ON THE BRAIN

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Acromagely

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effects, must be given life long, and can cost more than $30,000 a year. A form of a normal brain hormone, somatostatin, is most commonly used and can restore hormone levels to normal in about half of patients. A newer medication, which blocks the effects of growth hormone, may also be used but does not treat the tumor itself. Finally, radiation therapy may be used for patients not cured by surgery and who do not respond to medications. This therapy can often take years to be effective. All forms of radiation therapy damage the normal pituitary gland and, rarely, other brain tumors can develop many years after therapy in radiated brain areas.

Although research has provided a number of new diagnostic approaches and treatment options, this disease has received little attention in terms of public awareness or research priority. Given the profound effects of this rare disease on health and quality of life for patients, increased attention to acromegaly, and patients suffering from it, is well warranted.

ON THE BRAIN
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THE HARVARD MAHONEY NEUROSCIENCE INSTITUTE LETTER

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Harvard Mahoney Neuroscience Institute Prize

The Eighth David Mahoney Prize Presented to Emmy Award Winning Journalist Charlie Rose

On Wednesday, October 29, 2008 the Harvard Mahoney Neuroscience Institute (HMNI) awarded the eighth David Mahoney Prize to Charlie Rose, Emmy award–winning journalist. Hildegarde E. Mahoney, HMNI Chairman, presented the award to Mr. Rose at a dinner at The Pierre in New York City.

"Once again, this is an evening of celebration, of passion, gratitude, and hope," said Mrs. Mahoney to the approximately 130 guests attending. "Celebration of the progress that has been made and continues to be made, celebration of the people who have made this progress possible, passion for the work that has yet to be done, gratitude for the many possibilities that are being discovered every day, and hope for the future."

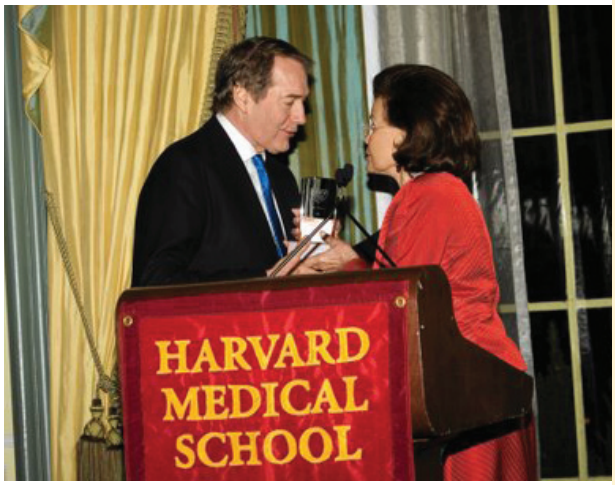
The event began in The Pierre's Wedgewood Room with a lively discussion between Harvard University Provost Dr. Steve Hyman, Nobel Laureate Eric Kandel, and Charlie Rose. Topics ranged from memory and its loss, autism diagnosis and treatment, exercises to promote brain health, and a discussion about how to attract young scientists to the field of neuroscience. A comprehensive question and answer period moderated by Edward Rover, President of the Charles A. Dana Foundation and a council member of HMNI, concluded the symposium.

Guests were invited to a reception in the Regency Room, where the Bob Merrill (H '81) Trio performed. Dinner followed in the Cotillion Room, beginning with an invocation by the Reverend Gerard Reedy of Fordham University in New York. The keynote presentation was offered by newly appointed Chair of Neurobiology at Harvard Medical School, Dr. Michael Greenberg, whose groundbreaking work on the genes and pathways behind neurological disorders have changed the way we think about disease and treatment.

Following Dr. Greenberg's remarks, Mrs. Mahoney spoke about the work being done at the Harvard Mahoney Neuroscience Institute and introduced the prize recipient, Charlie Rose. "Tonight the tradition continues because we honor a man, who like David, is a true believer in making a difference," she said, "who continually gives back by enlightening the nation thanks to the many dedicated scientists he invites on his nightly interview program. That man is none other than the Emmy award–winning television journalist, Charlie Rose."

Mrs. Mahoney then presented Rose with a crystal pillar from Steuben, engraved with his name, the year of the prize, and the dedication: "For building a bridge between the public and scientists dedicated to brain research by the Harvard Mahoney Neuroscience Institute."

The David Mahoney Prize was established in 1995 to recognize individuals who have helped increase public awareness about brain science and about disorders of the nervous system. Past recipients include President and Mrs. Ronald Reagan in 1995, Mike Wallace in 1996, Roone Arledge in 1998, Larry King in 2000, William Safire in 2002, Senator Ted Stevens in 2004, and Dr. James Watson in 2006. The next prize will be awarded in 2010.



