

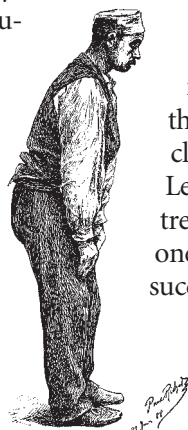
ON THE BRAIN



Present and Future Treatment of Parkinson's Disease

In 1817 a British physician, James Parkinson, published a monograph called "Essay on the Shaking Palsy." That title describes the major symptoms of the disease that now bears his name: tremor (shaking) and immobility (palsy). Parkinson's disease is usually a disorder of old age, although it can begin as early as the 20s. The condition gradually becomes worse, at different rates in different people. Some have only mild symptoms for many years, but a few progress rapidly to an invalid condition.

Often the first noticeable symptom is a tremor of one hand that disappears temporarily during voluntary movements. The other symptoms appear so gradually that they may be present for months or years before the diagnosis is considered. People with Parkinson's disease have difficulty starting and completing movements. Their posture becomes stiff, and they may freeze in mid-motion as though the body is resisting the brain's commands. They walk hunched forward in a shuffling gait without a normal arm swing (as shown above), often losing their balance and stumbling. They can no longer execute the rapid movements needed for fine motor control, such as shuffling cards or buttoning clothes. Their handwriting becomes smaller, with words more crowded together. Facial muscles may stiffen too, causing a loss of expression that gives the face a mask-like appearance. Some patients have difficulty swallowing and lose the capacity to blink normally.



Treatment Comes From Understanding the Disease Process

Today we have a fairly good idea of what is wrong. Nerve cells in a part of the brain called the substantia nigra are dying and producing less of a chemical neurotransmitter, dopamine, that is needed to control body movements. Under a microscope, the cells can be seen to contain clumps of abnormal tissue called Lewy bodies. We now have effective treatments for Parkinson's disease — one of contemporary medicine's great success stories. A patient's life

expectancy can be extended 10 to 15 years with a drug called Sinemet — a combination of L-dopa, a substance the body uses to manufacture dopamine, and carbidopa, which prevents the liver from breaking L-dopa down before it reaches the brain. Taken two to four times a day, Sinemet works for a person with Parkinson's disease the way insulin works for a person with diabetes.

Although Sinemet allows many patients to live useful lives for years, they may need higher or more frequent doses as time passes, and there are

(Continued on page 4)

A Tribute In Appreciation of David J. Mahoney

David Mahoney died on May 1, 2000 at the age of 76. With his death, brain science everywhere lost a passionate advocate, but his loss is particularly felt by the Institute that bears his name at the Harvard Medical School.

David Mahoney spent all of his early years working in marketing and, by the 1970s, in his capacity as Chairman of the conglomerate Norton Simon Inc., was considered one of corporate America's most widely watched business leaders. His second career, as a fighter for neuroscience, began in the mid 1980s.

He had come to realize that problems with the brain underlay many of the disorders he cared most about — disorders such as depression, addiction and memory loss. And he felt

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HMNI Honors Larry King

The Harvard Mahoney Neuroscience Institute at Harvard Medical School has named Larry King the recipient of the fourth David Mahoney Prize. The award will be presented to Mr. King at a dinner in his honor on October 23rd in New York.

King is being honored for his outstanding contribution to increasing public understanding about the brain and brain research. In particular, his interest in stroke, migraine, and depression has focused nationwide attention on these conditions. "By using television to present important topics about brain health and brain disorders, Larry has raised public awareness of the critical role brain research can play in finding effective treatments and therapies," explained Hillie Mahoney, who will be presenting the award to Larry King.

Larry King has been in the interviewing business for more than 40 years. With more than 30,000 interviews to his credit, King is one of the most respected personalities in the industry. Dubbed the "most remarkable talk-show host on TV - ever" by TV Guide, the Emmy award winning King hosts Larry King Live, the first worldwide phone-in television talk show and the network's highest rated

program. He also hosts Larry King Weekend for CNN, as well as a series of specials for CNN's sister network, TNT. In addition, he writes a weekly column for USA Today and has written 11 books.

A symposium on Stroke, moderated by Larry King, will be held in conjunction with the dinner. Participants in the symposium will be: Dr. Louis Caplan, Professor of Neurology at Harvard Medical School and Director of the Cerebrovascular Unit at Beth Israel/Deaconess Medical Center; Dr. Anne Young, Julieanne Dorn Professor of Neurology at the Harvard Medical School and Chief of Neurology at Massachusetts General Hospital; and Dr. Emilio Bizzi, Eugene McDermott Professor of Brain Sciences and Human Behavior at Massachusetts Institute of Technology.

