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Parkinson's Disease Update: Treatments and Animal Models

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Parkinson Disease – research techniques update

Parkinson's disease (PD) is the second most common central nervous system neurodegenerative disease that affects movement, mobility and causes additional non-movement related problems. PD affects 1% of the population with the average age for the onset of the disease being between 55-60 years of age while 10-15% of patients are diagnosed before the age of 50 (1). Parkinson's patients pathologically exhibit loss of dopaminergic neurons (DA) in the substantia nigra pars compacta (SNpc), presence of cytoplasmic protein aggregates called Lewy bodies containing alpha synuclein and ubiquitin, and a reduction of approximately 80% of dopamine in the striatum (2). Loss of DA neurons and dopamine has been attributed to mitochondrial dysfunction, oxidative stress, neuroinflammation, and insufficient autophagic or proteosomal protein degeneration. In addition, PD also affects the dorsal motor nucleus of the vagus nerve, the nucleus basalis of Meynert, the locus coeruleus, olfactory structures, and the hypothalamus (3). While these structures may account for the movement and mobility disorders associated with PD Lewy bodies have also been observed in the myenteric plexus (4). Nonmotor symptoms of PD include depression, incontinence, disturbances of sleep patterns, anosmia, cognitive impairment, constipation, and disturbances of some autonomic functions. There is no known cause of PD, however, environmental factors and/or genetic mutations have been theorized to be implicated. As age increases the risk of developing the disease also increases. Since the clinical symptoms are due to loss of dopamine neurons and dopamine, drugs have been developed to treat the disease and animal models developed to study the progression and possible cause(s)of the disease. PD is classified as a progressive degenerative disease of the brain with four major neurological signs:

1) Resting tremor – this is an involuntary movement most noticeable in fingers and thumbs and has classically been called pill rolling tremor because its appearance resembles the movement of pharmacists preparing (rolling) a pill. However the tremor may begin in the legs, hands or face on one side of the body. To test for a resting tremor the patient is asked to touch their finger to their nose. At rest the tremor will be present however it will diminish as the arm is moved and the patient tries to touch their finger to the tip of their nose.

2) Cogwheel rigidity – is defined by rigidity mainly in the arms, legs or neck and is due to increased muscle tone. When asked to move an arm or leg the patient exhibits brief relaxation in the muscles of the limb thus giving the movement of the limb a cogwheel (ratchet) movement instead of a smooth fluid movement.

3) Bradykinesia – slowness of voluntary movement. This results in increasing difficulty performing common daily movements such as getting out of a chair, using a knife to cut food, shortened steps when walking, and slow dressing.

4) Postural reflex changes – These changes refer to a patient's increased difficulty in maintaining their balance making walking increasing difficult and falling and injury due to falling an increasing probability.

In addition to the above symptoms people with PD often exhibit decreased automatic movements such as blinking, smiling, swinging of arms, dementia (thinking problems), emotional changes (increased fear, anxiety, loss of motivation), depression, and bladder control problems. Other associated changes include constipation, diminished sense of smell, fatigue, and decreased sexual desire.

Is there a cure for PD?

At the present time there is no known cure for PD with more and more patients being diagnosed with PD every year. The overall effect due to loss of neurons and accompanying loss of dopamine is an increasing number of clinical symptoms being observed in patients with PD as the population continues to live longer.

What drugs are used to treat PD?

There are several pharmaceuticals that can help to alleviate some of the symptoms of PD. However, these are not a cure and as time progresses clinical symptoms will reappear.

Levodopa

One of the most common and widely used drugs is levodopa, also called L-dopa. Levodopa crosses the blood brain barrier and accumulates in the neurons producing dopamine and then is converted into the neurotransmitter dopamine thus increasing the amount of available dopamine in the CNS. Patients initially diagnosed with PD demonstrate improvement in the clinical symptoms related to PD. However as time passes this treatment becomes less and less effective.

Sinemet is a combination of L-dopa and carbidopa that increases the effectiveness of L-dopa while reducing its side effects such as nausea, vomiting and cardiac arrhythmia. Sinemet comes in two forms; controlled (slow) release form and immediate-release form. Long-term use may cause dyskinesia, restlessness, confusion, and abnormal movements. Other drugs similar to Sinemet are Entacapone (Comtan) and Tolcapone (Tasmar).

