



*Researcher Paul Newhouse, M.D.,  
traces the good effects of a classically “bad” substance.*

# the Chemistry of cognition

*by* JEFFERY LINDHOLM

**For much of his career in medical research,**

Paul A. Newhouse, M.D., has been studying the benefits of nicotine. The very notion of nicotine having a “good” side may seem strange to many people. Nicotine, especially as it is present in tobacco products, is associated with health risks, including cancer and emphysema. But researchers such as Newhouse are increasingly showing benefits of specific doses and delivery of nicotine in treating Alzheimer’s disease and other forms of dementia, depression, Parkinson’s disease and other movement disorders, attention deficit hyperactivity disorder (ADHD), Tourette’s syndrome, and more.

People who suffer from these conditions seem to have instinctively realized nicotine’s beneficial effects. For instance, almost 90 percent of people with schizophrenia smoke, three times more than in the general population. Teenagers with ADHD are much more likely to smoke than are normal teens. Newhouse suggests that both these groups of people are self-medicating — reaping the beneficial effects of nicotine, which really can help people calm down and focus their thoughts.

“We’re increasingly knowledgeable about brain circuits involved in attention, in provoking and maintaining reception,” says Newhouse, professor of psychiatry and director of the UVM Clinical Neuroscience Research Unit. “We think that the nicotinic receptors are not the attention system itself, but they can modulate the activity of that system.”

*photography by* ANDY DUBACK



#### NICOTINE AND CHOLINERGIC RECEPTORS

Chemically, nicotine binds with receptors located on the surface of neurons in the brain. These receptors, which modulate neuronal transmission, are designed to bind with the naturally occurring neurotransmitter acetylcholine, but they will also accept other substances, including nicotine. Similar cholinergic receptors exist throughout the body, controlling a variety of functions from sweating to sexual activity. However, they play an especially important role in the brain, where they have an effect on learning, memory, and emotion.

Acetylcholine was one of the first neurotransmitters isolated and identified, but it does not lend itself well to research. “It turns out that the transmitter is inactivated rather quickly so it’s been technically difficult to study,” says Newhouse. “It’s only in the last fifteen, maybe twenty years, that a lot of molecular and electrophysiological advances have been made in understanding how these cholinergic receptors work.”

In the late 1970s, the cholinergic system was identified as one of the key systems lost due to Alzheimer’s disease. Newhouse’s specific interest in the system was also developing at the same time, during his ten years as a U.S. Army psychiatrist.

#### Newhouse and postdoctoral researcher Julie Dumas, Ph.D., in the MRI lab at Fletcher Allen Health Care.

During a residency in psychiatry in Washington, D.C., in the late 1970s, he worked on pharmacologic studies regarding the cholinergic system’s role in movement, which sparked the interest that continues today. Soon after, he did a stint in a basic neuropharmacology laboratory at the Walter Reed Institute for Research, studying how cholinergic activation affected basic second-messenger systems in cells. He returned to human research at the National Institutes of Health and continued this work when he came to UVM in 1988.

“By the late 80s we were fully into trying to understand the cholinergic nature of cognitive function,” says Newhouse. “We knew there was a cholinergic story in Alzheimer’s disease. Those of us who were interested in trying to explore this and understand it were trying to think of ways to probe the activity of the cholinergic system in humans. The best way to do that at the time was to use drugs.” For instance, if it is known that a certain drug blocks nicotinic receptors and the drug affects learning, memory, or motor skills, a researcher might be able to conclude that nicotinic receptors

## Tracking other brain functions

Dr. Paul Newhouse’s work at the College of Medicine into possible therapeutic benefits of nicotine has attracted national attention and funding. Newhouse, professor of psychiatry and director of UVM’s Clinical Neuroscience Research Unit, is working with other UVM scientists on a variety of current projects.

#### ATTENTION DEFICIT HYPERACTIVITY DISORDER

Newhouse and postdoctoral associate Alexia Potter, Ph.D., are working to better understand the effects of nicotinic stimulation on attention, motor performance and delay aversion in adolescents and young adults with attention deficit hyperactive disorder.

One major aspect of the study is behavioral inhibition — the ability to stop a motor action once it has started. People with ADHD are known to be very impulsive and usually do not respond to cues such as stern looks or verbal warnings. Results show that nicotine seems to correct this deficit, as does the drug Ritalin. However, while Ritalin speeds up stopping responses, it also speeds up other responses; nicotine appears to have a more specific effect on the deficit.

Other trials by Potter and Newhouse have shown nicotine’s effectiveness in another core ADHD deficit: delay aversion, which is a dislike for waiting. Using a computer task in which subjects can collect a small number of points quickly or a greater number through a longer process, subjects with nicotine patches showed a greater ability or willingness to wait for the greater reward than those not receiving nicotine.

