects, memory, attention, general language skills (fluency), abstraction, delayed recall, and orientation.

Speech and language are assessed using a new technique.¹ Spontaneous (“tell us a story”) and evoked (“describe this picture”) speech are recorded at 44.1 kHz for one minute using state-of-the-art CD-quality audio recording equipment. Sound spectrograms are then analyzed for speech structure and language use, and various quantitative measures are derived for further analysis and association with other data.

Magnetoencephalography data are acquired at 1,017 kHz for one minute while the subject rests using a high-spatial-density system with 248 axial gradiometer sensors. From these data, 30,628 synchronous neural interactions (SNIs) between all possible pairs of sensors are computed. The SNI data reflect communication among neuronal populations; these interactions are the essence of brain function. Information about SNIs forms the basis for evaluating functional brain health and has been shown to identify certain brain diseases (eg, functional abnormalities in persons with post-traumatic stress disorder).²⁻⁴

Structural magnetic resonance imaging (sMRI) is done to assess gray-matter volume. The data are acquired using a Philips 3T Achieva XL magnet with a SENSE 8 channel head coil. Approximately 500,000 voxels per brain are analyzed. In the first analysis, the volume of about 100 separate brain regions is calculated using FreeSurfer software (www.surfer.nmr.mgh.harvard.edu). This provides a coarse-grain, volumetric analysis of areas of the brain. In the second analysis, called voxel-based morphometry, the density of each voxel is assessed for a fine-grain analysis of each area.⁵ Typically, gray-matter volume decreases with age but at rates that are different for different people, for different areas of the brain, and for men and women. In that sense, one can talk about “gray-matter age” versus chronological age. A person may be 68 years old but have the gray-matter volume of a 50-year-old. Defining brain age based on measurements (as contrasted with chronological age) is a pervasive theme in this project.

Diffusion tensor imaging (DTI) is used to assess the integ-

rity of the white matter and to visualize major tracts for rough anatomical connectivity. Each voxel is assigned a fractional anisotropy value. Typically, low fractional anisotropy values indicate damage to the white matter.

Functional MRI (fMRI) is used to assess blood-oxygenation level dependent activation. This measure indirectly reflects local brain activity. Data are acquired every two seconds for five minutes while the subject is at rest. From these data, a rough measure of functional resting-state connectivity is computed.⁶ This measure informs us about the nature of interactions between various areas of the brain. The MEG measurements are the gold standard, as they directly reflect neural activity. The resting fMRI measurements are second-best, as they only indirectly relate to neural activity; but they are easily accessible because MRI machines are readily available.

Magnetic resonance spectroscopy (MRS) is used to roughly assess neuron health. Typically, we consider the ratios of N-acetyl aspartate, glutamine+glutamate, and choline over creatine.

Participants also are asked to provide demographic and lifestyle information. It is well-known that educational level, exercise, smoking, medical conditions such as hypertension, diabetes, and high cholesterol can affect cognitive function and increase the risk for development of dementia.⁷ Therefore, taking these factors into consideration is an important aspect of the project.

Finally, DNA is assessed for specific brain-related polymorphisms that are related to cognitive function^{8,9} such as the alleles for apolipoprotein-E, brain-derived neurotrophic factor, and catechol-O-methyl transferase.

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Data Management

All data will be entered in a relational database. Although the database will contain approximately 30 GB of data per subject, it will be set up in a way that will facilitate data extraction and calculation of targeted relations among variables of interest. Large-scale data analysis will be supported by the high-performance computing cluster at the Brain Sciences Center. The complexity of this project requires the use of informatics approaches.

One focus is the derivation of scores that will express the status of an individual subject with respect to several domains. Scores for three domains will be derived initially, and more will be added as needed. The first is relative score (R-score). Essentially, it reflects how healthy a brain is compared with others in the same sex and age group. The second is normative score (N-score). The N-score reflects how healthy a brain is as compared with a younger one. The third is the global Euclidean distance score (G-score), which is an indication of how similar two brains are over all the measurements.

A major challenge will be finding effective and efficient ways to combine measures of brain structure and function with information about cognition, language, and genetics to characterize brain status over time. Although the Minnesota Women Healthy Aging Project’s focus is women, it is anticipated that it will one day be extended to men and that the data could also provide insight

into whether there are differences between various ethnic and racial groups.

Conclusion

Brain science is on the cusp of a new era. For the first time ever, the structure and function of the brain can be assessed comprehensively; brain health can be promoted; and susceptibility to brain disease at various stages of life can be assessed, modified, and even forecasted. All of this has become possible because of advances in brain imaging, biomedical engineering, molecular neurobiology, and genomics. In addition, we are gaining greater understanding of how environmental insults can affect the brain and which brains are more vulnerable to those influences, as well as the importance of early intervention for disorders of the brain, the feasibility of prevention of such disorders, and the possibility of altering brain function to ameliorate disease symptoms and promote brain health. The challenge now is to combine the information we have in ways that will help us make sense of it. When we do, we will have an unprecedented understanding of how the brain changes during the lifespan. **MM**

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Hearing Loss and Dementia

New Insights

By Kristi Albers, Au.D.

■ The aging brain is a hot topic among researchers and health professionals worldwide. Although our knowledge of the way the brain changes with age is in its infancy, research into hearing loss and dementia has gained momentum. Recent studies suggest that persons with hearing loss are more likely to develop Alzheimer's disease or other forms of dementia over time. This article discusses recent findings.

According to the Centers for Disease Control and Prevention (CDC), 37 million adults in the United States had difficulty hearing in 2006.¹ This was a substantial increase from 2000, when 31.5 million U.S. adults reported having some form of hearing loss.² National Institute on Deafness and Other Communication Disorders (NIDCD) data show hearing loss increases with age, with 30% percent of people between the ages of 65 and 74 years and 47% of those 75 years or older reporting some degree of hearing loss.³ Data from the 2010 National Health Survey released in December 2011, show 37% of U.S. adults age 65 and older report hearing loss.⁴

The exact percentage of people living with hearing loss is somewhat difficult to measure for a number of reasons. Prevalence can differ depending on how hearing loss is defined (ie, if any degree of hearing loss is included), how it is measured (self-report versus objective testing), the age groups included in the data, and other variables. Recent research by a team from Johns Hopkins University reported in the *Journal of Gerontology* demonstrated that age-related hearing loss, or presbycusis, may be more common than we once thought. The researchers analyzed data from the 2005-2006 cycle of the National Health and Nutrition Examination Study, which is the first to ever include hearing assessments on adults 70 years and older. They found that hearing loss is prevalent in nearly two-thirds of adults aged 70 years and older.⁵

Another prevalent and growing health concern among older adults is dementia. Data from the first nationally represented population-based study of dementia in the United States, published in 2007, suggest that about 3.4 million Americans age 71 and older (ie, one in seven people in that age group) have some form of dementia and 2.4 million of them have Alzheimer's disease.⁶ As the population ages, those numbers are expected to increase.