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. Larry King joins a list of distinguished recipients of the David Mahoney Prize, which includes: Former President Ronald Regan and his wife Nancy; Mike Wallace, interviewer and co-editor of the CBS television news pro-



Larry King photo: Gregory Heisler

gram 60 Minutes; and Roone Arledge, former Chairman of ABC News.

The Harvard Mahoney Neuroscience Institute, founded in 1990 by the late David Mahoney, and his wife, Hillie, maintains an ongoing effort to increase public awareness of the critical importance, and the promising future, of neuroscience research. The Institute seeks to make the public aware of the pace of scientific discoveries about the brain, the importance of these discoveries, and to increase the funding that makes this possible. □

From the Director

As the new director of the Harvard Mahoney Neuroscience Institute, I would like to welcome readers to the renewed Institute newsletter. I am honored to be the successor of Dr. Gerald Fischbach, who is now serving as Director of the National Institute for Neurological Diseases and Stroke at the National Institutes of Health. I am Professor of Psychiatry and Neurology at Harvard Medical School and Director of the Gerontology Research Unit at Massachusetts General Hospital. My special

field of interest is aging — the changes in cognitive and brain function that occur as we grow older and diseases of older persons, such as Alzheimer's disease.

The Institute is most fortunate to have an outstanding and committed Board of Directors. We are indebted to Hillie Mahoney, Ed Rover and Dr. Daniel Tosteson, who have helped guide and develop the Institute since its inception. Dr. Joseph Martin, the Dean of the Harvard Medical School, joined the board two years ago. As an

internationally recognized neuroscientist, his support and guidance are greatly valued. Most recently, Dr. Carla Shatz, newly appointed Chair of the Department of Neurobiology, and Herb Siegel, President of Chris-Craft Industries, Inc. joined the Board. Having known them personally for a number of years, I know the Institute will benefit greatly from their energy and wisdom.

Since the Harvard Mahoney Neuroscience Institute was founded by David and Hillie Mahoney in 1990,

(Continued from previous page)

the world of neuroscience has undergone great changes, and there has been remarkable progress in many areas of brain research. Scientists are making exciting new discoveries, and we are already beginning to see the fruits of their work in the treatment of brain disorders — moving from the laboratory bench to the patient's bedside. I am deeply saddened by David Mahoney's recent death, but know that he was passionate in the belief that these discoveries would lead to better ways of preventing and treating the disorders of the brain so many of us care about.

We have decided to change the format of the newsletter to emphasize

this connection between new findings and improved treatment of brain diseases, concentrating on one disorder or group of disorders in each issue. We'll discuss the disorder's effects on the brain, its current treatments, and new treatments that are under development, with a particular focus on their relationship to recent results in basic research. We will pay special attention to the genetics of each disease, its possible environmental causes, and their interaction. Where we can, we'll also try to say what we think the future holds.

We intend to discuss not only the neurological aspect of these disorders and the brain science itself, but also the psychiatric aspects — whether these disorders produce psychiatric

conditions and how the patient and the patient's family and friends can best cope with the emotional and social consequences of the illness. The subject of the present issue is Parkinson's disease. The next issue will be about Attention Deficit Disorder in children and adults.

We are eager to hear from our readers so we can address questions raised by the information in the newsletter. We would also like to learn what you think of the new format and which topics you would like us to cover. In future issues we hope to be able to answer readers' questions suggested by the articles. □

— Dr. Marilyn Albert

In Appreciation of David J. Mahoney

(Continued from page 1)

that Neuroscience was on the verge of making great progress in the treatment of these problems. He believed that if more people knew about this, and supported it in whatever way they could, progress would come about even sooner.

Neuroscientists who watched David Mahoney make this vision a reality, found it an inspiring experience. Along with his wife Hillie, David Mahoney founded the Harvard Mahoney Neuroscience Institute in 1990, in order to increase public awareness of neuroscience and to provide fellowships for neuroscientists in their early careers. In 1992, he spearheaded a world-wide alliance of neuroscientists, by establishing the Dana Alliance for Brain Initiatives and, subsequently, the European Dana Alliance on the Brain. Through these organizations, he engaged the energy of preeminent neuroscientists in the task of communicating the progress and promise of neuroscience. Brain Awareness Week, one of the products of

this alliance, last year involved 1100 organizations from 41 countries around the world.