Dopamine Agonists

Dopamine agonists are a class of drugs that do not convert to dopamine but mimic dopamine thereby activating the dopamine receptor and trimeric G-proteins, which leads to changes in gene transcription. Included in this class are promipexole (Mirapex), ropinole (Requip) and rotigotine (Nuepro). These drugs effects tend to last longer, however they are accompanied by side effects such as body swelling, hallucinations, increased compulsive behaviors such as gambling, eating, hypersexuality and sleepiness. These drugs can be taken alone or in combination with Sinemet and are usually prescribed first with levodopa added, if they do not alleviate the patient's symptoms. The above listed drugs are usually better tolerated and long-term use poses smaller risk of side effects when compared to L-dopa.

Partial dopamine agonists include; Quinpirole, Salvinorin, Phencyclidine (PCP) and Aripiprazole (Abilify). Symmetrel is used to treat patients with mild PD and increases the amount of dopamine available to the brain, however it may cause confusion and memory problems in some patients.

MAO-A/MAO-B inhibitors:

MAO-A inhibitors prevent the breakdown of dopamine, serotonin and norepinephrine. MAO-B inhibitors are medications that inhibit the enzyme monoamine oxidase B (MAO-B) that breaks down dopamine in the brain. Drugs of these classes include: Non-Selective MAO-A/MAO-B inhibitors Isocarboxazis (Marplan), Nialamide (Niamid) Phenelzine (Nardil, Nardelzine) and Hydracarbazine; Selective MAO-A inhibitors Moclobemide (Aurorix, Manerix), Pirlindole (Pirazidol), and Toloxatone (Humoryland Selective MAO-B inhibitors Rasagiline (azilect) and Selegliline (Deprenyl, Eldepryl, Emsam, and Zelapar.

Hallucinations are a side effect of some of these drugs coupled with numerous drug and dietary interactions. Some evidence suggests that Eldepryl may slow the progression of PD, however, nausea, dizziness, fainting and stomach pain are associated side effects. Likewise, initial evidence suggests Azilect may also slow the progression of PD but side effects include headache, joint pain, indigestion and depression.

Catechol-o-methyltransferase inhibitors – COMT – prolong the effects of Levodopa. Entacapone (Comtax) has been shown to be mildly effective in relieving some of the symptoms of PD.

What other treatments are available for PD?

In addition to drug therapy for the treatment of PD other methods have shown some success in relieving the symptoms of the disease. Like drug therapy these techniques are not a cure for PD.

Deep Brain Stimulation (DBS)

Deep brain stimulation (DBS) is a neurosurgical procedure where an electrode is inserted into the brain and an electrical generator (neurostimulator or brain pacemaker) placed into the chest. Electrical impuses are then generated and sent through the electrode into various parts of the brain. (see fig. 1 on next page)

Benabid et al first reported DBS in 1991 (5) where they reported alleviating symptoms of PD (tremors) by stimulation of the ventral intermediate nucleus of the thalamus in humans. Electrical impulses were generated and sent to the electrode in the brain to alleviate PD symptoms. DBS is used not only for the treatment of PD it is also used for the treatment of dystonia, Tourette syndrome, pain, depression and obsessive compulsive behavior. Stimulation of the internal portion of the globus pallidus or subthalamic nucleus can reduce bradykinesia, ridigity, tremors and difficulties associated with walking (gait) in patients with PD. For excellent review articles concerning DBS see Permutter and Mink 2010 and Moro and Lang 2006 (6,7). This type of treatment has been shown to be effective in reducing PD tremors and involuntary motor movements, however it is usually reserved for patients with advanced PD.

Surgical risks (bleeding in the brain and infection) and associated problems such as placement of the electrode and neuropsychiatric side effects can occur with this type of treatment. However the advantages of DBS are the reduced time patients are in less effective medication states and reduced dosage needed for medications in patients with PD.

