

ON THE BRAIN

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A 'Biochemical Roadmap' of Drug Addiction

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COCAINE ABUSE is a significant public health problem in the United States. According to the 2004 National Survey on Drug Use and Health, an estimated 1.5 million Americans may be dependent on or abuse cocaine. More than 34 million Americans over the age of 12 have tried cocaine at least once in their lifetime. The highest rate of use is in the 18- to 25-year-old age group.

Since the late 1980s ~~to the present~~, says Bertha Madras, Ph.D., a professor of psychobiology at Harvard Medical School (HMS) and chair of the Division of Neurochemistry at the New England Primate Research Center, the hypothesis that most scientists agree on is that dopamine mediates the pleasure sensation of drugs and triggers adaptive responses in the brain, leading to addiction. Dopamine is a neurotransmitter that is involved in the brain's reward system, among other functions. The focus on dopamine, however, "is simplistic and keeps us from casting a wider, more systematic net" in the study of drug addiction and the brain, she says.

Cocaine provides an excellent paradigm for the study of drug abuse because addiction to cocaine can occur relatively rapidly (within two years) and is hard to break.

Dopamine and drug addiction

The dopamine theory behind cocaine addiction posits that the immediate high produced by snorting, smoking or injecting the drug is caused by a buildup of dopamine in the brain. Cocaine produces this buildup wherever the brain has dopamine transporters, proteins that dopamine cells use to retrieve dopamine molecules from their surroundings. These dopamine cells are highly concentrated in the brain's limbic system, which is primarily responsible for our emotions, particularly the nucleus accumbens and the amygdala regions of the brain. This buildup of dopamine causes cells in the nucleus accumbens to produce feelings of

pleasure and satisfaction. The amygdala is a memory center in the brain that helps us remember what we did that led to pleasurable sensations such as those produced by cocaine.

Hans Breiter, M.D., an assistant professor of psychiatry at HMS and co-director of the Motivation and Emotion Neuroscience Collaboration at Massachusetts General Hospital (MGH), has used functional MRI to determine that certain areas of the brain, including the nucleus accumbens, subcallosal cortex and the amygdala, are involved in the "rush" of a cocaine high. All of these regions of the brain have differing levels of dopamine, and, once ingested, cocaine goes to each of these regions.

In a 2004 paper in the journal *Neuron*, Breiter reported that, in cocaine addicts, the amygdala is smaller than it is in healthy study subjects. "No one anticipated such a specific pattern of volume reduction in the amygdalas of cocaine addicts," he said in an MGH news release, "pointing to the potential problems in a small number of subregions of this brain structure." Breiter and his colleagues are conducting further studies to better understand the implications of these changes in the brain.

Communication system is key to many drug-induced brain changes

All drugs of abuse invade the brain's communication system for a simple reason: they are chemical imposters of the neurotransmitters (chemical messengers) used by the brain to communicate. Amphetamines and cocaine have features in common with dopamine, the backbone of LSD is identical to serotonin, and the active ingredient of marijuana (THC) can be modeled on the brain's own anandamide.

This communication system is geared toward neurotransmitters made by the brain (e.g., dopamine and serotonin), but not to drugs.

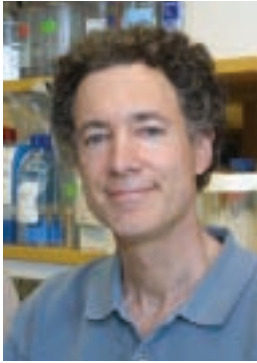
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Bertha Madras, Ph.D.

The Aging Brain: Gene Expression in Middle Age May Hold Clues to Cognitive Decline



Bruce Yankner, M.D., Ph.D.

MOST OF US IN OUR middle years and beyond know what it feels like to grow old: our vision and hearing may start to fade; we become less flexible, oftentimes with stiffened joints; we lose muscle mass unless we stay physically active. And, perhaps, most frustrating, our mental abilities, including our memory and executive functions such as decision making, planning and problem solving, begin to decline.

Researchers at Harvard Medical School (HMS) may have found a clue to this cognitive decline and the rate at which we age in the way genes are expressed – or turned on and off – in our brain as we age.

