



## ATYPICAL PARKINSONISM ASSOCIATED WITH INGESTION OF A COMMON TROPICAL FRUIT

Soursop is the English word for the fruit, though it is guanabana in many Spanish-speaking countries. In the 1500's, Soursop was carried by ships from the Americas to tropical parts of the old world where it became widely distributed from southeastern China to Australia and the lowlands of eastern and western Africa. It grows wild and is cultivated today in Bermuda and the Bahamas, from sea level to an altitude of 3,500 ft throughout the West Indies and from southern Mexico to Peru and Argentina. It is one of the most abundant fruits in the Dominican Republic and one of the most popular in Cuba, Puerto Rico, Colombia and northeastern Brazil. The tree leaves, fruit, bark and roots have a long history of use in natural herbal medicine. The fruit and juice are said to rid the body of worms and parasites, cool fevers; increase the milk of a nursing mother; and relieve diarrhea and dysentery. The crushed seeds are known to eliminate head lice and worms. When swallowed, the seeds are believed to cause uterine contractions inducing abortion. The bark leaves and roots are used to sedate, lower blood pressure and function as an anti-spasmodic, to sooth cramping.

Once the major ingredient in juices, sherbets and cooling shakes, the fruit of the graviola tree is under scientific scrutiny in the island nation of Guadeloupe for its apparent role in an atypical form of parkinsonism. The 2005 edition of Movement Disorders contains a research study conducted by a team of French investigators reporting on a cluster of people suffering from atypical parkinsonism on the island. The Neurology department

of the University Hospital in Guadeloupe, documented 22.5% of the parkinsonian patients fell under the diagnostic umbrella of idiopathic PD, while 77.5% presented with variant forms of the illness, characterized by slowness of movement affecting both sides of the body, rigidity of the trunk or torso, and impaired balance evident early in the course of illness. Symptoms included impaired eye movements, little to no response to levodopa, and intellectual decline. Investigators suggested an environmental factor might be the cause of the malady due to the unusually high number of patients presenting with atypical clinical features, the cross-ethnic make-up of the affected subjects, and the association of symptoms related to diverse brain systems.

An association between Soursop consumption and atypical parkinsonism appeared in a case control study set in the French West Indies and published in the journal, Lancet in 1999. People who suffered from atypical PD consumed significantly more fruit, infusions or decoctions of the leaves from the plant bearing the Latin name *Annona muricata*, than did those with idiopathic PD. Traditional Creole medicine of the islands has used the plant for its sedative properties, for heart and digestive problems and as a tonic to maintain health from early childhood to old age. People of the tropics enjoy the fruit canned in juices, in frozen ices, sherbets and shakes. In the western world, *Annona muricata* is available in healthfood stores and shops selling herbal remedies. In capsule form the product claims to act as an anti-depressant, combat cancer, viruses and parasites.

### **INSIDE . . .**

Anesthesiologists at Increased Risk for Parkinson's Disease? ~ **page 1082**

Deep Brain Stimulation: Downside ~ **page 1083**

Bones About PD ~ **page 1085**

Gene Therapy for PD ~ **page 1088**

## MEDICAL PUBLISHING COMPANY

Laboratory studies found two major groups of potential neurotoxins. They rank among the most potent inhibitors of a step in cellular respiration and function the same way as the pesticide rotenone. When researchers infused the toxin annonacin chronically into rats, lesions developed in the substantia nigra and basal ganglia resembling those seen in patients with atypical parkinsonism.

Investigators estimated the quantity of annonacin consumed per year by eating one fruit or a single can of nectar per day, was comparable to the dose inducing widespread neurodegeneration in the basal ganglia and midbrain, when rats were infused with the toxin continuously for 28 days. They admit it is a mere estimation, as they are uncertain about the bioavailability of the toxin consumed orally, versus when ingested into a vein.

The authors caution people of the tropical latitudes eat fruit of other *Annona* species and these too may be sources of toxicity. The journal, *Movement Disorders*, reported atypical parkinsonism among immigrants to the United Kingdom of Afro-Caribbean and Indian origins, in 2000. In 2004, the same journal reported atypical parkinsonism in New Caledonia (off the East coast of Australia).