Clinicians and researchers have long been aware that there is a relationship between hearing loss and cognitive decline in older adults. This article discusses that relationship and new findings that suggests that hearing loss is a risk factor for dementia.

Presbycusis and Untreated Hearing Loss

Presbycusis most often starts to affect people in their 60s; it may worsen with age. Age-related hearing loss begins in the higher frequencies and spreads to the mid and low frequencies over time. Typically, the first signs of presbycusis are evident at the highest two frequencies tested, 6000 and 8000 Hz. Examples of sounds affected by hearing loss at such frequencies are birds chirping and the rustling of dry leaves.

When hearing loss begins to affect frequencies between 1000 and 6000 Hz, people begin to notice a change in their ability to hear. These frequencies are important for understanding speech. Persons with presbycusis often will report that they can hear but can't always understand because of the reduced audibility of consonant sounds. For example, they may not be able to discriminate between words such as "cat" and "sat."

Hearing professionals have long been aware of the negative effects of untreated hearing loss. Clinical observation has shown that individuals living with untreated hearing loss often experience social isolation. They become afraid to interact with others, as they fear making mistakes in conversation.

In 1999, the National Council on Aging published a landmark study, involving 2,300 individuals with hearing loss who were older than 50 years of age, demonstrating the effects of untreated hearing loss. The study looked at people with untreated hearing loss and at people who had treated their hearing loss with hearing aids. It found that the individuals who used hearing aids reported improvements in many areas including their relationships with friends and family members,

self-confidence, social life, and self-esteem.⁷

In addition to affecting one's quality of life, untreated hearing loss also may affect a person's safety. They may fail to hear alarms or important public messages, and they may make mistakes when following directions regarding health-related issues such as wound care, medication use, or adhering post-surgical restrictions. Although accidents or deaths related to hearing loss are not tracked by public agencies, the risks to those with hearing loss are real.

Hearing Loss and Cognitive Function

Recent research suggests that untreated hearing loss may affect a person's cognitive functioning as well as their quality of life. A study by investigators from Johns Hopkins University and the National Institute on Aging using data from the Baltimore Longitudinal Study on Aging suggests that hearing loss itself is associated with an increased risk of developing dementia.⁸ The team studied the association between hearing loss and dementia in 639 individuals. The participants, none of whom exhibited signs of dementia at the time they enrolled in the study, underwent audiometric testing between 1990 and 1994. The investigators defined hearing loss by a pure-tone average of hearing thresholds at 0.5, 1, 2, and 4 kHz in the ear with better hearing. Normal hearing was defined as pure-tone thresholds averaging less than 25 dB. Of the 639 individuals tested, 125 had mild hearing loss (thresholds between 25 and 40 dB), 53 had moderate hearing loss (41 to 70 dB thresholds), and six had severe hearing loss (thresholds >70 dB). These same individuals were followed for the development of dementia or Alzheimer's disease through May 31, 2008. At follow-up, 11.9 years after study participants were first tested, 58 cases of dementia were diagnosed, 37 of which were Alzheimer's disease. Further analysis of the data showed that as the extent of hearing loss increased so did the risk of developing dementia.

The researchers estimated that more than one-third of the risk for incident all-cause dementia was associated with hearing loss among individuals older than 60 years. They noted, "whether hearing loss is a marker for early-stage dementia or is actually a modifiable risk factor for dementia deserves further study."⁸ These findings are consistent with those from previous studies demonstrating an association between hearing loss and dementia. In 1989, a study involving 100 persons with Alzheimer's-type dementia found hearing loss to be "significantly and independently associated with the severity of cognitive dysfunction." The authors of that report indicated that the results lent support to the hypothesis that hearing loss may contribute to cognitive dysfunction in older adults.⁹

Another study conducted in 1996 involved patients receiving treatment at a memory clinic to find out if certain hearing loss screening tools were adequate for determining hearing loss in this population. The population consisted of 52 patients, 30 of whom met the criteria for probable Alzheimer's disease and 22 of whom met the criteria for other forms of cognitive impairment. Audiometric testing and questionnaires showed 49 of the

52 had significant hearing loss.¹⁰ The investigating team found a discrepancy between self-reports and reports by family members regarding hearing loss for the 30 patients with Alzheimer's disease. For patients with other forms of cognitive impairment, the discrepancy was not as significant. The researchers concluded that because of the high prevalence of hearing loss they observed and the lack of validity of self-reporting of hearing loss for those with Alzheimer's disease, a hearing assessment should be part of any assessment of cognitive function.¹⁰

In a follow-up study of National Health and Nutritional Examination Survey results, the Johns Hopkins group analyzed data from the 1999-2002 cycles, during which participants ages 60 to 69 years underwent audiometric and cognitive testing. In this study, hearing loss was defined by a pure tone average of hearing thresholds at 0.5, 1, 2, and 4 kHz in the ear with better hearing.¹¹ The Digit Symbol Substitution Test (DSST), a nonverbal test that assesses executive function and psychomotor processing, was used to evaluate cognitive functioning. Information on hearing aid use, medical history, and demographics was obtained through interviews. The results indicated greater hearing loss was significantly associated with lower scores on the DSST after adjustments were made for both demographic factors and medical history. In fact, the study's authors noted that the reduction in cognitive performance associated with mild hearing loss (25 dB thresholds) was equivalent to that associated with someone seven years older than the person tested. In regard to hearing aid use, a positive association was observed in terms of cognitive functioning, meaning persons who reported using hearing aids scored better on the DSST on average.¹¹

The Importance of Screening for Hearing Loss

The prevalence of hearing loss in older people is significant. The new research discussed in this article suggests that hearing loss may put older adults at risk for developing Alzheimer's disease or other forms of dementia. Additional research is still needed to further examine the relationship between hearing loss and dementia; however, at this time, there is enough evidence to support routinely screening and treating older adults for hearing loss.

A comprehensive hearing evaluation is the gold standard for objectively identifying hearing loss. Given the need for properly calibrated test equipment and a sound-treated space, such testing may not be feasible during routine wellness visits. Standardized screening tools with documented validity are an effective alternative. These are easy to use and quickly determine the need for further evaluation.

The Hearing Health Quick Test is a 15-item questionnaire developed by the American Academy of Audiology.¹² (It is available at www.audiology.org.) The test can be administered in the physician's office by a medical assistant or nurse, or completed independently by the patient in the waiting room. Patients indicate whether or not they encounter difficulty hearing in a variety of situations. Scoring is simple, with a referral for a hearing evaluation warranted if the patient responds "yes" to two or more of

the questions. For patients with possible cognitive impairment, it is recommended that the questionnaire be completed with input from a family member or other caregiver, as persons with Alzheimer's disease have been shown to have poor self-reporting of hearing loss.¹⁰

Patients' also may be screened in the physician's office with a small, hand-held device that emits pure tones. The nurse or medical assistant places the instrument in the patient's ear and instructs him or her to respond when a beep is heard. Only a few frequencies are tested—often 1, 2, and 4 kHz—and failure at any frequency warrants a referral for a complete hearing evaluation. For best results, the screening should be performed after an otoscopic exam to rule out the presence of cerumen.