“There are at least 400 to 500 genes that change in the brain as we age,” says Bruce Yankner, M.D., Ph.D., a professor of neurology and co-director of the Glenn Aging Laboratories at HMS and lead author of the first study to examine human brain aging by using genomic approaches. “About 60 percent of these genes showed reduced expression,

while the rest showed increased expression.” That means that more than half the genes were turned down with aging and the others were turned up. The genes that were turned down – or down-regulated – were potentially the most consequential to age-related cognitive declines.

How our brain ages

A number of factors may contribute to the aging and gene damage our brains can experience as we get older, including oxidative stress and DNA damage. During the natural process of oxidation – turning oxygen into energy – the human body produces free radical toxins that can damage cells and DNA. Free radicals are groups of atoms formed by natural biological processes that can damage cells, proteins and DNA by altering their chemical structure. Generally, these free radicals are consumed by antioxidants (substances that hamper oxidation) before they can do any damage. This process, however, becomes less efficient as we age, and the free radicals damage molecules in the body, interfering with the normal, healthy functioning of cells. This especially damages the membranes and DNA of cells.

In addition, internal and external toxins can damage DNA, the genetic material contained in each cell, but our body has developed intricate repair systems that help DNA maintain its integrity. Like the process of oxidation, this repair system becomes less efficient with age. In fact, some scientists believe that accumulated DNA damage is a major cause of aging.

“DNA damage has been most intensely studied in the progression of cancer,” says Yankner. “In some types of cancer, DNA rearrangement can trigger abnormal cell growth by inducing abnormal expression of genes. The role of DNA damage is not as well understood in neurodegenerative diseases of the brain. In Alzheimer’s and Parkinson’s disease, there is evidence of increased DNA damage in the brain, but it is not clear if this contributes to the symptoms of the diseases.”

Identifying aging genes

In their study, Yankner and his colleagues analyzed the expression of about 30,000 genes (nearly the



entire human genome) in postmortem tissue of individuals ranging in age from 26 to 106 years. They focused on the brain's prefrontal cortex, which is responsible for a number of higher-level cognitive functions that have evolved in humans.

The researchers found that gene expression was down-regulated, or turned down, in groups of genes that are vital for synaptic plasticity, the ability to make new neuronal connections that are essential for learning and memory. Additionally, they found that the promoter regions of these genes, the part of the gene that controls if it is turned on and off, were selectively damaged. They then showed in laboratory experiments with brain cells that damage to promoter regions, some of which are highly sensitive to oxidative stress, impairs the turning on of these genes. Yankner's team found that these down-regulated genes suffered more accumulated DNA damage in the aging brain than genes that were up-regulated, or turned on.

One of the more intriguing aspects of Yankner's study was his finding about the variability of aging. The gene profile showed that declines in gene expression in the brain begin around age 40, an age at which many people feel they are in the prime of their life. Gene profiles of those under 40 and over 70 are relatively homogeneous, he says, but much less so in the 40 to 70 age bracket.

"The young adult and extreme aged human populations are relatively homogeneous in their gene expression patterns in the prefrontal cortex," Yankner and his colleagues wrote in *Nature*. "However, the middle-age population between 40 and 70 years of age exhibits much greater heterogeneity. Thus, individuals may diverge in their rates of aging as they transit through middle age, approaching a state of 'old age' at different rates."

Reversing the aging process

While the scientific community accepts that oxidative stress plays a key role in age-related DNA damage, there is no consensus on the effectiveness of using antioxidants to slow down or stop this process. Antioxidants act as "scavengers" that gobble up free radicals before they can do damage to the body.

"Antioxidants would seem to be a reasonable approach to preventing DNA damage and are frequently advocated as potential remedies," says Yankner. "The concept has been supported by laboratory experiments, but the effectiveness of current antioxidant therapies for human aging and disease is still unknown."

Scientists, including Yankner and his team, are studying ways to repair age-related DNA damage. In his lab, Yankner's group has genetically manipulated cells so that they overproduce the proteins needed to repair damaged DNA. This procedure has shown some functional restoration of damaged genes.