What can one surmise from this? Are the folklore remedies of the tropics poisoning populations? Why has it taken so long to make a connection between a widely consumed fruit and its deleterious effects? One answer may lie in pover-

ty and inadequate access to medical care. The poorer the population, the heavier the people may rely on natural fruits to supplement their diet and on herbal preparations to treat disease. With the shorter life expectancies in the past, many individuals did not live long enough to manifest the atypical parkinsonism. Now that life expectancy is increasing, the appearance of these diseases is becoming more evident.<sup>1</sup>

*Editors Note: Soursop is found around the world and the name for it is impressively varied. In El Salvador, like in other Spanish-speaking Caribbean nations, the fruit is known as guanaba; in Mexico, it is often known as zopote de viejas, or cabeza de negro. In Venezuela, the fruit is catoche or catuche; in Argentina, it is anona de puntitas or anona de broquel; in Bolivia, sinini; in Brazil its called araticum do grande, graviola, or jaca do para. People of the Netherlands Antilles, Surinam and Java call the fruit sorsaka or zunrzak. In French-speaking areas of the West Indies, West Africa, Southeast Asia, and especially North Vietnam, the fruit is corossol, grand corossol, corossol epineux, or cachiman epineux; in Malaya, it is durian belanda, durian maki or seri kaya belanda; and in Thailand, it is thu-rian-khack.*

## ANESTHESIOLOGISTS AT INCREASED RISK FOR PD?

When PD occurs at a high frequency in geographic clusters or in certain occupations, the likelihood of discovering an environmental cause is increased as exemplified by the story of soursop and atypical parkinsonism. There is evidence for a relationship between chronic exposure to anesthetic gases and an increased risk of developing PD. An Italian study published a few years ago reported that a history of general anesthesia was associated with a two-fold increased risk of acquiring PD. To further explore whether chronic exposure to anesthetic gases could be implicated, a collaborative study was conducted in the US to test whether anesthesiologists are at increased risk of developing PD. The researchers collected data about anesthesiologists and for comparison, internists. The Physician Master File of American Medical Association provided data on demographic issues and the mortality records in the National Death Index, provided the cause of death and any contributing causes.

Researchers used the prevailing rates of PD in the U.S. population between 1979 and 1995 to

### PARKINSON'S DISEASE UPDATE

Issued Six Times Per Year

Issue #151, 2006

**Publisher**..... Sylvia A. Sack  
**Managing Editor**..... Juan R. Sanchez-Ramos, PhD, MD  
**Production Manager**..... John Paone

**Parkinson's Disease Update** is published bi-monthly by the **Medical Publishing Company**, P.O. Box 450, Huntingdon Valley, PA 19006, (215) 947-6648. FAX (215) 947-2552. Subscription \$40.00 per year (U.S. and Possessions. Outside U.S. add \$10.00 for Air Mail). © Copyright 2006 by The Medical Publishing Company in the United States and the World. Reproduction of any part of this newsletter is forbidden without written permission.

While it is the purpose of this newsletter to report and explain current information on Parkinson's Disease, it is not intended to furnish medical answers to individual problems. This is best done by your own doctor.

Unsolicited material must be accompanied by a self-addressed stamped envelope. The Medical Publishing Company cannot be held responsible for loss or damage of unsolicited material.

ISSN 0885-4807

attain the expected number of deaths from PD. Analysis of direct mortality comparisons revealed anesthesiologists had a small, non-significant increased risk of dying with PD, or having PD contribute to death. During the first ten years of follow-up, anesthesiologists experienced a relatively lower mortality risk compared to internists, though an elevated risk followed after the initial ten-year period.