The use of any screening method is better than none at all; however, the combination of screening with pure tones and a questionnaire has been demonstrated to yield the best results.¹³

Identifying and treating hearing loss sooner rather than later may have far-reaching benefits in terms of reducing the risk for developing Alzheimer's disease or other forms of dementia and maintaining a good quality of life for older adults. **MM**

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Nonfatal Work-Related Traumatic Brain Injury in Minnesota, 1999-2008

By Chia Wei, M.S., Jon Roesler, M.S., and Mark Kinde, M.P.H

■ The Centers for Disease Control and Prevention has identified traumatic brain injury (TBI) as a public health problem in the United States; it is notable that some variables of work-related TBI are different from those of non-work-related TBI. The Minnesota Department of Health has been conducting epidemiologic surveillance of cases of hospitalized TBI since 1993. Although most of the surveillance efforts have focused on all TBIs, the department does collect data on work-related TBIs and their associated outcomes. This article summarizes trends for nonfatal, work-related TBI cases over person, place, and time in Minnesota from 1999 to 2008. The greatest proportion of cases involved persons 35 to 44 years of age, and the most common causes were falls, motor vehicle traffic crashes, and being struck by objects. Most injuries occurred in the home, a location not routinely subjected to oversight for occupational safety concerns. The work-related TBI rate has been decreasing since 2004. This article also discusses the role of the physician in identifying and treating TBI.

Traumatic brain injury (TBI) is a significant public health concern. Broadly defined as brain injury from externally inflicted trauma, TBI often results in long-term or lifelong physical, cognitive, behavioral, and emotional changes.¹ Each year, an estimated 2 million people in the United States sustain a TBI.² Many of these individuals experience a mild injury and do not seek immediate medical treatment. However, others experience serious, acute consequences: Each year 52,000 people in this country die as a result of TBI, 275,000 are hospitalized, and 1.4 million are treated

and released from an emergency department. The leading causes of TBI are falls (35.2%), motor vehicle crashes (17.3%), being struck by an object (16.5%), and assaults (10.0%).³

About one-third of adults hospitalized with a TBI still need help with daily activities one year after injury.⁴ Even persons with mild TBI can experience problems with short-term memory, concentration, learning new tasks, organization, judgment, and executive skills that can limit their ability to function independently.⁵ Patients with TBIs are often referred to as “the walking wounded.” Even though they appear physically “nor-

mal,” they may experience various levels of disability. Ideally, treatment of these patients involves a multidisciplinary approach, with the physician working in collaboration with the patient, family, psychologist, therapist, social worker, and staff from community-based organizations such as the local chapter of the brain injury association.

In Minnesota, more than 10,000 cases of hospital-treated TBI are reported annually. According to Minnesota Department of Health data, each year TBI results in more than 800 deaths, 4,300 nonfatal hospitalizations, and 6,500 nonfatal emergency department (ED) visits. Males are twice as likely as females to have a TBI, and the highest rates occur among individuals younger than one year of age, between 15 and 19 years of age, and older than 65 years of age.⁶

Work-related TBIs comprise only 4% to 5% of all reported TBIs, but these injuries can result in large claims and are the most serious of occupational injuries reported.^{7,8} Annegers et al. estimated that 5% of all TBI cases in Olmsted County, Minnesota, that occurred between 1935 and 1974 were work-related.⁹ A recent Canadian study found that the age and

gender of the patient, mechanisms of injury, Injury Severity Score, length of hospital stay, and in-hospital death rate associated with work-related TBI were significantly different than those associated with non-work-related TBI.¹⁰

In order to get a more comprehensive understanding of work-related TBI trends in Minnesota, staff from the Minnesota Department of Health reviewed all reported nonfatal, work-related TBI cases. This article shares their findings, focusing on the distribution of occupational TBI by age, gender, and mechanism of injury, with discussion of the role of the physician in caring for patients with work-related TBIs.

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Methods

When it established the mandate for a statewide registry of hospitalized TBI cases in 1991, the Minnesota Legislature defined TBI as sudden insult or damage to the brain or its coverings caused by an external physical force that may produce a diminished or altered state of consciousness and that results in 1) impairment of cognitive or mental abilities, 2) impaired physical functioning, or 3) a disturbance of behavioral or emotional functioning. These disabilities may be temporary or permanent and may result in partial or total loss of function.¹¹ The Department of Health includes in the registry all reports of hospitalized cases and deaths in hospitals that are coded with one or more of the ICD-9-CM diagnostic codes established in Minnesota Rules, either as a principal or secondary diagnosis.¹² Those include all of the TBI codes used by the Centers for Disease Control and Prevention (CDC),¹³ as well as other codes associated with TBI.

Additional criteria include whether the injured person was a Minnesota resident, whether the injury occurred in the state, and whether the injured person was transferred from a Minnesota emergency department to an out-of-state hospital. Out-of-state hospitals are asked to report cases in which the patient is a Minnesota resident or was injured in Minnesota. Excluded from the registry are patients who are seen in and discharged from an emer-

Figure 1

Occupational TBI Rate by Year Minnesota, 1999-2008

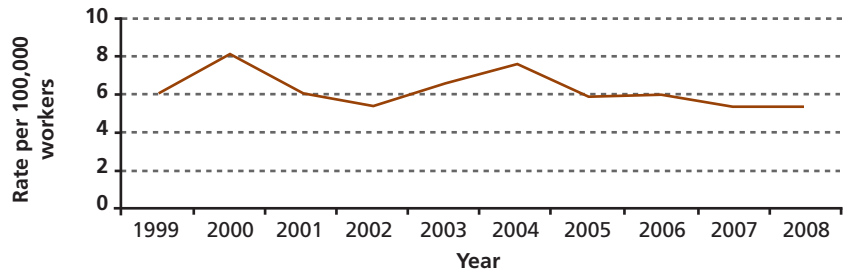


Table 1

Minnesota Occupational TBI by Age Group and Gender, 1999-2008

Age Range	18-24	25-34	35-44	45-54	55-64	≥65	Total
Male	195	229	304	240	182	156	1,306
Female	34	50	67	69	59	137	416
Total	229 (13%)	279 (16%)	371 (22%)	309 (18%)	241 (14%)	293 (17%)	1,722 (100%)

gency department; admitted as outpatients for observation and then discharged; or admitted directly to a long-term care or rehabilitation facility. Data were reported to the Minnesota TBI Registry using the Minnesota Report of Injury.¹⁴

This analysis included all admissions to the Minnesota TBI Registry from 1999 to 2008 of persons who were at least 18 years old who were injured while working for income. The TBI rates were calculated from 1999 to 2008; denominators were the number of people employed in Minnesota, estimated from Minnesota Department of Employment and Economic Development statistics.¹⁵

“Working for income” was defined as working for wages or a salary, bonuses, or other types of income (eg, contract, barter, etc.).¹⁶ We used the primary ICD-9-CM external cause of injury code¹⁷ to analyze the causes of TBI. Patients who had multiple hospitalizations associated with an injury were only counted once in this study. Outcomes were assessed using the Glasgow Outcome Scale (GOS) at the time of discharge from the hospital.¹⁸ The GOS categories include “Good Recovery,” “Moderate Disability,” “Severe Disability,”

and “Vegetative State.” Those expected to make a good recovery include persons with mild disability.