"We've shown," he says, "that if you introduce specific DNA repair enzymes into the cells, oxidative DNA damage can be reduced considerably. This is not hard to do in the lab, but may be much more difficult with human subjects because the brain is

"There are at least 400 to 500 genes that change in the brain as we age," ... "About 60 percent of these genes showed reduced expression, while the rest showed increased expression." That means that more than half the genes were turned down with aging and the others were turned up. The genes that were turned down – or down-regulated – were potentially the most consequential to age-related cognitive declines."

less accessible than other parts of the body and there may be unanticipated side effects from disturbing the normal balance of repair and cell growth."

Yankner's lab is also investigating the gene and DNA damage profiles of blood lymphocytes, a type of blood cell, to determine how predictive the results of this type of test are for gene-related changes in the brain.

"The goal is to develop tests to determine who is likely to age at what rate," Yankner adds, "so that measures can be taken early in life to reduce subsequent age-related decline. It's hard to say when this type of test would be available, but certainly, we hope, in our generation."

A Cup of Coffee for the Brain

HA VE YOU EVER wondered why you need a cup of coffee to wake up in the morning? The answer may be in the reaction of a chemical called adenosine that is found in virtually every cell in the human body.

Nearly 15 years ago, scientists discovered that adenosine binds to cells in the brain, causing drowsiness by slowing down nerve cell activity. They also found that the caffeine found in coffee, tea, soft drinks and chocolate blocks the action of this natural brain chemical, setting off a number of reactions that make us more alert.

Adenosine and sleep

A key player in sleep and wakefulness, adenosine is a byproduct of working cells, involved in energy storage and providing power for the brain to operate. The more energy used, the more adenosine is produced. As a neuromodulator (a brain chemical that either augments or inhibits the transmission



of nerve impulses), adenosine acts to quiet down many parts of the brain. When adenosine binds to proteins called receptors in the brain, neural activity slows down, creating a feeling of sleepiness.

“Adenosine is a powerful messenger that induces sleep after wakefulness,” says Robert McCarley, M.D., a professor of psychiatry at Harvard Medical School (HMS) and chairman of psychiatry for the VA Boston Healthcare System, who first identified adenosine as an inhibitor of wake-active neurons in the basal forebrain, a region of the brain that mediates the wake-sleep cycle.

Adenosine, he adds, inhibits wakefulness cells and acts as a homeostatic feedback system. Thus, the longer you are awake, the higher the levels of

adenosine rise in your basal forebrain. This increase of adenosine in the brain creates a greater propensity for sleep.

The brain and caffeine

Caffeine, perhaps the leading “drug” of choice in the United States in the form of coffee, is an adenosine-receptor antagonist, meaning that it binds to the same receptors as adenosine, without reducing neural activity. Thus, fewer receptors are available to take up the adenosine and its slowing action.

Clifford Saper, the James Jackson Putnam Professor of Neurology and Neuroscience at HMS and chairman of Neurology at Beth Israel Deaconess Medical Center (BIDMC), says that adenosine can either increase or decrease the activity of nerve cells, depending on the adenosine receptors that are involved. The A₁ receptor is an inhibitory receptor, which makes it harder for nerve cells to fire. The A₂ receptor is excitatory, making it easier for nerve cells to fire.

“Caffeine is an antagonist of *both* adenosine receptors,” Saper says, “so it blocks the A₁ effect on wake-producing neurons in the basal forebrain, but also blocks the A₂ receptor, which activates sleep-producing cells in the brain. The net effect, therefore, is to reduce sleep.”

Stimulant effects and withdrawal

Caffeine is a well-known stimulant of the central nervous system. In addition to making us more alert, it also increases our heart rate, blood pressure, and body temperature at high levels if we are not accustomed to it. These effects, which can begin as quickly as 15 minutes after consumption, can last up to six hours. (McCarley says that while caffeine does produce these effects, tolerance develops rapidly so that most habitual coffee drinkers don’t experience them.) When caffeine consumption is decreased or withdrawn completely, people often suffer headache, fatigue or drowsiness, irritability, and difficulty concentrating, perhaps because the body becomes oversensitive to adenosine. All of these effects are alleviated with caffeine intake.

“It is likely that in people who take regular doses of caffeine,” says Saper, “the adenosine receptors are hypersensitive, so that when caffeine is withdrawn, one gets these effects.”