Authors of the investigation concluded their findings were moderately supportive of an elevated risk of PD existing among anesthesiologists, especially beyond the first ten-year follow-up. If anesthetic gases (or infectious agents) were to cause PD, then prolonged exposure with an extended period before symptoms appeared might be expected.<sup>2</sup>

### **DEEP BRAIN STIMULATION: DOWNSIDE**

Patients resort to surgical methods to control disabling dyskinesias, or shaking symptoms, and hold hopes surgery will improve their quality of life. Surgeons introduced deep brain high-frequency stimulation of the thalamus to treat tremor in 1987, and in 1993 applied the technique to the subthalamic nucleus to improve the symptoms of advanced Parkinson's disease. Prior to electrical stimulation, patients underwent lesioning, or planned destruction of tiny areas in the brain, in efforts to relieve tremors that had come to dominate their days. The darker side of surgery warrants discussion. As neurosurgeons implant electrodes in the brain with greater frequency, a variety of other outcomes as well as suicides have increased.

In the last few years, surgical teams have reported suicides and varying outcomes of patients who underwent deep brain stimulation. Suicide rates were as high as 4.3% (six patients in a one hundred forty killed themselves). This contrasts sharply with the suicide rate reported by the Center for Disease Control in Florida, for the years 1990-1994, in which there were 15.4 suicides for every 100,000 people (a rate of about 0.015%).

The research team reporting increased patient suicides, found risk factors for killing oneself included a history of severe depression and successive deep brain stimulation surgeries. They found no relationship between those who killed themselves and the underlying movement disorder, the stimulation target area, the electri-

cal parameters used or how the treatment was modified. They also note, "Paradoxically, all patients experienced an excellent motor outcome following the procedure."

Neurosurgeons normally work in tandem with a team of healthcare professionals preparing patients for surgery. Psychological evaluations determine if prospective patients are intellectually intact, or whether they suffer from dementia, depression or other mood disorders. Dementia may disqualify people seeking neurosurgery since once secured inside the apparatus and bolted to the operating table the surgeon requires a reliable witness; someone able to communicate sensations he or she experiences while electrodes activate certain areas of the brain.

Counseling is necessary so patient and family have realistic expectations of surgery; what it will and will not correct, possible complications, how it will affect medication dosages and how recovery will proceed. However following surgery, counseling may be scarce. In 2002, the Journal of Neurology Neurosurgery and Psychiatry published a study conducted on behavioral disorders after subthalamic stimulation, in people with PD. All 24 patients were, "successfully treated" and evaluated after surgery for adjustment, psychiatric and personality changes. While motor disability improved by 69.5% and the daily dosage of levodopa fell by 60.5%, social adjustment was considered good or excellent in nine patients, moderately impaired in fourteen and severely impaired in one. Psychiatric disorders that previously passed unnoticed became obvious. Four patients experienced episodes of depression, eighteen patients experienced generalized anxiety and two others became dependent on illicit drugs. Fifteen of the twenty-four subjects became highly emotionally reactive. Personality traits as a whole improved in eight subjects, were unchanged in eight, and aggravated in eight.

In a brief communication to the journal Neurology, Dr. Berney reported his observations following PD patients post-operatively, after subthalamic deep brain stimulation. In the Swiss and Canadian study, twenty-four patients were evaluated prior to surgery and for six months after implantation of electrodes. Despite clear motor improvements, a quarter of patients experienced significant foul mood states, and three people became transiently suicidal.

Of course, not all surgical groups have

## MEDICAL PUBLISHING COMPANY

patients deviating from the expected course of recovery. The most recent of these reports is from Dr. Halbig of the University of Berlin and Mount Sinai Hospital in New York. In 2005, he reported in the *Journal of Neurology, Neurosurgery, and Psychiatry* on fifteen patients treated for dystonia, or uncontrollable positioning of the limbs and head, with bilateral deep brain stimulation to the globus pallidus internus. The healthcare team evaluated patients prior to surgery and 3-12 months after electrode placement, with a large battery of tests including quality of life and motor function measures. Surgery significantly improved symptoms of dystonia, functional abilities, and quality of life, allowing patients to significantly reduce anti-dystonic medications. The team noted no deterioration in cognitive scores or neuropsychiatric measures.