David Mahoney believed that "Some of us may get cancer. Some of us may get heart disease. But every last one of us will be affected by a brain disorder. And brain research is the answer." By 1993, he was called by the New York Times, "one of the foremost lay experts in neuroscience". In recognition of his singular contributions to brain science, he was posthumously awarded the first Mary Woodard Lasker Leadership in Philanthropy Award for "visionary leadership

David will always be remembered not just for his energy, enthusiasm and drive, but for his quite extraordinary capacity for friendship and his ability to encourage others to rise above themselves.

— Max Cowan

in educating the public and the donor community about the importance of brain research and for directing funds for the support of neuroscience."

One of the most remarkable things about the many tributes to David



David Mahoney photo: Cheryl Rossum

Mahoney, since his death, has been the comments about his qualities as a person, as well as a leader. Max Cowan, Former Vice President and Chief Scientific Officer of the Howard Hughes Medical Institute, summed it up perfectly. "For many of us, David will always be remembered not just for his energy, enthusiasm and drive, but for his quite extraordinary capacity for friendship and his ability to encourage others to rise above themselves." □

some serious side effects. If the dose is too high, many patients become confused and some have hallucinations. Another common side effect is inability to keep the arms, legs, or lips still; sometimes there are writhing movements known as dyskinesias.

Every Treatment has Limitations

Because cells in the substantia nigra continue to die, the effects of Sinemet usually begin to wear off after 5 or 10 years. The response of patients becomes unstable, and their symptoms may swing wildly, from slow movements and stiff joints to twitching limbs and inability to keep the legs still. During this phase doctors have to adjust the medication individually by trial and error.

Eventually Sinemet may no longer work, no matter how the dose is adjusted. Adding other drugs that enhance the activity of dopamine may help for a while. A recent experiment indicates that one such drug, ropinirole (Requip), may work as well as Sinemet, at least for the first five years, when taken either alone or in combination with a low dose of L-dopa. The main advantage of ropinirole is a lower rate of dyskinesias. But whatever medication they are taking, some patients eventually find that it is no longer doing much good. At that point doctors may consider surgery or transplantation of brain tissue.

The development of these techniques have been greatly aided by recent advances in basic research. Dr. Anne Young, Chief of Neurology at Massachusetts General Hospital and an expert on Parkinson's disease, says, "There has been an unbelievable change in the technology that can be applied to this disorder." She adds that as little as five years ago, "We were wandering in the wilderness, but now we have a clear road. We just have to

figure out what kind of transportation to use."

Breakthroughs in Research and Technology

Some of our new understanding comes from a chance observation by doctors who were treating heroin addicts. Certain young addicts developed classical symptoms of Parkinson's disease, and it turned out that they had recently taken a new street drug contaminated during its manufacture with a chemical called MPTP. Researchers soon discovered that

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the senses and intellects being uninjured.

Shaking Palsy (*Paralysis Agitans*) 1817

MPTP is a poison that kills the same brain cells affected by Parkinson's disease. Naturally, this increased the search for environmental toxins that resemble MPTP as possible causes of the disease. So far, patients have not shown a common pattern of exposure to drugs, medication, or any other substance in the environment. But now one can test new theories and new therapies, including surgery and transplantation, by giving MPTP to animals and analyzing their responses.

Surgery on human beings with Parkinson's disease has become possible because we now know how to create accurate images of the living brain and record distinctive patterns of signals from specific brain cells. Using these technologies, surgeons can damage precisely the part of the brain that is issuing misleading signals and causing symptoms. The technique is

Ultimately, we hope to learn how to do what no present treatment can accomplish — prevent the degeneration of nerve cells in the substantia nigra.

known as stereotactic surgery, and it is performed with a probe no bigger than a pencil lead. Because the usual target is a group of cells called the globus pallidus, the operation is sometimes called a pallidotomy. Results have often been spectacular in the short run, but we still don't know how long the effects will last and which patients or symptoms will be helped most. Recent research suggests that slowed movement and balance are affected less than tremors and dyskinesias. Some surgeons have been targeting another group of cells, the subthalamic nucleus, with encouraging preliminary results. This operation is called a thalamotomy.