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A 'Biochemical Roadmap' of Drug Addiction

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The brain has an extraordinary system of sending complex signals among its 100 billion nerve cells and to muscles, via these transmitters, in one-tenth to one-thousandth of a second. This communication system is not only very rapid, but very tightly controlled, as well. Signals involved in these complex functions are terminated quickly. One of the many ways the signals end is the removal of the neurotransmitter by a transport mechanism. But drugs can't be handled the same way that brain cells process neurotransmitters.

"Drugs don't fit the brain's transport mechanism," says Madras, "and can't be removed from their targets in a millisecond timeframe, as natural messages are. You can put a barking dog into a minivan and cart it away, but not an elephant, so the elephant can stay put under your window all night and keep on trumpeting. Drugs are like the elephant; they hang onto signaling targets in the brain for a long time."

This persistent, foreign chemical can produce an enduring, abnormal signal. Brain cells affected by drugs identify these signals as abnormal and then overcompensate for them. Eventually, the compensatory changes become so extreme that withdrawal from the drug leaves an abnormal brain. It is now adjusted to the drug signals and feels normal only when the drug is present.

"Repeated drug use leads to psychological and biochemical changes in the adapted brain," says Madras, "including profound dysphoria [a state of feeling unwell or unhappy] on withdrawal, irritability, anxiety and sleep problems. The compelling need to stop the dysphoria and recapture the euphoria or cues that trigger drug context memories drive the addicted person to seek the drug."

CREB, delta FosB and dynorphin

What are some of the adaptations made by the drug-exposed brain? Two transcription factors (proteins that bind to genes to turn genes on) are known to be involved in drug addiction. CREB is a transcription factor that is activated by cyclic-AMP (cyclic-adenosine monophosphate) immediately after a cocaine high. It activates genes to produce proteins such as dynorphin, which acts in opposition to cocaine's pleasure effects.

"CREB increases levels of dynorphin, which produces dysphoria and dampens the brain's reward circuit," says Madras. "The need to reverse this cycle may lead to repeated drug use."

On the other hand, delta FosB is a transcription factor that activates genes that counteract the effects of CREB and increase a user's sensitivity to a drug. Delta FosB slowly builds up with each exposure to the drug and remains active in the brain for weeks, long after the CREB effects have faded.

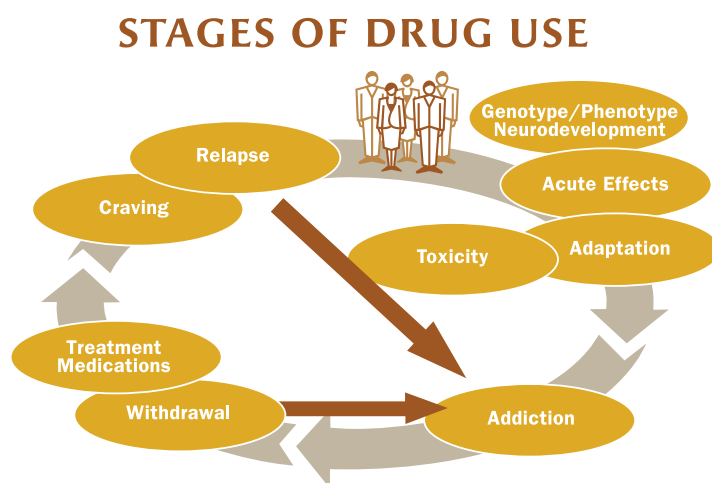
"Delta FosB modulates neurons to increase the rewarding properties of drugs," adds Madras. "This may be the mechanism for prolonged sensitization to certain drugs, an increased drive for drugs, and increased desire to use drugs after they have been withdrawn from the body."

Many scientists believe that the persistent nature of delta FosB and its ability to stay in the brain long after a user has been abstinent – sometimes for years – may contribute to relapse.

A biochemical roadmap of addiction

Madras says that drug addiction involves and changes many neurobiological mechanisms, in addition to CREB and delta FosB. "We don't fully understand all the mechanisms involved in drug abuse," she adds. "More than 100 genes are changed after repeated exposure to cocaine. CREB and delta FosB give us a relative biochemical roadmap of what changes in the brains of drug addicts, but they are only two of a host of possible processes."