The most dramatic case illustrating the power of deep brain stimulation to improve motor symptoms, while neglecting to affect psychic pain comes from Dr. Ghika of Lausanne University Hospital, in Switzerland. A wheelchair dependent patient underwent bilateral implantation of electrodes to the ventralis oralis anterior (VOA), to improve his dystonia, or uncontrollable positioning of the limbs and head. Earlier in life, deprived of oxygen he suffered brain damage, causing the tissue on both sides of the basal ganglia to die. Surgeons first placed electrodes within the globus pallidus interior, with little relief of symptoms. Six weeks later surgeons placed a second set of electrodes in the VOA, and saw a much better outcome. After four months of high intensity stimulation, the dystonias improved dramatically and the man was able to walk. Shortly after, the patient took his own life. No explanation was given for the patient's behavior.

What about longer-term effects? In 2004, a study published the health aspects of seventy-seven people who underwent bilateral deep brain stimulation to the subthalamic nucleus. The team followed and evaluated the intellectual, mood and behavioral effects for three years, performing evaluations before surgery, at one year after surgery and three years after surgery. Two intellectual or cognitive functions worsened and advanced age predicted these declines. The research group found depression improved, while thought disorders and apathy worsened. Major behavioral changes included two aggressive impulsive episodes, one suicide, four suicide attempts, one person became

permanently apathetic, one had a passing yet severe depression, four people became psychotic (one permanently so) and five became hypomanic (one permanently so).

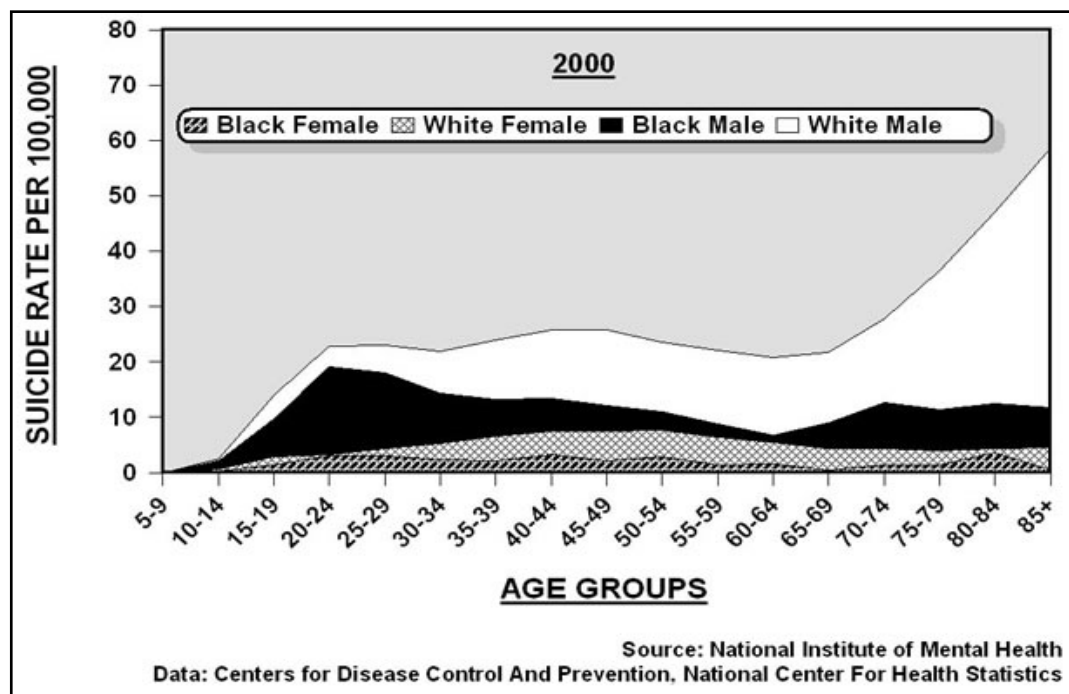
In 2002, Dr. Lagrange of Grenoble, France reported the results of a long-term follow-up questionnaire in a brief communication to the journal, *Neurology*. In this case, one year qualified as long-term. Sixty patients underwent bilateral subthalamic nucleus stimulation. All patients responded to questions prior to surgery and again twelve months following surgery. The French team found quality of life improved in the following: motor aspects improved by 48%, systemic aspects improved by 34%, emotional aspects improved by 29%, and social aspects improved by 63% dimensions. Choosing to see the glass as half empty or half full may depend on whether you are contemplating surgery for yourself or a family member. The same statistics tell you the quality of life remained unchanged or worsened in the following areas: motor aspects 52% of patients, systemic aspects 48% of patients, emotional aspects 71% of patients and social aspects 37% of patients.