Charlie Rose receiving the eighth David Mahoney Prize from Hillie (Mrs. David) Mahoney.

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HMNI Prize Dinner and Symposium at the Pierre Hotel

(L–R) Dr. Steven Hyman, Dr. Eric Kandel, and Charlie Rose in discussion at a Symposium prior to the Prize dinner.

William Safire and Ellen (Mrs. Arthur) Liman.

(L–R) Charles A. Dana III, Hillie (Mrs. David) Mahoney, Roz (Mrs. Henry) Walter, and James Crowley.

(L–R) Dr. Steven Hyman, Edward Rover, Dr. Eric Kandel, and Charlie Rose.

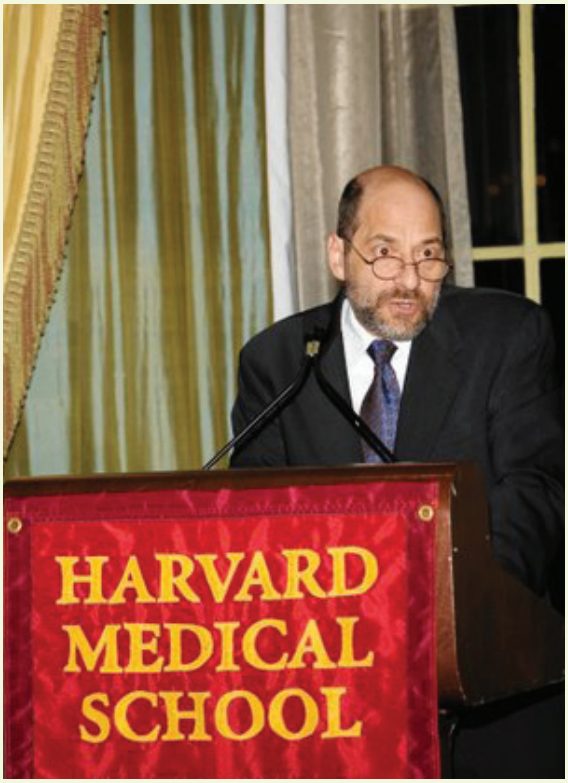
Bob Merrill, H'81, provided the music during cocktails.

The David Mahoney Prize, a Steuben Glass Tower on a wooden base.

Frederick Eberstadt and Barbara (Mrs. Steven Hyman) Bierer at the dinner.

The Hon. Joseph A. Califano, Jr. with Magda (Mrs. Edward) Bleier during dinner.

(L–R) Suzanne (Mrs. William McDonough), Ed Rover, and Tobey (Mrs. Fanklin) Roosevelt.



Dr. Michael Greenberg, Chair of Neurobiology at Harvard Medical School, giving the keynote address.

Nobel Laureate, Dr. Eric Kandel with Amanda Burden.

Acromegaly

This article was written by **Dr. Anne Klibanski,** MD, Director of the Neuroendocrine Unit at Massachusetts General Hospital. She is also a Professor of Medicine at Harvard Medical School and, in May 2009, will be appointed to the Chair in Neuroendocrinology that Mr. Leo Guthart has endowed at the Medical School.

Acromegaly is a relatively rare neurological disease that can be treated successfully in a number of ways if the disease is correctly diagnosed. Unfortunately, there is very little awareness of this disease within the medical community. As a result, the average time from onset to diagnosis is 10 years, the amount of time necessary for symptoms to become so obvious that relevant blood tests and brain scans are performed. More awareness of this disease within the medical community can result in much earlier diagnosis, treatment, and consequent reduction of the many co-morbidities that result from acromegaly. If untreated, life expectancy is markedly curtailed. If properly treated, life expectancy can return to normal.

The term acromegaly comes from the Greek words for "extremities" and "enlargement," reflecting its most characteristic feature—abnormal growth of the hands and feet. The symptoms of acromegaly are multiple as this disease affects all organ systems. Facial changes, which can be subtle over time and therefore may go unnoticed, include an enlarged jaw, broadened facial features, and increased dental spacing. Arthritis, joint problems, fatigue, increased sweating, carpal tunnel syndrome, poor sleep, and reproductive symptoms are all common. In many cases, these symptoms result in a diagnosis of fibromyalgia or fatigue syndrome or are attributed to "aging," and the root cause of the disease is not treated. Shortness of breath and edema can occur due to enlargement of the heart, with subsequent heart failure. Because it is a rare disorder and development of these clinical features is insidious, patients typically have acromegaly for many years, and see many physicians, before the correct diagnosis is made.