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Results

A total of 1,722 eligible subjects were identified from the Minnesota TBI Registry and included in this analysis. The number of work-related TBI cases per year ranged from a high of 219 in 2000 to a low of 147 in 2002, representing 4.2% of all TBI cases during the 10-year period.

In order to better understand the trends associated with work-related TBI, we calculated the TBI rate per 100,000 persons employed in Minnesota. Figure 1 shows the TBI rate from 1999 to 2008, which peaked in 2000 and again in 2004. The injury rate decreased after 2004 and has been fairly steady, averaging 6.2 TBIs per 100,000 workers over the 10 years. The total days of inpatient hospitalization per year for all occupational TBI patients ranged from a high of 1,301 days in 2004 to a low of 710 days in 2002.

An analysis of TBI by month suggests that the number of reported cases peaks during the summer and decreases from December to April. Among all oc-

Figure 2

Places Where Occupational TBIs Occur

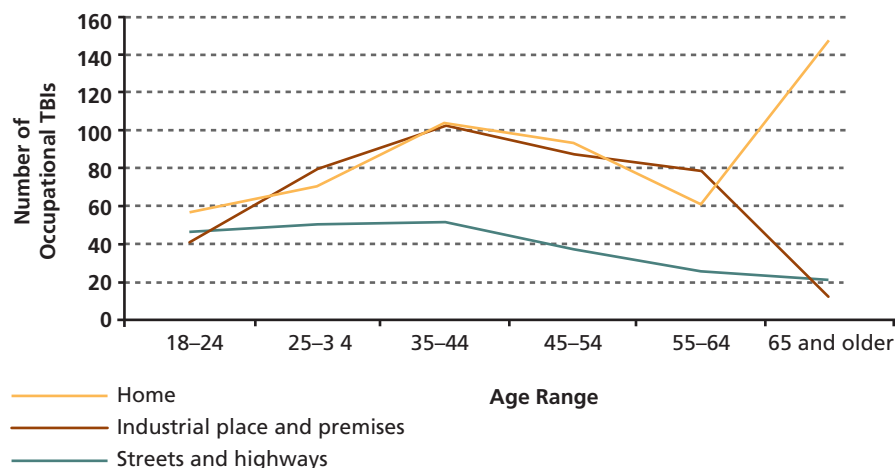


Table 2

Minnesota Occupational TBI Glasgow Outcome Scores and Discharge Outcome, 1999-2008

	Discharged	Good Recovery**	Moderate Disability	Severe Disability	Persisting Coma	Total
Home*		981	18	1	0	1,000
Inpatient Facility†		107	82	24	2	215
Other‡		51	7	4	1	63
Total		1,139	107	29	3	1,278

* Home includes: Home/foster home

† Inpatient facility includes: inpatient rehab facility, transitional care unit, inpatient facility with or without skilled nursing

‡ Other includes: Acute care hospital, home/foster home with skilled nursing assistance, jail

** "Good Recovery" includes mild disability

cupational TBI cases reported, the highest percentage of people injured while working for income were between the ages of 35 and 44 years (Table 1). The number of injuries was higher for males than females (1,306 and 416, respectively). (Denominators by gender of workers were not available to calculate rates.) Among males, the greatest proportion of occupational TBIs (23%) occurred among those 35 to 44 years of age. Among females, the greatest proportion (33%) occurred among those age 65 and older.

■ Causes

Based on the ICD-9-CM codes, the primary cause of work-related TBI was a fall (E880.0-E886.9, E888), accounting for the cause in 46% of all cases (N=785).

Of those, 24% (n=188) involved people age 65 and older. Twenty-nine percent of cases (N=496) were caused by motor vehicle accidents (E810-819.9) and accidents involving other forms of transportation (E800-807.9, E820-E829.9) including motorcycles, bicycles, snowmobiles, and ATV/off-road vehicles. The number of TBIs associated with traffic-related accidents among young adults (those 18 to 24 years of age) was twice that of TBIs from falls in that age group (103 versus 52). The third leading cause of work-related TBI among people of all ages is being struck by a falling object (E916-E917.9). Our analysis found 135 cases (14%) in which a person was struck unintentionally by an object (eg, a tree, rock, or stone). Other causes of work-related TBI included as-

sault (5%) and injury involving machinery (3%).

The top three places where occupational TBI occurs were homes not including farms, a place of industry or its premises, and streets and highways, respectively (Figure 2). Among those injuries occurring at home (N=532), a disproportionate number (28%) occurred among people aged 65 years and older. Twenty-five percent of those injured at industrial places were between 25 and 54 years of age.

■ Outcomes

Most patients (77%) who were hospitalized with a work-related TBI were discharged home (Table 2); 23% were discharged to an inpatient rehabilitation or skilled nursing facility. Of patients with a GOS score that indicated "Good Recovery," 86% were discharged home for self-care. Of those with a GOS that indicated "Moderate Disability," 77% were discharged to inpatient rehabilitation facilities.

Discussion

The public health approach to injury prevention is to collect surveillance data so that causes can be identified and interventions developed. This surveillance investigation gives us insight into occupational TBI trends between 1999 and 2008, the last 10 years for which data are available. This study's strength is that it is population-based, using data from the statewide Minnesota TBI Registry.

The occupational TBI rate of 4.2% that we found was less than the 5% reported by Annegers et al. for Olmsted County decades earlier, perhaps reflecting a true decrease in the risk of occupational TBI. Furthermore, we observed that the rate decreased slightly between 1999 and 2008 (Figure 1). To some degree, this mirrors the decline seen nationally in overall work-related injury fatality rates, occupational TBI fatality rates, and in the overall rate of TBIs (both occupational and non-occupational).¹⁹

In this investigation, we abstracted the external cause code from hospital data to determine the cause of TBI in Minne-

sota. The leading causes of occupational TBI in Minnesota are similar to those reported by the CDC, namely falls, motor vehicle crashes, being struck by an object, and assaults. Falling is an especially serious problem among persons 65 years of age and older. One study of fall-related injuries among the elderly, published in the *American Journal of Epidemiology* in 1990, found that approximately one-third of persons 65 years of age or older fall each year. Additionally, the authors noted that falling is a leading cause of death from injury for the elderly in the United States.²⁰ Our findings are consistent with theirs, in that the leading cause of occupational TBI is falling, especially among persons 65 years of age and older. Further work is needed to describe the range of activities associated with these falls. Although fall prevention is an essential element of occupational safety and health programs, specifically targeting those programs to elders who work at home might make sense given our results. Wellness and fitness classes aimed at increasing flexibility, job modifications to address chronic health problems such as visual or auditory deficits, and occupational therapy to rehabilitate previous injuries and reduce the chances of reinjury also may reduce the risk of falls and fall-related TBIs in older workers.²¹

Our study had some notable limitations. For example, the Minnesota TBI Registry currently lacks data on a person's occupation and the industry in which he or she works; these variables should be considered for inclusion in the registry. The activity of the patient at the time of injury is determined by the medical records coder; therefore, there is potential for a lack of precision in the category "working for income," as it is ascertained from the narrative in the medical record instead of direct patient interview. As a result, hospital medical record staff and trauma registrars who report to the TBI Registry may under- or over-report the occupational TBI rate. This potential for bias remained even after we reviewed all of the injury descriptions and reclassifications. Thus, clear definitions and training should be provided to hospital medical re-

ords staff for coding "work for income" and "unpaid work."