Dr. Okun suggested in the *Journal of Neurology Neurosurgery and Psychiatry*, in 2003 that placement of electrodes may be responsible for the foul moods some patients experience. "...optimal placement of electrodes in both the STN {subthalamic nucleus} and GPi {globus pallidus internus} seems to result in overall improvement in mood and is associated with a lower incidence of adverse mood effects than stimulation outside the optimal site. Preliminary data from this study, however, suggest that slight movement dorsal {towards the back} or ventral {towards the belly} to the site of optimal motor performance may be associated with more adverse changes in mood with STN than with GPi stimulation."

Reports of neuropsychiatric problems associated with deep brain stimulation highlight the lack of scientific understanding of the brain, its functioning and the mechanisms responsible for the rise of symptoms. Though many reports have concentrated on the depressive side effects of surgery, there have also been documented cases of hypomania, euphoria, mirth, and hypersexuality. Anxiety is hardly described and permanent intellectual complications are fortunately rare. Though motor disability will improve with surgical intervention, quality of life and the functions of the mind do not

## U.S. Suicide Rates by Age, Gender, and Racial Group.

*There is a dramatic rise in white male deaths beginning at 69 years of age.*



necessarily follow. Management of surgically related psychological changes brings challenges, as optimal treatment is unknown. Surgical innovation has advanced ahead of practical medicine and treatment by a seasoned clinician with sound judgment may provide the best guidance. Psychological follow-up should help to ensure the best possible long-term outcome.<sup>3</sup>

### BONES ABOUT PD

A British team of researchers investigating osteoporosis recently reported that patients with PD suffer from weakened bones. However, osteoporosis is age-dependent and occurs in the general population at about the same rate as in age-matched patients with PD. This is interesting for several reasons, especially because of conflicting findings reported in previous research. In addition, patients with PD develop poor balance and experience more falls than otherwise healthy people of the same age. Because of fragile bones and increased falls, PD patients are more likely to sustain serious fractures. A Japanese study inquiring into whether levodopa affects bone mass revealed that 54% of women and 26% of the men were osteopenic, that is had low bone density (see chart below for definition). A Chinese study of 22 male PD subjects found significant levels of osteoporosis in the spine. In 1995, a study comparing bone mineral density in 55 PD

subjects with 55 age, and sex-matched control subjects found a small but significant difference in the density of hipbones, but no difference in the density of spinal vertebra. A year later, a Spanish study assessing bone density with three different methods provided data showing a tendency towards reduced bone mass in those with PD, compared to control subjects.

The British research team from Northumbria, in the United Kingdom assessed the prevalence of osteoporosis in people attending a PD clinic. The one hundred five subjects consenting to participate in the study had an average age of 74.5, though participants ranged in age from 54 years to 92 years. Approximately 47% were men, and 91% of all subjects were living independently. A single trained nurse using a scanner, the HOLOGIC QDR-4500A, measured bone density. The scanner measured bone mineral content in three areas at the head of the femur and in the first four lumbar vertebra. Measures for the hip, or femur head, were added separately from the four measures of the spinal vertebra. The bone mineral content was divided by the separate areas producing density values for both hip and spine.

In sum, forty-four subjects or 41.9% met the World Health Organization's classification of osteoporosis, while an additional thirty-six, or 34.3% met the criterion for osteopenia. As a group, 76.2% of the participants had seriously

low bone densities. Divided according to the sexes, ten men or 19% of participants had scores classified as osteoporosis, while an additional 41% had scores classified as osteopenia; 60% of male participants had seriously low bone densities. The female group had thirty-four cases of osteoporosis. Sixty three percent of women ranked within that classification, while another 15 cases or 28% ranked as having osteopenia; 91% of female participants had seriously low bone densities. Only 5 women, a mere 9% had normal bone density. As an entire group, there was a statistically significant association between increasing age, an elevated geriatric depression score, greater impairment, worse gait and balance, and osteoporosis. In other words, the oldest participants tended to be more depressed, less able to function, have more problems walking and be more apt to break bones in a fall.