If stereotactic surgery is performed on both sides of the brain, a patient's ability to speak may be affected, so surgeons usually operate only on the right side. But often that means the symptoms improve only on the left side of the body, which is controlled by the right brain. European surgeons are now trying a different approach. They implant small electrodes in the globus pallidus or the subthalamic nucleus to interrupt abnormal signals. The electrodes can be adjusted as needed (even turned off), and they can be placed on both sides of the brain, helping with symptoms on both sides of the body. It is still too early to say how successful this treatment will be.

Promising New Treatments on the Horizon

The newest therapy for Parkinson's disease is the transplantation of living tissue to replenish the brain's dopamine. Today the most promising source of this tissue is the substantia nigra of a human fetus. It survives and improves the symptoms 30% or 40% of the time, although again we don't know how long the effects will last. Partly because the use of fetal tissue is controversial, investigators are now developing another approach

based on modern genetic engineering. They give the patient's own cells the genetic machinery to make dopamine and then implant them in the brain. So far this procedure has been tested mainly in monkeys. Ultimately, we hope to learn how to do what no present treatment can accomplish — prevent the degeneration of nerve cells in the substantia nigra. One possibility is the use of substances called trophic factors, which are produced by the brain to nourish nerve cells and help them recover when damaged. Researchers are considering the transplantation of cells genetically engineered to secrete a synthetic variant of one of these trophic factors.

In about 10% of cases, Parkinson's disease runs in families and is clearly a genetic disorder. In these patients it usually begins at an earlier age and causes more severe symptoms. The actor Michael J. Fox is perhaps the most celebrated person with an early-onset form of the disease. In some of the susceptible families, researchers have found altered

genes responsible for the changes in the substantia nigra, and they are studying how these genes work in the brain. We do not yet know whether the same mechanisms operate in the more common type of Parkinson's disease, but it is now possible to test new theories by the use of transgenic mice — mice in which the human genes that promote the disease have been implanted before birth. What we learn from these animals should provide clues for treatment and prevention.

Outlook and Exercise are Key

How well a person manages Parkinson's disease depends greatly on attitude and lifestyle. Patients may want to discuss their feelings with a counselor or with groups of other patients. They should always try to keep working as long as possible, and they should not try to conceal the disease—that only causes embarrassment and distress for all— or withdraw from usual activities and contacts because of anxiety about

what people will think. It is especially important to keep moving. Patients need exercise to prevent their joints from freezing, their ligaments from shortening, and their circulation from slowing. They should be careful to put their major joints (ankles, knees, hips, spine, shoulders, elbows, and wrists) through a full range of motion regularly. Walking or swimming is also recommended, and there are a few exercises designed specifically for Parkinson's-related symptoms, such as loss of facial expressions.

New drug treatments are often reported in the newspaper or on TV, and a vast amount of information is available on the Web — not all of it reliable, and some of it supplied by people who are trying to sell something. One reliable source of information is The Parkinson's Web (<http://pdweb.mgh.harvard.edu>) that offers up-to-date information about Parkinson's Disease, including support and treatment resources. □

Parkinson's Disease and Mood Disorders

Parkinson's disease affects over 1 million people in the US, and about half of those afflicted will develop depression as a result. Some researchers believe this is a natural reaction to debilitating symptoms, but others think the disease itself causes changes in brain function that lead to depression.

Anthony P. Weiss M.D., a psychiatrist at Massachusetts General Hospital, is among the latter. "Parkinson's disease and depression are both diseases of the brain," he says. "It's likely that the two are related."

Question: Is depression in people with Parkinson's disease different from depression in general?

AW: Yes, but the diagnosis is a bit tricky because there are no physical tests for depression. We diagnose it by the symptoms, which include lack of sleep (or sleeping too much), lack of concentration, slowed movement, sad-

ness, hopelessness, and even thoughts of suicide. Since Parkinson's disease can also produce some of these symptoms, we focus on low mood in diagnosis.

Question: Does Parkinson's disease cause depression?

AW: There are two schools of thought on this question. The rate of depression among people with Parkinson's disease is very high — at least 30 percent, perhaps as high as 70 percent. In the general population, it is roughly 10 per percent. According to one school, people with Parkinson's disease are simply reacting to their movement difficulties and the resulting social isolation. But depression is much more common among these patients than among people with other disorders that seriously limit physical movement, such as rheumatoid arthritis. Also, the most physically disabled Parkinson's patients are not necessarily the most depressed.



Anthony P. Weiss M.D.

Question: So you believe the brain mechanisms that lead to Parkinson's disease may also be contributing to depression?