Stem Cell Therapy

Another type of surgical procedure is the culturing of stem cells for implantation into the brain. Using a variety of cell culture techniques, immature cells are engineered into dopamine producing cells and then implanted into the brain of people with PD. The overall goal of this type of technique is to replace lost dopaminergic neurons and to restore or reconstruct nigrostriatal pathways. Initial re-

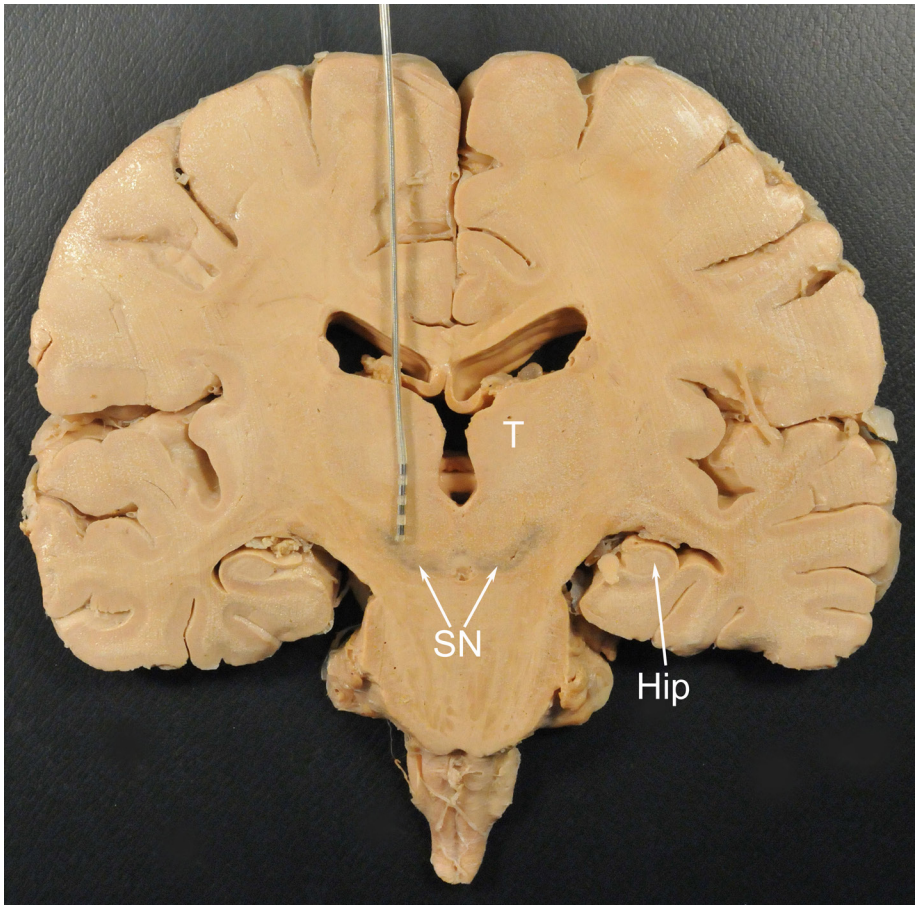

Fig. 1. This cross-sectional view of the human brain illustrates the positioning of the quadripolar electrode within the STN. The SN is ventral to the STN. The stimulation characteristics for most PD patients are as follows: mean frequency = ~135 Hz; mean voltage = ~2.3 V; mean pulse width = ~65 µs for either the right or left STN.

Note that high stimulation parameters are required to maintain an optimal prophylactic effect. Nevertheless, levodopa medication is continuously reduced after DBS (mean equivalent dose before STN DBS = ~1066 mg and ~955 mg after STN DBS).

Abbreviations: Hip = Hippocampus, T = Thalamus. (originally published in *Carrier* #69, 2010).

sults demonstrated some success in reducing the locomotion difficulties experienced by patients with PD, however over time the original symptoms reappeared. Like any surgical technique there are risks involved and this technique was mainly reserved for people with advanced PD where drugs were not able to alleviate the PD symptoms. See PDF (Parkinson Disease Foundation Local or National chapter) homepage for the latest news and updates on this type of therapy for PD.

Other Therapies (Treatments) For Alleviating PD Symptoms

Altering nutritional intake and diet by increasing fiber content, fruits, vegetables, and whole grains accompanied by increased fluid intake and increased amounts of omega-3 fatty acid has shown to relieve some of PD symptoms as has increased exercise (walking, swimming, dancing etc.). Increasing the amount of exercise has also shown to decrease depression. The shuffling gait associated with PD has also decreased when the patients were asked to look forward and not at their feet. This helped with their heel to toe strike thereby improving their gait.