Scientists are now using the knowledge gained by understanding some of these neurobiological and neurochemical mechanisms to develop effective clinical therapies to treat drug addiction.



The cycle of addiction. The pathway to addiction is governed by many factors, including the genotype and phenotype of the user, subject-specific response to the acute effects of a drug, to neuroadaptation and to progression of increased frequency of use, binge use and finally addiction. Upon drug cessation in the adapted brain, physical or psychological withdrawal symptoms become prominent, and after these symptoms dissipate, drug craving can set in during abstinence. Treatment can be initiated at any point in the cycle, with brief interventions proving effective during the initial period of use or after frequent use, during the addictive phase, withdrawal and abstinent phase. Relapse to use can be triggered by drug-associated cues, stress and other factors.

The Placebo Effect: Blending the ‘Art’ and ‘Science’ of Medicine



Ted Kaptchuk

SINCE THE 1955 publication of *The Powerful Placebo* by Harvard Medical School (HMS) anesthesiologist Henry Beecher, placebos and the placebo effect have played an integral role in medicine and medical research.

Broadly defined, a placebo – from Latin for “I shall please” – is a treatment that has no specific or physiological effect on an illness. The placebo effect is sometimes described as the effect of an inert pill or sham device.

Ted Kaptchuk, an assistant professor of medicine at the Osher Institute at HMS, has studied the placebo effect for years and recently published studies that shed new light on this often-controversial topic. He considers the idea of placebo to be a challenging oxymoron: the effect of something that has no effect.

“The placebo effect is the underlying structure of all healing interventions,” says Kaptchuk. “It seems that the appearance and imagination of health care – going through the motions and giving dummy treatments without any physiologically active content – affects the reality of health care. All genuine interventions that comprise the ‘science’ of medicine are necessarily intimately linked to the context and ritual of medicine, or what can be called the ‘art’ of medicine. Placebo research tries to put the ritual and art of medicine under the microscope of science. It uses science to study the art of medicine.”

While effective medications and procedures change the course of and help to prevent disease, Kaptchuk’s studies on the placebo effect show that the performance of medical behaviors without their active ingredients also seems to have significant impact on illness and health.

Sham treatments and brain pathways

In a study published in the *British Medical Journal* in February, Kaptchuk and his colleagues examined whether a sham acupuncture device had a greater placebo effect than an inert pill in people suffering from severe arm pain caused by repetitive use. In the first phase of the study, 135 people were given sham acupuncture, while another 135 received a placebo pill. Neither approach proved to have an enhanced placebo effect over the other. Over the next several weeks, half the patients remained on the sham device or placebo (the other half received the active treatment). The patients receiving the sham acupuncture reported a more significant reduction in pain than those receiving the placebo pills.

“The sham device had a greater impact on pain reduction than did the placebo pill,” says Kaptchuk. “We were able to demonstrate that placebo effects can be modulated by the type of placebo given.”

The researchers also found that what patients are told about a procedure’s side effects may have a persuasive influence on the side effects they actually report. Prior to the study, the participants were told they might experience temporary soreness from the acupuncture treatment and sleepiness and dry mouth from the pain medication. Twenty-five percent of those receiving sham acupuncture and more than 30 percent receiving placebo pills reported the same side effects they were told to expect.

“We found that reported side effects entirely mirrored the information provided to participants,” the investigators wrote.

In another study, published in *The Journal of Neuroscience* in January, Kaptchuk and his colleagues used functional magnetic resonance imaging to examine the brain networks that are activated by sham acupuncture. They found that placebo effects are particularly associated with specific brain regions, including the anterior insular cortex, an area of the brain that is activated by bodily feelings, including pain, and emotional stimuli. The study builds upon other studies that have discovered different pathways in the brain, involving the prefrontal cortex, striatum and brainstem, for the processing of placebos.



“FIND OUT WHO SET UP THIS EXPERIMENT. IT SEEMS THAT HALF OF THE PATIENTS WERE GIVEN A PLACEBO AND THE OTHER HALF WERE GIVEN A DIFFERENT PLACEBO.”