Although this analysis only included hospital data reported through the Minnesota TBI Registry, future efforts might link data from the Minnesota TBI Registry with Minnesota Department of Labor and Industry data in order to conduct a more comprehensive study of occupational TBI in Minnesota.

The Physician's Role in Treating Patients with Work-Related TBI

Physicians need to be aware of the problem of work-related TBI and how it may manifest through patients complaining of frequent headaches, fatigue, ringing in the ears, blurred or double vision, depression, and other symptoms that have causes that are difficult to pinpoint. Given that these symptoms are not specific to TBI and are often associated with other chronic illnesses, it is important for physicians to be especially vigilant with older patients who are still working.

Many TBI survivors, particularly those who sustain mild injuries, do not receive formal medical follow-up. However, even those who have had rehabilitation or have reported contact with their primary care physician are often unable to recount any discussions about the return to work process. Given the invisibility of the consequences of their injury and the persistent symptoms affecting their ability to work, the lack of advice and guidance on the best time to resume working means that many may return before they are ready.

It is important for physicians to anticipate the rehabilitation needs of patients who have sustained a TBI.²² Successful rehabilitation of a TBI survivor requires the recognition of possible long-term sequelae, with appropriate referral for treatment of medical, cognitive, and behavioral problems in order to promote recovery and enhance reintegration into the community. Describing those at greatest risk for work-related TBI is the first step toward helping physicians identify individuals who may need further evaluation.

Conclusion

Work-related TBI is a public health problem that affects workers of all ages. It is costly, as even mild cases can cause problems with short-term memory, concentration, learning new tasks, organization, judgment, and executive skills—all of which can affect one's productivity and ability to live independently.

Although the injuries themselves can be acute, the functional deficits from TBI may place a tremendous long-term burden on individuals, families, and the health care system. TBIs have been a leading cause of long-term disability in the United States, even before the current military conflicts, and are a leading contributor to increasing health care costs. Successful rehabilitation of a patient with a work-related TBI requires physicians to be able to recognize, refer, and treat the associated medical, cognitive, and behavioral problems in a timely way.²³

Identifying those at greatest risk for occupational TBIs is the first step toward preventing them and for helping physicians recognize individuals who may need further evaluation and treatment. **MM**

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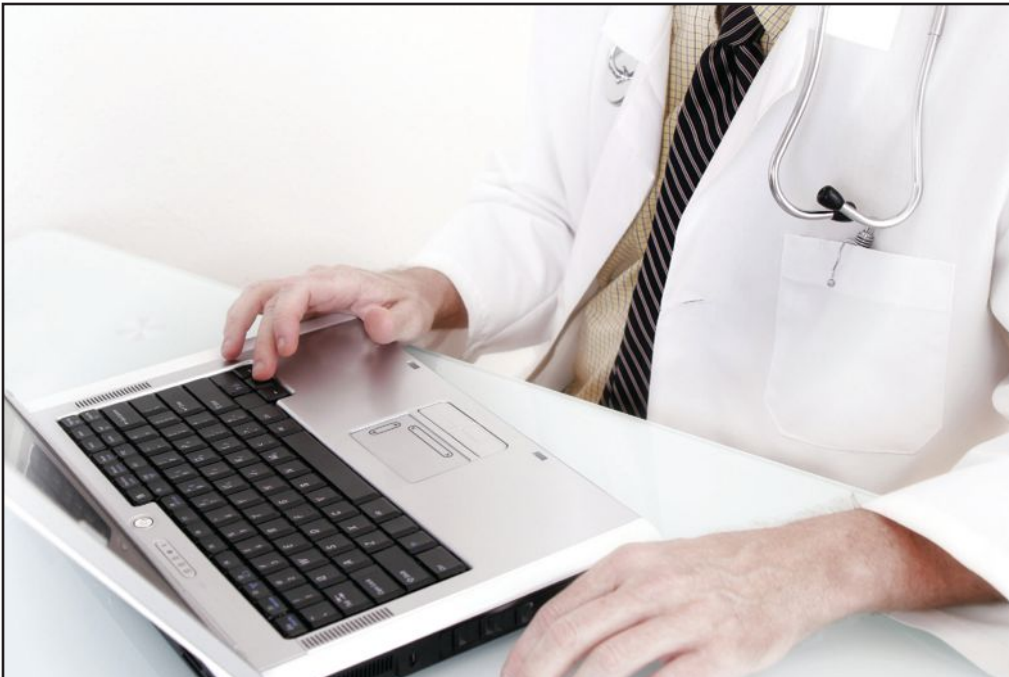
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Motorcycle Helmet Use and Legislation

A Systematic Review of the Literature

By Matthew Byrnes, M.D., and Susan Gerberich, Ph.D.

■ Although there has been a marked improvement in the safety profiles of cars and in car crash outcomes, there has been a marked worsening in outcomes of motorcycle collisions. Motorcycles account for only 2% of vehicle registrations in the United States, but motorcycle collisions account for 10% of traffic deaths. Further, motorcycle riders are 34 times more likely to die in a traffic collision than automobile drivers. Motorcycle helmet use has been suggested to be an effective way to reduce death and disability after traffic collisions, and enactment of universal helmet laws has been suggested as a means to enforce helmet use. This article presents findings from an analysis of National Highway Traffic Safety Administration data and studies in the medical literature on the impact of motorcycle helmet use and helmet legislation on the risk of death or injury in motorcycle accidents. The authors found voluminous support for motorcycle helmet use as a way to prevent severe traumatic brain injury and traffic fatalities.

Trauma is the most common cause of mortality among children and young adults. Many trauma-related deaths are the result of traffic collisions. According to the National Safety Council, approximately 40,000 traffic fatalities occur each year in the United States. Although there has been a marked improvement in the safety profiles of cars and in automobile-related crash outcomes, there has been a marked worsening in outcomes of collisions involving motorcycles. Motorcycle fatalities increased by 89% from 1997 to 2004.¹ Although motorcycles account for only 2% of vehicles registered in the United States, collisions involving motorcycles account for 10% of traffic deaths.^{1,2} Further, motorcycle riders are 34

times more likely than automobile drivers to die in a traffic collision.³ Motorcycle-related fatalities have been steadily increasing over the past 15 years. This roughly corresponds to a time period during which helmet use has decreased by 20%.² As such, motorcycle injuries represent a significant public health issue.