#### CHRONIC PAIN

Newhouse is interested in possible hormonal manipulation to provide relief from chronic pain; Magdalena Naylor, M.D., Ph.D., associate professor of psychiatry, is working on behavioral manipulation to deal with pain. Together, they plan to use the academic health center’s new functional MRI to locate structures in the brain that are involved in generating abnormal stress reactivity seen in both

chronic pain and post-traumatic stress disorder.

Together with Newhouse, Naylor has received a grant from the National Institutes of Health to study specific techniques to treat patients with chronic pain to prevent relapse after they have completed cognitive behavior group therapy. Twenty patients will be enrolled in a pilot study.

Studies done at Harvard have shown exaggerated reactions of the amygdala, the part of the brain that governs anxiety and fear, in patients with post-traumatic stress disorder — even when exposure to stressful images is so quick they aren’t consciously aware of the images. Naylor’s study will test whether similar action is present in people with chronic pain.

#### TAMOXIFEN AND COGNITION

Newhouse and post-doctoral associate Julie Dumas, Ph.D., are focusing their efforts on the effects of tamoxifen on cholinergic-induced changes in cognition.

In some tissue systems, such as bone, tamoxifen acts in a manner similar to estrogen and strengthens those systems. In others, such as breast tissue, tamoxifen acts as an antiestrogen. “What we want to address in our study,” says Dumas, “is what is it doing in the brain — is it working like estrogen, for which there’s some evidence that it improves cognition, or is it acting as antiestrogen, thereby blocking the benefits of estrogen and thereby causing some impairment?”

The study group will include 30 healthy post-menopausal women with no history of breast cancer. They receive tamoxifen or placebo for three months, then undergo tests while taking a drug that temporarily blocks cholinergic receptors for memory and attention. “If we impair your memory for two hours and you’ve taken estrogen, this impairment should be less than if you haven’t taken estrogen,” says Dumas. Newhouse and Dumas will look at a wide range of cognition skills, including spatial, verbal, and attention tasks as well as psychomotor speed.

are involved in the task of attention.

Newhouse has become known for trying to use chemical and cognitive probes of the brain to help discern the role certain chemical systems play in cognition.