Despite acromegaly's complexity and its striking and often permanent effects, the diagnosis itself is relatively easy to make. Blood tests for growth hormone levels and a liver hormone, IGF-1, that increases under the influence of growth hormone, can make the diagnosis. Brain imaging using MRI is also critical. The major obstacle is not that there are no tests to diagnose acromegaly but rather the fact that most physicians are not knowledgeable enough about this disease to order the appropriate tests.

Acromegaly is a rare disorder that usually results from a growth hormone producing a tumor in the pituitary gland. The pituitary is a small gland at the base of the brain that makes hormones that control many endocrine glands and metabolic functions. These tumors, called adenomas, are typically large enough to cause neurologic problems such as headaches and vision changes. Although it is estimated that about 60 out of every million people suffer from the disease at any time, the diagnosis is often missed, and these numbers underestimate the true frequency of the disease. It usually takes patients many years after disease onset to be diagnosed. Untreated, life expectancy is decreased by an average of 10 years. The most serious health consequences of acromegaly are type 2 diabetes, hypertension, increased risk of cardiovascular and cerebrovascular disease, sleep apnea, arthritis, infertility, and bone loss. Patients with acromegaly are also at increased risk for colon polyps, which may develop into colon cancer if not removed. Importantly, disfiguring facial and body changes can have profound effects on quality of life.

These tumors cause neurologic problems by affecting nearby brain structures and nerves, resulting in visual field loss and cranial nerve damage. Pressure caused by the tumor can cause debilitating headaches. As the tumor expands, the normal pituitary may be compromised so that the pituitary hormones controlling the thyroid gland, which makes thyroid hormone, the adrenal glands that make cortisol, and the reproductive glands may all be affected. Some adenomas grow slowly, but others grow more rapidly. Younger patients tend to have more aggressive tumors. In most cases, these tumors are not inherited but rather result from an acquired mutation in cells of the normal pituitary gland. Research has shown that this mutation, acquired after birth, leads to pituitary cells escaping from the normal inhibitors to tumor formation. Once the process of unchecked cell multiplication in the pituitary starts, a tumor is formed and grows.

Currently, treatment options include neuro-surgical removal of the tumor, medical therapy, and radiation therapy. Most patients require two or more such therapies. Goals of treatment are to restore normal hormone levels, alleviate symptoms, and treat the tumor mass. Neurosurgery is the first option. However, for most patients, surgical cure occurs less than 50 percent of the time as the tumor is large by the time of diagnosis. In addition, these results are from top neurosurgical centers and much lower for most surgeons. There are several options for medical therapy which involve monthly or daily injections. These medications have side-

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Obesity and the Brain

This is the second in a series of articles on how internal and external forces affect the brain.

Obesity, which causes an estimated 300,000 premature deaths in the United States each year, has far-ranging effects on our health—from high blood pressure and diabetes to arthritis and cancer. While many people consider obesity to be an eating disorder, research increasingly points to the brain's role in regulating how obesity occurs. Yet, scientists are unclear just what the connection is between obesity and the brain and how the strain of obesity and overweight affect brain function.

Right brain hypothesis of obesity

The control of appetite is a function of the brain's hypothalamus, which regulates a number of basic bodily functions. A collection of neurons in the hypothalamus, called the arcuate nucleus, coordinates our need to eat in relation to how well our body is fed via communication between the gastrointestinal system and fat-storing tissue. Two circuits within the arcuate nucleus promote or suppress appetite, helping to regulate our nutritional state and balance our body weight, respectively.

In addition, the brain's limbic system—the "pleasure center"—contains information on food preferences that we have acquired based on taste and smell. Our sensory organs send signals to the brain, causing the release of dopamine, which plays an important role in motivation and reward.

"We associate certain foods with certain tastes," says Harvard Medical School instructor in neurology Miguel Alonso, MD, MSc, of Beth Israel Deaconess Medical Center's Berenson-Allen Center for Noninvasive Brain Stimulation, "so eating really starts before we even put food in our mouths."

Alonso, along with HMS neurology professor Alvaro Pascual-Leone, MD, recently developed what they call a "right brain hypothesis" for obesity. That is, the right hemisphere of the brain's prefrontal cortex (PFC) plays a critical role in the cognitive control of food intake, which refers to our capacity to process information and make decisions about the food we eat.