(Continued from previous page)

AW: In one neuroimaging study, researchers using PET (positron emission tomography) compared Parkinson's disease patients with and without depression. The depressed patients had lower blood flow and energy consumption in two regions of the brain — the caudate nucleus and the frontal cortex — that have been implicated in mood disorders. This is only one study, and not many conclusions can be drawn from it, but it is provocative. The caudate is part of the basal ganglia, a region long thought to be responsible only for body movements. There is growing interest in the role it plays in mood changes. Parkinson's disease is caused by the loss of dopamine neurons in another area of the brain, the substantia nigra. Neurons from that region have branches that go to the basal ganglia, and particularly into the caudate and the nearby putamen. These areas are connected to the frontal cortex, the seat of judgment and planning. A developing theory is that abnormalities along this pathway contribute to psychiatric disorders, especially schizophrenia, obsessive compulsive disorder, and depression.

Question: How is depression in patients with Parkinson's disease treated?

AW: Ordinarily it is treated just like any other form of depression — with medications, cognitive behavior therapy, and, in severe cases, electroconvulsive therapy. There are some reports of antidepressant medication making tremors worse, but that is not common, and the potential benefits outweigh the risk

Question: What is the most important thing to understand about depression and its relation to Parkinson's disease?

AW: Depression is not a failure on the part of the patient but, most likely, an effect of the disease itself. It is highly treatable, but many physicians do not look for it. One problem is that some patients lose facial expression, so

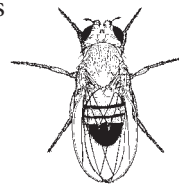
they don't smile. As a result they may seem depressed, but if you ask them whether they are sad, they will say no. That makes it difficult to tell when a Parkinson's patient really is depressed.

Another problem in diagnosis is that many patients develop transient periods of depression because the drugs used to treat their motor symptoms can cause fluctuations that lead to mood changes. Patients feel better when they take the drug, but as it

SYNAPSHOT

Fruit Flies and Parkinson's Disease

New research reported this spring shows that the brain deterioration and symptoms of Parkinson's disease can be reproduced by genetic manipulation in a form of life only distantly related to Homo sapiens. Two Harvard Medical School researchers, Mel B. Feany and Welcome W. Bender, made the discovery by providing fruit flies with the human gene that directs the manufacture of a protein called alpha-synuclein. This protein is the main component of the Lewy bodies that are a characteristic sign of Parkinson's disease.



Ordinary fruit flies do not develop anything that resembles Parkinson's disease, but the transgenic flies created by Feany and Bender are different. When they reach late middle age (about a month after birth), their tiny brains begin to lose dopamine neurons and accumulate Lewy bodies that closely resemble those found in human beings. Their body movements are also affected. Normally, fruit flies that are tapped to the bottom of a test tube will climb to the top. As they grow older, they climb more feebly and eventually fall back before reaching the top. Flies carrying the

human alpha-synuclein gene lose their climbing ability earlier in life.

Instead of the normal human alpha-synuclein gene, some flies were given a mutant type of the gene that is associated with a rare familial form of Parkinson's disease. These flies began to fall back at an even younger age.

Researchers now have at their disposal flies with many of the typical features of Parkinson's disease. In a process that begins late in life, they lose dopamine neurons, accumulate Lewy bodies, and develop difficulties in controlling their body movements. Fruit flies are ideal for experimentation because of their small size and brief lives and our thorough knowledge of their genetic makeup. Researchers can look for other genes which may suppress or enhance the effects of the alpha-synuclein gene or the formation of Lewy bodies. They can try to find out whether the abnormal protein deposits are toxic in themselves or merely byproducts of neuronal death. Of most immediate concern to people with Parkinson's disease, the flies can be used to test new drugs that promise relief for their symptoms.

wears off hours later, their movement problems recur, and then they feel worse. Although they may be sad for a good part of their day, the periods of depression are so brief that they are difficult to describe and treat.

But the main point I want to make is that depression associated with Parkinson's disease, however difficult it may be to diagnose, is similar to the more common forms of depression and can be treated in the same ways. □

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Harvard Medical School*

Writers, Editorial Advisors

James Bakalar, Diana Griffith, PhD

Harvard Mahoney Neuroscience Institute
MGH East (149-9124)

149 13th Street, Charlestown, MA 02129

Internet address: www.med.harvard.edu

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Correspondence/Circulation:

MGH East (149-9124), 149 13th Street
Charlestown MA, 02129

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