Though over three quarters of the subjects in this study had abnormally low bone density levels, the investigators noted, "...the prevalence of osteoporosis is similar to other people of similar age. As such, osteoporosis in PD may not be more common than in the general population." Despite this comment, PD patients fall due to their poor balance and their fragile bones contribute to increased morbidity and mortality. Therefore it is important to build up the strength of bones as well as to work on gait and balance.

***Boning Up: Fighting Osteoporosis***

Bone is made up of mineral salts, collagen fibers, proteins and water. Calcium and phosphate form tiny crystals, accounting for 65-70% of bone's dry weight, providing it with solidity. Collagen fibers of varying lengths and orientations anchor these mineral salts. The collagen fibers are tough, yet pliable and resist stretching. They account for 25-30% of the dry weight of bone. Ground substance surrounds the mineral-embedded collagen fibers. A gelatinous material cements the collagen fibers together and consists mainly of protein polysaccharides, called glycosaminoglycans. Water disperses amidst collagen fibers, and ground substance, and surrounds mineral crystals. A smaller quantity of water flows through cavities housing bone cells, or osteons, carrying nutrients to living bone tissue.

Bone is one of the most metabolically active tissues in the body and continues to remodel, and adapt to the mechanical demands placed on it

throughout one's lifecycle. Only dentin and the enamel in teeth are harder. As well as providing rigid surfaces for muscle attachment sites, and protecting our internal organs, bone serves as a reservoir for essential minerals in the body, especially calcium.

Bone density measurements provide insight into one's structural bone health, and are particularly important for the individual with balance and gait impairments, who has an increased risk of falling. Density measurements taken at the hip and spine are relevant indicators of one's total bone density. Taken at the wrist, measurements have a wider range of normal and less clinical relevance.

Restructuring the living environment by eliminating throw rugs, hiding electric cords, providing night-lights and grab bars in the toilet and shower areas can reduce falls. However, accidents occur anywhere. Fashioned as underwear, hip protectors resemble a girdle with padding over the hips, and aim to cushion bones in a fall. Albeit not the pinnacle of fashion, cushioning is preferable to broken bones, as a fractured femur can initiate a downward spiral in health. Following a hip fracture, 10-20% of people die in the subsequent 6 months, 50% are unable to walk without assistance, while 25% require long-term care.

<p><b><i>World Health Organization Definitions of Osteoporosis Based on Bone Density Levels</i></b></p> <p><b>Normal</b> – Bone density is within 1 standard deviation (+1 or -1) of the young adult average</p> <p><b>Low Bone Mass: Osteopenia</b> – Bone density is 1 to 2.5 standard deviations below the young adult average (-1 to -2.5)</p> <p><b>Osteoporosis</b> – Bone density is 2.5 standard deviations or more below the young adult average (&gt; -2.5 SD)</p> <p><b>Severe osteoporosis</b> – Bone density is farther than 2.5 standard deviations below the young adult average, with 1+ osteoporotic fractures</p>
---

Bone mass measurements typically provide two comparison scores. The T-score compares one's bone mass to that of an optimally healthy, 30 year old person. The farther to the left of this value, the lower one's bone density and the more likely bones will fracture in a fall. The reverse is also true-the farther right in comparison to this

## MEDICAL PUBLISHING COMPANY

norm, the higher one's bone density, and the less likely bones are to fracture upon impact. The Z-score provides a comparison to an optimal individual of one's age, and body size. The World Health Organization bases its definition of osteoporosis on T-scores (see chart, previous page).

The cycle of bone accumulation in women ceases before or during late puberty, though men may continue to build bone throughout their twenties. Adulthood marks a period of bone maintenance, where bone deposited ordinarily equals bone reabsorbed by the body. Increased bone mass will accumulate with sufficient calcium in the diet, an excess of 1000mg daily, and consistent weight bearing exercise. This remains true throughout the life span. However, aging causes our intestines to become less capable of absorbing dietary calcium, so to maintain an ample supply; one's supplement will need to increase.