Use of helmets has been suggested as an effective way to reduce death and disability caused by collisions involving motorcycles. Laws requiring the use of helmets were on the books in nearly every state in the 1970s (see “Helmet Laws in the United States,” p. 62).^{2,4,5} Those laws have been steadily repealed in many states over the past three decades. In 1968, Minnesota enacted a universal helmet law. It was revised in 1977, requiring helmet use only among those 17 years of age and younger.

In this article, we review the literature on motorcycle helmet use and helmet laws as they pertain to injury prevention.

Methods

This review is based on a search of articles listed in PubMed during the past 25 years, using the search terms “motorcycle helmet and injury” (363 references); “motorcycle helmet laws” (110 references); and “motorcycle helmet legislation” (165 references). We excluded case reports and articles that were not published in English. We evaluated abstracts and obtained full copies of those studies that appeared to be original research or meta-analyses. Studies that focused on countries other than the United States were excluded, as each country has unique legislative and traffic considerations, making international comparisons difficult. The bibliography sections of the selected articles were reviewed to identify additional references.

Table

Summary of National Studies Evaluating Helmet Laws

Study	Year	Years included in study	Mortality difference present?	Mortality difference reported	Database utilized	Other metrics
Branas et al.	2001	1994-1996	No	None	FARS	Unadjusted mortality lower among universal helmet law states
Coben et al.	2007	2001	n/a	n/a	Healthcare Cost and Utilization Project	Evaluated nonfatal injuries. Noted 41% decline in most severe form of brain injury
Dee et al.	2009	1988-2005	Yes	27%	FARS	Noted that observed fatality reduction exceeded expected value
French et al.	2009	1990-2005	Yes	24%	FARS and other compiled datasets	20% reduction in nonfatal injuries
Houston et al. [*]	2007	1975-2004	Yes	31%	FARS	Study was focused on partial vs. universal laws
Houston et al. [†]	2010	1975-2004	Yes	22%-33%	FARS	Partial laws had reduction in mortality of 7-10%
Houston et al. [‡]	2007	1975-2004	Yes	11.1%	FARS	Reported that partial law fatality rates were similar to states with no laws.
Mayrose et al.	2008	1995-2003	n/a	n/a	FARS	Evaluated helmet use—more common with universal helmet laws
McGwin et al.	2004		Yes	Relative risk 0.76	FARS	Evaluated skills testing and licensing
Morris et al.	2006	1993-2002	Yes	Percentage not given	FARS and NOAA	Controlled for weather differences
Sass et al.	2000	1976-1997	Yes	29%-33%	FARS	
Sosin et al. Sosin et al.	1990 and 1992	1979-1986	Yes, only subgroups	No change in overall mortality. Head injury deaths reduced by 16%	National Center for Health Statistics	

* Houston DJ. Are helmet laws protecting young motorcyclists? *J Safety Res.* 2007;38(3):329-36.

† Houston DJ. The case for universal motorcycle helmet laws. *South Med J.* 2010;103(1):1-2.

‡ Houston DJ, Richardson LE, Jr. Motorcycle safety and the repeal of universal helmet laws. *Am J Public Health.* 2007;97(11):2063-9.

Effect of Helmet Use on Morbidity and Mortality

A number of studies have looked at the effect of motorcycle helmet use on outcomes of motorcycle crashes.^{3,6} (A full list of the studies examined is available online at www.minnesotamedicine.com.) Although their methodologies vary, these studies almost uniformly demonstrate the benefits of helmet use in reducing mortality. A total of 29 studies were found that evaluated the effect of motorcycle helmet use on traffic injuries and fatalities in the United States; each one noted a benefit to helmet use.

Studies done by the National Highway Traffic Safety Administration (NHTSA) concluded that for every 100 motorcycle fatalities, 37 lives could be saved through helmet use.² Two meta-analyses have been conducted on helmet use and injury.^{6,7} They included 61 and 53 primary studies, respectively (although there is significant overlap of primary studies included in them). The meta-analyses found that the highest-quality studies reported that the incidence of brain injury could be reduced by 72% and the

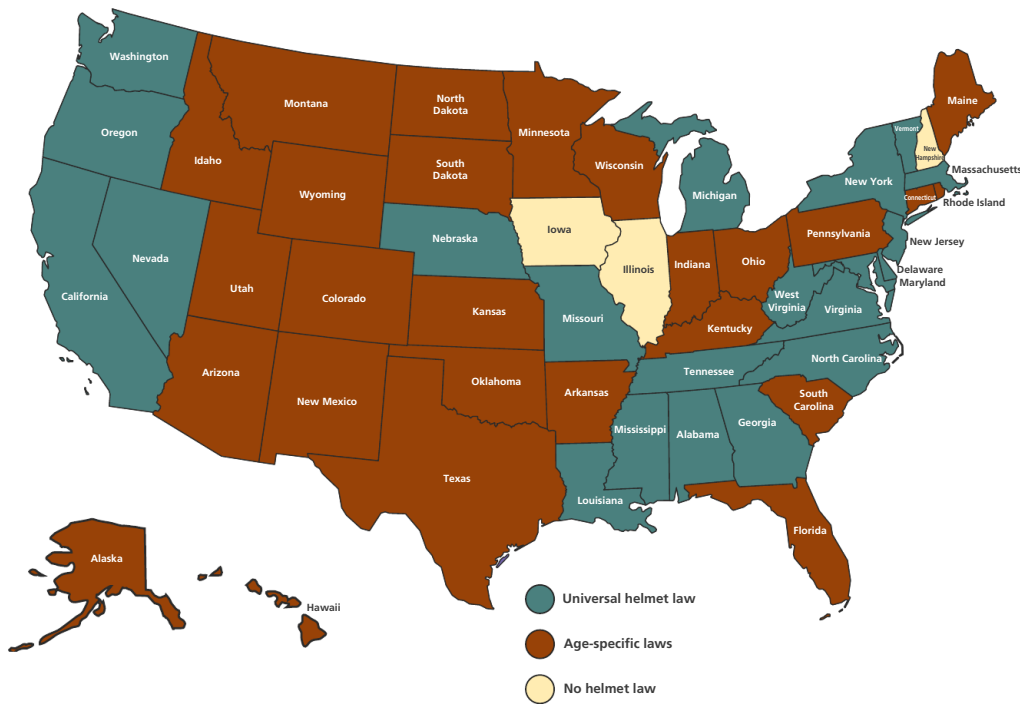
risk of death could be reduced by 42% with helmet use.

Anti-helmet lobbyists have argued that helmets may reduce the risk of head injury but that they increase the risk of spine fractures. Several studies evaluated this theory, and none have found any difference in the incidence of cervical spine fractures among helmeted riders.⁸⁻¹¹ As such, the bulk of the literature does not support the argument that helmet use results in greater cervical spine injury rates.