A certain amount of activity in the right PFC is required to control our appetite. According to a study by Alonso and Pascual-Leone, published in the April 25, 2007 issue of the *Journal of the American Medical Association*, in obese people, activity in this area of the brain is diminished, and this could lead to poor food choices and thus contribute to obesity.

"The right PFC is not necessarily damaged," says Pascual-Leone, "but it is working too little."

In addition, the right PFC is critical for "moral cognition," the process by which we ascribe "good" and "bad" values to certain foods, influencing our decisions about what to eat. According to their hypothesis, dysregulation of the right PFC then could result in a "failure to appropriately weigh the adverse consequences of indulging in a bad diet," Pascual-Leone says, and lead to behaviors that contribute to obesity.

Obesity and cognitive decline

While the overall health effects of obesity are well documented, several studies suggest that excess weight can also increase the risk of cognitive decline. Researchers at Boston University found in a 2003 study that obesity and high blood pressure, both alone and in combination, have a negative effect on cognitive function in men but not in women. In 2004, scientists at the San Francisco Veterans Affairs Medical Center linked cognitive decline to metabolic syndrome—a cluster of conditions, including high blood pressure, high cholesterol, insulin resistance, and abdominal obesity—that occur together and increase the risk of heart disease, stroke, and diabetes. About 30 percent of study participants with metabolic syndrome and a high level of inflammatory markers in the blood stream showed significant cognitive decline on standard neurological tests.

"Our current diet and activity patterns may be placing humans in the range beyond what the hypothalamus was developed to regulate," says Saper. "Like the rest of our brain, the hypothalamus evolved in a world where humans were hunter-gatherers, not sedentary agriculturalists…"

Clifford Saper, MD, PhD, the James Jackson Putnam Professor of Neurology and Neuroscience at HMS and chief of neurology at Beth Israel Deaconess Medical Center, is not convinced that obesity has been demonstrated to have any effect on brain function, other than being a risk factor for cardiovascular disease. Atherosclerosis (the buildup of blood flow reducing plaque on artery walls) and small strokes due to high blood pressure may take a toll on mental faculties, including memory, attention, learning, and decision-making. High cholesterol, along with high blood pressure and family history, is a risk factor for Alzheimer's disease.

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Keeping the Brain Healthy and Sharp as We Age

Like almost every one of our body systems, our brains, too, are on a downward slope as we age. But, like those other systems, how we care for our brain as we get older may be key for keeping our minds healthy and sharp in our later years.

Several physiological changes occur to our brains as we get older, but most notably they shrink. Our brain loses anywhere from 5 percent to 10 percent of its weight between the ages of 20 and 90, with the most pronounced loss occurring beginning around age 60. Certain areas, like the frontal lobe (where most of our mental abilities are stored) and the hippocampus (the seat of our memory), shrink more than others. The brain's outer surface, or cortex, thins slightly as we get older, primarily from a decrease in synaptic connections (which begins when we're around 20 years old) that allow brain cells to communicate with one another.

Scientists at Harvard Medical School, led by pathology professor Bruce Yankner, MD, PhD, have shown that, after age 40, brain tissue exhibits genetic changes that may contribute to the aging process, including cognitive decline.

In addition, studies have linked aging with decreases in white matter, which contains myelin, a substance that also helps brain cells communicate. Changes in white matter alter our speed of cognitive processing and, thereby, impact multiple cognitive processes, including memory, attention, problem solving, and decision making. And, our aging brains produce fewer neurotransmitters, particularly dopamine and acetylcholine, chemicals that carry messages between brain cells.

"These changes occur across the board," says Aaron Philip Nelson, PhD, an assistant professor of psychology at Harvard Medical School and chief of neuropsychology at Brigham and Women's Hospital, "but the rate and pace of change differs among individuals depending on genetic and environmental factors. Some people are genetically blessed, while others don't have it so well."

Building in redundancy

When we are born, our brains have many more neurons than we keep, many of which may be unused. Scientists are not certain why we have so many extra neurons, but many believe this redundancy is built into our brains for protection. Throughout our lifetime, however, we may lose some of that protection.

"Under normal circumstances," says Sharon Inouye, MD, MPH, a professor of medicine at HMS and director of the Aging Brain Center at Hebrew SeniorLife's Institute for Aging Research, "one can continue to function despite this loss of redundancy. As we get older and our system gets more stressed from illness, medications or surgery, our system gets overwhelmed and our brains begin to fail."

Use it or lose it

Despite the brain's downward slope with age, the news is not all bad. Under a steady state, says Inouye, many of the changes to our brain do not cause any significant problems—as long as we maintain our health. With stress and disease, however, these changes can lead to cognitive impairment.