Though the process leading to osteoporosis cannot be stopped, it may be controlled or suspended if consistently opposed. Still, several factors are unavoidable. Slender women, weighing 127 lbs or less, of Asian and Caucasian ethnicity have a higher incidence of osteoporosis for several reasons. These women typically accumulate less bone mass during their youth, experience menopause—a time susceptible to rapid loss of bone mass, and they tend to out-live men.

Weight-bearing exercises are performed against gravity. Walking, jogging, skipping, dancing, leaping and jumping rope all force our body weight onto the muscles and joints of the spine and hips. Exercising in water eliminates the force of gravity, so while body movements in the pool may ease the pain and stiffness of arthritis, they will not build bone mass.

Weight training is another method to stress muscles, forcing bones to accumulate greater density. The area stressed is the region targeted for bone remodeling. Therefore, biceps and triceps curls will encourage greater density in the humerus, radius and ulna-bones of the arm.

A report from the surgeon general states, "Although results may vary, studies suggest that high-impact loading such as jumping, strength-training exercises, or a combination of these can slightly increase or conserve spine bone mass in healthy postmenopausal women and also has a positive effect at the hip." To continue opposing the forces of osteoporosis, exercising must be regular

and consistent. The Nurse Health Study found walking at least 4 hours per week was associated with a 41% lower risk of hip fractures, compared to walking less than an hour per week, even among women who performed no other exercise.

Before donning gym shorts or sports bra and throwing a towel over your shoulder, you may wonder how much exercise is enough. The Center for Disease Control and Prevention recommends the following for adults. You may want to consult your clinician to decide whether this suitable for you.

- **You do not engage in regular physical activity** – incorporate a few minutes of physical activity into each day, gradually building to 30+ minutes of moderate-intensity activity

- **You are active at less than the recommended levels** – strive to adopt more consistent activity:

- moderate-intensity physical activity for 30+ minutes on 5+ days per week
- vigorous-intensity physical activity for 20+ minutes on 3+ days per week

- **You engage in moderate-intensity activity for at least 30 minutes, 5+ days per week** – you may achieve greater health benefits by increasing the time spent or intensity of activity

- **You regularly engage in vigorous-intensity activity 20 minutes or more, 3+ days per week** – continue to do so

In addition to regular aerobic activity, weight or resistance training twice a week for 30-45 minutes, on a consistent basis for a year, is sufficient to cause increases in bone density.

For those unable to exercise, pharmacological methods protect against bone loss. A prescription and recommendation by one's clinician will ensure these drugs do not interfere with other daily medications.

Medications useful for preserving bone integrity include:

- **Bisphosphates** – Classified as anti-resorptive medications, they slow or stop bone reabsorption. Alendronate (brand name Fosamax), Ibandronate (brand name Boniva), Risedronate (brand name Actonel)

- **Raloxifene** – brand name Evista is one of a new class of drugs called Selective Estrogen Receptor Modulators (SERMs).

## MEDICAL PUBLISHING COMPANY

- **Teriparatide** – a newly approved osteoporosis medication, increases the rate of bone formation.
- **Calcitonin** – a hormone that slows bone loss while helping to increase bone density: available in nasal spray form.
- **Calcium and Vitamin D** are important to maintain bone health or mass.<sup>4</sup>

### GENE THERAPY FOR PD

In December 2004, the University of California at San Francisco and Lawrence Berkeley National Laboratory began a phase I study, titled: An Open Label Safety Study of Intrastratial Infusion of Adeno-Associated Virus Encoding Human Aromatic L-Amino Acid Decarboxylase. The shorter form of the project is Gene Transfer: AAV-hAADC-2. Similar to deep brain stimulation, the surgery benefits people with PD who have moderate to advanced stage disease, who experience motor fluctuations, particularly wearing-off. In corporation with the principal investigator Dr. Michael Aminoff, neurosurgeon Dr. Philip Starr injects genes into a region of the brain called the globus pallidus. When taken into certain cells, the genes encourage a reaction converting levodopa to dopamine.