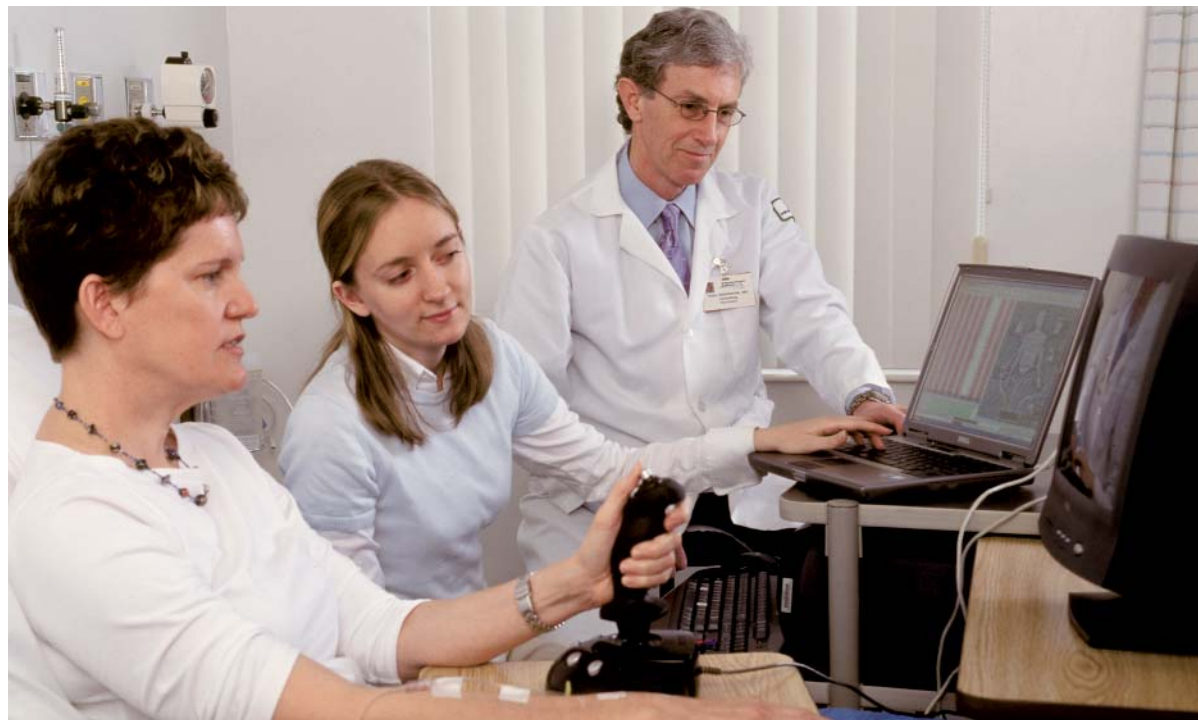
#### **NICOTINE BENEFICIAL?**

So why, if nicotine has such a bad reputation, would doctors want to use it as a treatment? The first and strongest reason is because it works. The human brain does not have receptors specifically designed to accept nicotine. But, as Newhouse explains, "It turns out that naturally occurring plant molecules often have the same three-dimensional structures as naturally occurring chemicals in our bodies. Nicotine has a three-dimensional shape that somehow fits in cholinergic receptors, even though it's from a different source. The receptor doesn't care what comes along as long as it fits."

#### **NICOTINE AGONISTS**

Synthetic drugs that mimic the effects of nicotine, called nicotine agonists, might provide benefits without nicotine-associated side effects such as addiction and narrowing of blood vessels. They

**Newhouse and research assistant Jessica Salerno study participant Julia Bergerow's reactions to tasks on a computer model.**



might also provide a more focused effect on specific receptor systems affected in different conditions.

For years, researchers have tested a variety of novel nicotine-like molecules to see if they have similar or better ways of activating the cholinergic system without nicotine's problems. In the late 1990s, Newhouse and his associates published the first paper on the effect of a novel nicotine agonist in humans, specifically, a small group with Alzheimer's disease. The condition is characterized by the loss of both cholinergic neurons and nicotinic receptors in the basal forebrain. Compromise of this system affects the regulation of cerebral blood flow as well as cognitive performance.

Newhouse notes that, where Alzheimer's disease is concerned, a small effect on cognitive function is a positive thing. "Even the best cholinergic drugs now on the market produce quite small effects on cognitive function," he says. "No one pretends that nicotine agonists are likely to produce a cure for this disease, but I think they may form part of a therapeutic package."

#### **NICOTINE PATCHES**

Of course, smoking is an extremely bad way to attempt to trigger the benefits of nicotine. First and foremost is the obvious cancer risk. Smoking also delivers nicotine too quickly in the human body to be lasting and beneficial.

## the Newhouse file

Paul A. Newhouse, M.D.  
Director, Clinical Neuroscience Research Unit  
Professor, Department of Psychiatry

#### **EDUCATION**

B.S., 1974: Agriculture, magna cum laude, Kansas State University

M.D., 1977: Stritch School of Medicine, Loyola University

#### **UVM PROFESSIONAL/CLINICAL POSITIONS**

• 1994-Present: Director, Clinical Neuroscience Research Unit, Department of Psychiatry, University of Vermont College of Medicine

• 1993-Present: Research Director, Memory Center of Vermont, Fletcher-Allen Health Care, University of Vermont

• 1988-Present: Director, Geriatric Psychiatry Service, Department of Psychiatry/ Fletcher-Allen Health Care, University of Vermont College of Medicine

#### **PROFESSIONAL AND MILITARY EXPERIENCE**

• 1977-1978: Categorical Intern, Loyola University Medical Center, Maywood, Illinois

• 1978-1981: General Psychiatry Resident, Walter Reed Army Medical Center, Washington, D.C.

• 1981-1982: Division Psychiatrist, Third Infantry Division, VII Corps, 7th U.S. Army, Schweinfurt, West Germany

• 1982-1983: Chief, Psychiatry Outpatient Clinic, Department of Psychiatry, 130th Station Hospital, Heidelberg, West Germany

• 1983-1984: Chief, Community Mental Health and Consultation Service, Assistant Chief, Department of Psychiatry, 130th Station Hospital, Heidelberg, West Germany

• 1984-1985: Medical Staff Fellow, Clinical Neuropharmacology Section, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland

• 1985-1986: Research Ward Administrator, Clinical Neuropharmacology Section, Laboratory of Clinical Science, National Institutes of Mental Health, Bethesda, MD. Executive Secretary, National Institute of Mental Health Clinical Research Review Board

#### **POSTGRADUATE STUDIES**

• 1977-1978: Categorical Psychiatry Internship, Internal Medicine, Psychiatry, and Neurology, Loyola University Medical Center

• 1978-1981: Psychiatry Residency, Walter Reed Army Medical Center, Washington, D.C.