The question, then, is how to keep these preventable effects from occurring. What can one do to keep the brain healthy as one ages?

Both Nelson and Inouye are proponents of the "use-it-or-lose-it" phenomenon, one facet of the theory of cognitive reserve developed by Columbia University neuroscientist Yaakov Stern. The idea

behind the theory is that one builds a reserve of cognitive ability that is essentially resistant to neuropathology over a lifetime of engagement in mentally stimulating activity, which is especially important when we reach our 60s. In part, the theory aims to explain why some people with Alzheimer's disease pathology (an accumulation of plaques and tangles in the brain) function better than others with an equal degree of disease burden.

"We can see two individuals, who, on imaging, have equally bad disease, but one does okay while the other does not," says Nelson. "That's cognitive reserve; the one with the greater cognitive reserve resisted the [AD] pathology."

Cognitive reserve can be built up over one's lifetime by remaining healthy and intellectually engaged. "By remaining engaged intellectually," says Nelson, "you continue to create new memories, use

your synapses, strengthen neuronal connections, and build cognitive reserve. That, in turn, helps you develop a greater resistance to pathology."

Inouye says that MRI studies show that people who are mentally and physically active use their brains in different, more efficient ways than those who are disengaged. In addition, she adds, they are able to perform new tasks more efficiently using a smaller portion of their brain.

"If you use your brain a lot, then your brain knows when you need to use it and it's ready to be used," she says. "Animal models show us that parts of the brain function less efficiently if they're not used. Those parts of the brain are not open for business. Our brains are efficient that way."

The question is, can you start up those areas after they've been dormant? Scientists are not certain this can be done, so Inouye recommends "using your brain—challenge it, keep it going."

Just like mental activity, physical exercise and a healthful diet are essential for a healthy brain. Exercise and nutrition, says Nelson, help the brain because they can reduce the likelihood or severity of cardiovascular risk factors, such as high blood pressure, high cholesterol and diabetes, which can ravage the brain. In addition, exercise can contribute to cognitive reserve. A University of Illinois study found that even a short phase of moderately strenuous exercise like brisk walking improves cognitive function in older adults.

Other ways of optimizing brain health include avoiding smoking or excessive alcohol consumption, which can impair brain function. Regular health–care screenings for high blood pressure, high cholesterol, and diabetes can also aid in keeping the brain healthy.

Societal costs are "staggering"

While the health consequences of brain decline are significant, the economic and social implications are staggering. More than 5.2 million Americans today are living with Alzheimer's disease, the sixth leading cause of death in the country, according to the Alzheimer's Association. The direct and indirect costs of Alzheimer's disease and other dementias is more than $148 billion annually.

In addition to the financial costs of the disease, Alzheimer's and other forms of dementia carry a considerable social burden, with the burden significantly placed on caregivers who are often spouses or other family members.

"The real issue," says Inouye, "is that our population is aging, so these problems will expand in the future. We need to do something about it quickly; there's no health epidemic of greater significance in the country."

While some people—because of genetics or environmental factors—are destined to develop Alzheimer's or other neurodegenerative diseases that affect brain function, others who are not genetically predisposed to these diseases are in a much better position to preserve brain function as they age.

"You need to use your brain your entire life," says Inouye. "The time to start is before now, but it's never too late."

Obesity and the Brain

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"You have to recognize," says Saper, "that epidemiological evidence that obesity elevates the risk for cognitive decline does not necessarily mean that obesity causes cognitive decline."

It may be, he adds, that cognitive decline could be causing obesity. That is, as people with ongoing cognitive decline become less interested in life and less active, they may gain weight or fail to try to control their weight as they did when they were healthy. Another possibility is that a neurodegen–erative disorder that causes loss of cognitive function may also disrupt the feeding circuitry in the brain and cause obesity.

Saper says the social and cultural effects of obesity may outweigh risk of cognitive decline. Changes in the way we live our lives and our levels of activity may play a significant role in weight gain. A researcher at the University of Chicago found that restricting sleep to four hours per night increases appetite, especially for sweet and fatty foods, in healthy young men.

"Our current diet and activity patterns may be placing humans in the range beyond what the hypothalamus was developed to regulate," says Saper. "Like the rest of our brain, the hypothalamus evolved in a world where humans were hunter–gatherers, not sedentary agriculturalists. To the extent this increases cardiovascular risk, I think it is dangerous. There is also probably a price to pay in deterioration of the skeleton. Beyond that, I am not persuaded that obesity is a risk factor for such things as cognitive decline."