Effect of Helmet Laws on Traffic Fatalities and Injuries**■ National Studies**

We found 13 studies that evaluated the effect of helmet legislation on the outcome of traffic collisions involving motorcycles in the United States.^{2,4,12-21} A summary of these studies is listed in the table on this page. Among them, 12 showed a benefit of universal motorcycle helmet legislation, and one showed no difference with

Helmet Laws in the United States



History of Helmet Laws

Prior to 1966, only New York, Massachusetts, and Michigan had laws mandating helmet use. Helmet laws have been considered to be a states' rights issue, so Congress has created incentives for having helmet laws rather than imposed regulations. In 1966, Congress passed the federal Highway Safety Act, which withheld federal highway dollars from states that did not implement universal helmet laws. Because of this legislation, all but three states (California, Illinois, and Utah) enacted universal helmet laws by 1975. In 1975, Congress rescinded the penalty for not having a universal helmet law. Within four years, 25 states repealed their helmet laws. In 1991, Congress passed the Intermodal Surface Transportation Efficiency Act, which reintroduced an incentive for states to pass helmet laws; this law was repealed four years later. In 1997, Arkansas became the first state in more than a decade to repeal its mandatory helmet law. Several other states followed suit during the following decade. Today, only 20 states have universal helmet laws (see map); 27 have partial helmet laws (directed at riders younger than 18 or 21 years of age); and three states (Iowa, Illinois, and New Hampshire) have no helmet law.

Motorcycle Helmet Legislation Timeline

1965 and earlier	Only New York, Massachusetts, and Michigan have helmet laws
1966	Highway Safety Act
1967	22 states enact helmet laws
1968	Additional 14 states enact helmet laws
1975	47 states have helmet laws
December 13, 1975	Congress repeals economic penalties to encourage helmet laws
1976–1979	25 states repeal helmet laws
1991	Congress passes Interstate Surface Transportation Efficiency Act (ISTEA)
1992	California passes helmet law
1995	ITSEA incentives repealed
1997–2003	5 states repeal helmet laws
2004	Louisiana re-enacts helmet law
2005	15 states introduce legislation to repeal helmet laws
2011	20 states have universal helmet laws 27 states have laws for youths 3 states have no helmet laws

legislation. The advantage of national studies is that they are able to evaluate trends in all states and can compare outcomes in states with universal helmet laws with those of states without universal helmet laws. The disadvantage is that nearly all of these studies draw from the same database, the Fatality Analysis Reporting System (FARS) database, which tracks motorcycle deaths in every state and is administered by the NHTSA.¹⁸ This database only includes fatalities, which prohibits us from making inferences with respect to nonfatal injuries. Additionally, studies that evaluate the same database utilize the same cohort of subjects, so repeated studies do not represent unique study samples. The NHTSA data show two major upward trends in motorcycle fatality rates since 1975. The first began in 1976 and the second began in 1995. Both years correspond to the repeal of federal legislation that provided states with incentives to enact helmet laws. Although this observation does not take into account other factors that affect traffic fatalities, it provides a framework for discussion.

Houston et al. conducted multiple analyses of FARS data from 1975 to 2004.^{4,15,22,23} During this time period, multiple legislative changes took place, including the repeal of helmet laws in some states. They noted a 12% to 23% increase in fatalities in the states that most recently repealed their laws compared with states that still have universal helmet laws. They also noted a 28% reduction in fatality rates in the calendar years in which states had universal helmet laws compared with the years after they repealed their helmet laws.

French et al. compiled an extensive, multi-agency database that may not be subject to the selection biases suggested in the FARS database and allows for a much more in-depth evaluation of traffic fatalities.¹⁴ They used it to evaluate motorcycle crashes from 1990 to 2005 and found that universal helmet laws reduced nonfatal injuries by 20%. They also found a 24% reduction in fatalities in states with universal laws compared with states that had partial laws or no laws. They concluded that of the various public policy options, universal helmet laws have the greatest potential to reduce motorcycle fatalities.

In 2001, Coben et al. used the Healthcare Cost and Utilization Project database, which includes data from 33 states, to evaluate nonfatal injuries.¹³ Using a cross-sectional design, they identified a difference in intracranial injuries between states with and without universal helmet laws (16% vs. 11%, respectively) and noted that riders in states with universal helmet laws were 41% less likely to have severe brain injuries than riders in states without such laws. In states with universal helmet laws, the need for long-term care following motorcycle crashes also was reduced.

The number of lives that would be saved by universal helmet laws was calculated by Dee et al.² They noted that between 2,000 and 2,500 motorcycle fatalities occur each year among unhelmeted riders and estimated that 650 lives would be saved every year if all states had universal helmet laws, assuming that every rider wears a helmet and that helmets are 25% to 35% effective in preventing fatalities.

Not all studies demonstrated a positive effect of helmet leg-

islation, however. Branas et al. evaluated the FARS database from 1994 to 1996.¹² After controlling for multiple variables, they found no changes in the fatality rate per motorcycle registrations. This study has been criticized because of the very narrow time period examined, the lack of inclusion of the repeal time period, and its statistical model.¹⁵ Additionally, a power analysis was not conducted.

■ State-Based Studies

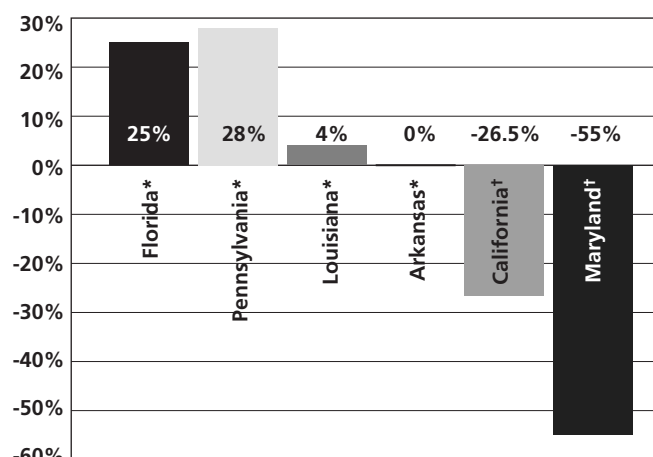
Our literature review included 16 state-based studies. Of those, 14 showed a benefit to universal helmet laws, and two showed no changes with universal helmet laws (Figure). Six states repealed helmet legislation in the years that followed the Congressional action of 1995; two additional states have reinstated helmet laws in recent years. We examined the effect of law changes in Florida, Pennsylvania, Louisiana, Arkansas, California, and Maryland, as these are the states in which studies on this topic have been published.

FLORIDA • Florida repealed its universal helmet law in 2000. Okeefe et al. evaluated motorcycle riders who presented to a single hospital in Miami following a crash.²⁴ They noted that fatalities increased between 1997 (n=22) and 2003 (n=43); however, the number of fatalities standardized for motorcycle registrations did not change. This study has been criticized for its limited geographic range and its dependence on hospital records rather than population-based databases. Another study found that brain injuries increased after the state's universal helmet law was repealed.²⁵ Yet another that utilized a statewide database concluded that repeal of the law resulted in a 25% increase in crash fatalities;²⁶ 117 additional deaths were attributed to the law's repeal during the years 2001-2002.