• 1980: Research Traineeship, Neuroendocrinology and Neurochemistry Branch, Department of Medical Neurosciences, Division of Neuropsychiatry, Walter Reed Army Institute of Research

• 1984-1986: Geriatric Psychopharmacology Research Fellowship, Clinical Neuropharmacology Section, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Md.

#### **HONORS**

• 2004: Excellence in Psychiatry Academic Teaching Award, University of Vermont

• 2002: Profile of Courage Award, Assembly of the American Psychiatric Association

• 2002: Exemplary Psychiatrist Award, National Association for the Mentally Ill- Vermont (NAMI)

• 2000: Excellence in Psychiatry Teaching Award, University of Vermont

• 1991: Army Achievement Medal, U.S. Army, for Operation Desert Storm

• 1988: Meritorious Service Medal, U.S. Army

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Nicotine patches, with their measured doses, are one way to deliver the chemical. Studies done for FDA approval and subsequent use of the patches have shown that small doses of nicotine appear free of major side effects and, very importantly, don't contribute to dependency.

Newhouse is now heading a multicenter study looking at whether the use of transdermal nicotine patches can improve attention and memory in people with mild cognitive impairment—a precursor of Alzheimer's disease. UVM is the lead center, working with Duke and Georgetown, a group in England, and others. Newhouse also ran a pilot study testing patches on fifteen patients with Parkinson's disease. This study suggested that nicotine could substantially improve movement and relieve mental difficulties for such patients.

Newhouse and his colleagues recently published a paper in the journal *Pharmacology* in which they reported nicotinic stimulation directly improves a type of inhibitional attentional failure in children and young adults with ADHD. "This finding may help answer several questions," says Newhouse. "It first contributes to the indirect question, why do they smoke? It also gives us a clue to some of the underlying neurobiological problems in this disorder, suggesting that this specific cognitive failure that is so characteristic of ADHD seems to be modulated by nicotinic cholinergic receptors." Studies to understand further this aspect of ADHD continue. (See sidebar on page 27.)

#### FUNCTIONAL MRI

With Fletcher Allen Health Care's new functional magnetic resonance imaging (MRI) system, Newhouse and his team are taking the next step, beginning to locate the cholinergic systems associated with nicotine and estrogen receptors as the chemical reactions happen, in real time. Other new equipment has been added, including a new high-field magnet, and software to a medical MRI that allows them to acquire 3-D, color, functional images of brain activity. "At the end of the day it'll let us create brain slices incorporated with three-dimensional reconstruction to see where the activity is occurring inside the brain during a particular cognitive process," says Newhouse. "We want to be able to map out the circuitry."

Newhouse has designed studies and applied for funding to do this. "We're also starting to look at

the cholinergic process related to the role estrogen plays in cognition in postmenopausal women, and we're also going to be looking to how we can see if nicotine may alter the processing of attentional information in ADHD," he says.

#### VIRTUAL REALITY

Newhouse and his associates are also interested in exploring the basic mechanisms of cognitive performance that control spatial learning in children. Newhouse embarked on this interest through the work of Robert Astur, Ph.D., of the Olin Institute in Hartford, Conn. Astur has a virtual reality lab in which he's designed environments that replicate a standard task. A computer screen integrated into an MRI apparatus allows subjects to maneuver through the virtual environment while their brains are scanned for cholinergic activity.

"Such a virtual reality system allows neuroscience researchers to do work that we can't do in a standard laboratory," says Newhouse. "We want to understand whether spatial navigation is affected by particular drugs and these receptors. The advent of enhancement of pure technology and imaging allows us to do a lot more with interrogating the brain in terms of helping us understand the activity of these chemical systems on cognitive performance."

#### LOOKING FORWARD

"I'm blessed to work with a wonderful group of colleagues," says Newhouse. "It's been very gratifying to work with the students, post-docs and other faculty members in this department and other departments, as well as the General Clinical Research Center. With the new MRI system, we have a great collaboration with the Department of Radiology. They are allowing us to graft onto their equipment. Also, we have great cooperation with Fletcher Allen's Information Services Division. It's been a pleasure working with everyone to get this research off the ground."

Newhouse maintains an enthusiasm for his work, no matter where it leads him. "Our program is really quite broad-based in the sense that we span the range from very focused human studies of normal volunteers and trying to understand the cognitive operations better to clinical trials looking at treatment of memory disorders," says Newhouse. "One of the fun things about this work is that we can ask questions all the way from the most basic questions of human cognition to treatment." VM

*In 1905, when the College of Medicine completed its third home at the corner of Prospect and Pearl Streets in Burlington, the main lecture room, where students spent so much of their time, was named Hall A. The Hall A magazine section seeks to be a meeting place for all former students of the College of Medicine.*