Sidney Harris. *Stress Test: Cartoons on Medicine*. New Brunswick, NJ: Rutgers University Press, 1994: p. 59.

“The divergent brain pathways uncovered by different placebo investigators using different placebo procedures,” says Kaptchuk, “suggests that the neural mechanisms underlying the placebo effect may vary depending on the context in which the placebo is administered. Besides magnitude of placebo effect, which was examined in our first study, this study suggests that the brain pathways of placebo may differ depending on the type of ritual.”

Rituals in medicine

All medicine, says Kaptchuk, is embedded in rituals of behaviors and words that are barely recognized because they are less spectacular than medications and perhaps because they are so common. Included among these are countless repetitive behaviors that are not part of the “science” of the treatment surrounding the dispensing of effective drugs. Kaptchuk is currently studying the delivery of different “doses” of the patient–physician relationship – attention, positive expectation, compassion, attentive listening, thoughtful silence, etc. – to see whether placebo effects and the patient–physician relationship can be delivered in a manner analogous to “dose dependent.”

“For example,” he says, “these rituals can include the unique behaviors of the trust and intimacy of the patient–physician relationship, seeing diplomas on the wall, or filling out insurance papers. The act of dispensing pills or performing a procedure may be an especially powerful ritual. Our studies demonstrate that these rituals have impacts on important health outcomes.”

Kaptchuk and his colleagues at other Harvard-affiliated teaching hospitals are now conducting clinical trials to determine the placebo effect’s role on different diseases. In the laboratory, they are gaining a greater understanding of the neurobiological and biochemical mechanisms of placebos.

“My research on placebos,” he says, “bridges the gap between what is usually considered the art of medicine – ritual and the patient–physician relationship – and the science of medicine – quantitative outcomes and measurable physiology. The imagination seems to have a role in health care, and it can be measured clinically and examined mechanistically.”

A Cup of Coffee for the Brain

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While we hear about many of its detrimental effects – including the above-mentioned stimulant effects – recent studies have shown that caffeine can have beneficial effects, as well.

Researchers at the Harvard School of Public Health have shown that men who drink four to five cups of caffeinated coffee daily cut their risk of developing Parkinson’s disease in half compared to those who drank little or no coffee (women who drink one to three cups a day cut their risk in half). Parkinson’s disease is a progressive neurodegenerative disease in which the brain’s dopamine cells are destroyed, causing muscle tremor, slowing of movement and weakness. Other studies have demonstrated caffeine’s potential protective effect against Alzheimer’s disease.

Caffeine, memory and learning

A study recently conducted by the U.S. Army showed that while caffeine cannot change a person’s intelligence, it can heighten mental performance, including reaction time, attention and logical reasoning.

In his laboratory at BIDMC, Saper is studying the effects of adenosine on spatial memory and hippocampal long-term potentiation. Spatial memory refers to our memory of our spatial environment and helps us to navigate around familiar surroundings. Long-term potentiation (LTP) is a form of neuronal plasticity – or long-term changes in the brain – that may form the biological basis of certain kinds of memory.

Saper’s work indicates that spatial memory and hippocampal LTP are impaired with prolonged sleep loss. He and his colleagues found that hippocampal LTP can be partially restored with an adenosine inhibitor, though they did not specifically use caffeine in their study.

“We have found that loss of sleep causes an increase of adenosine in the hippocampus, which blocks learning activity there,” he says. “A cup of caffeine at night, while you are studying, may therefore have a restorative effect on learning, but it does not increase it to the same level as a hippocampus that has had plenty of sleep.”

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CORRESPONDENCE/CIRCULATION

Landmark Center
401 Park Drive, Suite 22
Boston, MA 02215

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HARVARD MAHONEY
NEUROSCIENCE INSTITUTE

Council Members:

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Edward F. Rover
Daniel C. Tosteson, MD

Writers, Editorial Advisors:

Scott Edwards, Tamsen S. McMahon

Design:

Gilbert Design Associates, Inc.

Harvard Mahoney Neuroscience Institute

Landmark Center
401 Park Drive, Suite 22
Boston, MA 02215

Internet address:

www.hms.harvard.edu/hmni

Email address:

hmni@hms.harvard.edu

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