CALIFORNIA • California enacted helmet legislation for the first time in 1992. Kraus et al. evaluated medical records from

Figure

Change in Motorcycle Fatality Rates Associated with Helmet Legislation Changes in Six States



* Notes the change in fatality rates after universal helmet laws were repealed.

† Represents the change in fatality rates after universal helmet laws were enacted.

18 California hospitals in 10 counties between 1991 and 1993, and reported a reduction in skull fractures and traumatic brain injuries among motorcycle riders from 38% to 25% following the legislation.²⁷ This study has been criticized for using hospital records rather than population-based databases, its narrow time period, and the lack of control for other factors. The authors also evaluated police reports and death certificates in 11 California counties and found that fatality rates per motorcycle registration were reduced by 26.5%.²⁸

PENNSYLVANIA • Pennsylvania's universal helmet law was repealed in 2003. Mertz et al. evaluated the Pennsylvania Department of Transportation's database and noted that fatalities caused by head injury increased by 66% after repeal of the legislation.²⁹ This is likely the most complete state-based study, as it relies on a population-based database rather than individual hospital records.

ARKANSAS • Arkansas repealed its universal helmet law in 1997. Although total motorcycle fatalities did not increase, there was a significant increase in fatalities among unhelmeted riders.^{30,31}

MARYLAND • Maryland enacted a universal helmet law in 1992. Auman et al. reviewed fatalities in the state during a three-year period before and after the helmet law was enacted.³² They found the number of motorcycle-related fatalities dropped by 55% despite the number of motorcycle registrations remaining the same during that time period.

LOUISIANA • Louisiana repealed its universal helmet law in 1999 and then re-enacted it in 2004. During the repeal period, statewide motorcycle-related fatalities increased by 3% to 4%.³³ There have not been any studies published to date that have evaluated the reinstatement of the universal helmet law.

OTHER STATES • Mock et al. evaluated motorcycle trauma at a single trauma center in the state of Washington and noted a reduced incidence of traumatic brain injury after the state instituted its universal helmet law.³⁴ A similar trend was noted in Nebraska.³⁵ Proscia et al. compared outcomes in New York, which has a universal helmet law, with those in Connecticut, which has a partial law, and reported that riders wore helmets more often in New York and that the number of fatalities was higher in Connecticut.³⁶

STATES WITH PARTIAL LAWS • Twenty-seven states including Minnesota have partial laws regarding helmet use. These laws typically require riders under the age of 18 or 21 to wear a helmet. Houston et al. noted that fatalities among riders ages 15 to 20 years of age were 31% lower in states with universal helmet laws than in states with partial laws.²² Further, states with partial helmet laws had fatality rates similar to states with no helmet laws. Several other studies reached the same conclusion.^{37,38} It has been suggested that partial helmet laws are difficult to enforce, as police have to make a rapid determination of a rider's age, which likely leads to under-enforcement.

The effect of partial laws on nonfatal injuries has been studied less extensively. Coben et al. noted that a variety of nonfatal

injuries were seen less often in states with universal helmet laws than in those with no or partial laws.¹ Weiss et al. noted that the incidence of traumatic brain injury was 38% higher among youths in states with partial helmet laws than those in states with universal helmet laws.³⁷

Discussion

The actual effect of helmet legislation could deviate from the expected effects for a number of reasons.² The Peltzman hypothesis has suggested that the protective effects of universal helmet legislation may be mitigated by increased risk-taking among riders.² Additionally, universal helmet laws could give a false sense of security, thereby increasing the number of motorcycle riders, which could result in more fatalities. Alternatively, helmet laws could be more efficacious than predicted. Universal helmet laws could result in greater police scrutiny of motorcycle riders, which could result in fewer crashes. Additionally, some people may stop riding motorcycles if they are required to wear a helmet. Dee et al. evaluated these possibilities with a retrospective review of the FARS database.² This review was significant in that it focused on the years 1988 to 2005, which corresponded with changes in urban traffic, the size of motorcycle engines, and legislation. The expected reduction in traffic fatalities was estimated by assuming an opportunity to influence 50% of motorcycle riders with legislation as well as a 34% efficacy rate of helmets in reducing fatalities. This led to an expected 20% reduction in fatalities. Several national studies have reported actual reductions much higher than 20%, which suggests that the Peltzman hypothesis is incorrect and that helmet laws may have benefits that extend past simple helmet usage.

Weather differences among states can be a confounding factor in evaluating motorcycle fatalities. However, Morris, et al. found that there was a reduction in mortality associated with helmet laws despite controlling for weather differences.¹⁸ Similarly, in controlling for various states' licensing and training requirements, McGwin et al. noted that the relative risk of death was 0.77 among states with universal helmet laws.¹⁷

A concern with the interpretation of these studies is that there are a variety of ways to calculate mortality from traffic crashes.³⁹ As such, the metric used to calculate mortality rates varied across studies. The three most commonly used metrics in the national database studies were fatalities per motorcycle registration, fatalities per population, and fatalities per mile driven. These metrics have been used to standardize mortality rates. State-level studies typically report either unadjusted rates or fatalities per motorcycle registration. Although this has been a criticism lodged against motorcycle helmet studies, the conclusions that are drawn from them are consistent between methodologies. Regardless of the metric used, the majority of studies indicate that motorcycle helmets and helmet use legislation are effective in reducing motorcycle collision fatalities.^{2,14}

Other criticisms of helmet studies include the fact that it is difficult to evaluate driving habits across states. For instance,

it is possible that risk-taking behavior is higher in certain states and that these behaviors are the driving force behind increased fatalities. Additionally, helmet studies focus on various time periods, which make comparison between studies difficult. There also has been a trend toward motorcycles with larger engines that could result in increased fatalities, independent of helmet use.¹⁵ National studies have attempted to control for these variables by using time series analyses. The final criticism is that no studies are able to accurately evaluate fatality rates as a function of miles driven.

None of these criticisms significantly alter the conclusion of the vast majority of studies that motorcycle helmet use and universal helmet laws are associated with a reduction in traffic fatalities.

Conclusion

The evidence for the protective effects of motorcycle helmets is very strong. There is convincing evidence that motorcycle helmet use reduces both traumatic brain injuries and death after collisions. A preponderance of evidence also suggests that universal helmet laws are very effective in reducing fatalities and injuries associated with motorcycle collisions, although a couple of studies dispute the effect of helmet legislation. It is likely that 500 to 1,000 lives could be saved each year by national adoption of universal helmet laws.

MM

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Treatment Number Five *of electro-convulsive therapy (ECT) for depression*

By Mina Le, M.D.

The body on the bed jumped taut
And clenched from fist to teeth, strung out
On current while we rearranged
His worn-down ruts of dreary thought.
Escape at last had taken this route:
To lie, in hopes of waking changed,

Enchanted to jerk like a marionette
From where the gel in his white hair
Conducted a hundred sixty volts,
With only this to forestall regret:
Either faith the doctors wouldn't err,
Or else indifference to results.

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