Past researchers working with rodent models of Parkinson's disease succeeded in inducing behavioral recovery in their animals after introducing an enzyme, tyrosine hydroxylase (TH), which converts the amino acid tyrosine to dihydroxy-phenylalanine ( L-DOPA) in the brain. A second enzyme, aromatic L-amino decarboxylase (AADC), converts L-dopa to dopamine. Under the direction of Dr. Keiya Ozawa, researchers constructed two viral vectors to carry the genes. One contained the gene for the enzyme TH; the other contained the second enzyme, AADC. Rats receiving TH showed improvement in their movement disorder, though rats receiving both TH and AADC exhibited more significant improvement.

Phase I studies enlist a small number of participants to document safety, dosage and side effect issues involved in a therapy. The current study aims to enroll sixteen subjects. Three individuals have undergone the procedure, and a fourth person has a surgery date.

For more information, or to speak with the Clinical Coordinator, please call Rowena Mah at (415) 476-0947. To look up the research on the web use the following address: <http://www.ucsf.edu/brain/pdcenter/clinicalresearch.htm>

#### Sources

1. Champy P. et al. "Quantification of Acetogenins in *Annona muricata* Linked to Atypical Parkinsonism in Guadeloupe." *Mov. Dis.* Vol. 20 N. 12, 2005. [www.rain-tree.com/graviola.htm](http://www.rain-tree.com/graviola.htm). [www.hort.purdue.edu/newcrop/morton/soursop.html](http://www.hort.purdue.edu/newcrop/morton/soursop.html)
2. Peretz, C. et al. "Parkinson's Disease Mortality Among Male Anesthesiologists and Internists." *Mov. Dis.* V. 20, N. 12 Dec. 2005.
3. Burkhard P. R. et al. *Neurology*. 63:2004. Houeto J. L. et al. *J. of Neurol., Neurosurg. and Psych.* 72:2002. Berney A. et al. *Neurology*. 59:2002. Ghika J. et al. *Neurology*. 58:2002. Funkiewiez A. *J. of Neurol., Neurosurg. and Psych.* 75:2004. Okun, M. S. et al. *J. of Neurol., Neurosurg. and Psych.* 74:2003. Lagrange E. et al. *Neurology* 59:2002. Burn, D. J. and Tröster A.I. *J. of Geriat. Psych. and Neurol.* Vol. 17, No. 3, 2004. Benabid A.L. et al. *Current Opinion in Neurol.* 18(6): Dec. 2005. Hälbig T.D. et al. *J. Neurol., Neurosurg. and Psych.* 76:2005.
4. "Bone Health and Osteoporosis: A Report of the Surgeon General." United States Health and

Human Services. Available at [surgeongeneral.gov/library/bonehealth/chapter\\_6.html#TheEvidenceSupportingtheEffectofCalciumandVitaminDonBone](http://surgeongeneral.gov/library/bonehealth/chapter_6.html#TheEvidenceSupportingtheEffectofCalciumandVitaminDonBone). "Bone Mass Measurement: What the Numbers Mean." National Institute of Health Osteoporosis and Related Bones Diseases-National Resource Center. Available at [osteo.org/osteolinks.asp](http://osteo.org/osteolinks.asp). Glaser D. L, Kaplan F. S. "Osteoporosis: Definition and Clinical Presentation." *Spine* 22 (24S) Suppl. Dec. 1997.. Lowe, T. G. "Osteoporosis: Pain Management Treatment and Recovery." Available at [spineuniverse.com/displayarticle.php/article2693.html](http://spineuniverse.com/displayarticle.php/article2693.html). Nordin M. and Frankel V.H. "Biomechanics of Bone in Basic Biomechanics of the Musculoskeletal System" 2nd Ed. *Lippincott Williams & Wilkins*: Philadelphia, 1989. Riggs B.L, Melton L.J. "The worldwide problem of osteoporosis: insights afforded by epidemiology." *Bone* 5 Suppl. Nov.17, 1995.

*All articles written for PD Update  
by Catherine O'Neill*