Other alternative therapies that have shown mixed results in alleviating the symptoms associated with PD include:

Co-enzyme Q10 – in a small pilot study some of the PD symptoms improved however in a larger study there was no documented improvement.

Massages or massage therapy– has shown in some patients to relieve tension and increase relaxation however the effects were short lived.

Acupuncture has also shown to relieve some symptoms of PD in certain patients however the effect was also short lived.

Yoga, meditation, music, art, and pet therapy have all demonstrated small improvements in reliving some of the daily symptoms of PD however long term relief has not been demonstrated.

In summary, there is no definitive cause known for the onset of PD. It is known that the neurons in the SNpc die and the nigrostriatal system is affected in people with PD causing increased and more severe symptoms as the disease progresses. Likewise the decrease in the number of neurons decreases the amount of available brain dopamine. Drugs can alleviate for a time the clinical manifestations of PD but they are not a cure since they do not stop the death of brain neurons and become less effective over time. Genetic and environmental factors have been postulated to play a role in the onset of PD, however there have been no definitive studies proving this link. What has been conclusively demonstrated in the brains of people with PD (at autopsy) is the presence of Lewy bodies that are clumps of non-natural substances in the brain, specifically A-synuclein protein and alpha synuclein.

Since PD is the most common of the movement disorders, with no known cure and affects more and more of the aging population world wide, continued research is much needed. One of the main problems associated with PD research is the lack of a reliable animal model of the disease as animals do not naturally suffer from PD. Any animal model is therefore a non-natural form of the disease. However, a number of time tested animal models do exist, with each having its advantages and disadvantages.

Animal Models Of PD

PD is a progressive degenerative disease that affects the substantia nigra, pars compacta, nigrostriatal pathways, striatum and various other central nervous system structures in addition to the peripheral nervous system. Therefore both dopaminergic and nondopaminergic structures are involved. An ideal animal model would mimic both the pathological and clinical features of PD, however no such single animal model (vertebrate or invertebrate) exists. There are a number of animal models that exhibit some of the features of human PD. The following is a brief description of current animal models.

6-Hyroxydopamine

6-hydroxydopamine (6-OHDA) is a hydroxylated analog of dopamine isolated in 1959 by Senoh and Witkop (8,9) and first shown by Ungerstedt (10) in 1968 to be capable of inducing degeneration of both dopaminergic and noradrenergic neurons. Currently, 6-OHDA is used to lesion the dopaminergic system as a model for PD. 6-OHDA is injected unilaterally into the SNpc, striatum, or medial forebrain bundle where 6-OHDA produces cell body and axonal toxicity thereby producing a rapid (12h to 3 day) lesion of the nigrostriatal pathway (11,12). When injected directly into the striatum, 6-OHDA produces a slower more progressive type of damage more reminiscent of human PD (13). Injection of 6-OHDA produces both motor deficits (circling behavior) and nonmotor deficits such as cognitive and psychiatric impairment. Usually, 6-OHDA is injected unilaterally followed by a systemic injection of dopamine receptor agonists such as apomorphine. This model then produces a rotation always toward the lesion, thus each animal serves as its own internal control (14). This animal model has been used to test new drugs for their antiparkinson effects and neuroprotective capabilities. The disadvantage of a 6-OHDA animal model is that 6-OHDA does not cross the blood brain barrier, therefore direct injections are needed into the SNpc, medial forebrain bundle or striatum. There is also no olfactory loss, the brain stem is not affected nor is the locus coeruleus. This model has been extensively studied in monkeys, rats, and mice and has the disadvantages that surgical preparations (stereotaxic injections) are needed, the pos-

sibility of infections from the surgery exists, and it is time consuming.

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was first discovered in intravenous drug users in the early 1980's by Davis et al (15), and Langston et al (16). The intravenous drug users had injected synthetic merperidine, which contained MPTP. The PD like symptoms were relived by administration of L-dopa. MPTP is lipophilic, easily crosses the blood brain barrier and is metabolized by astrocytes where it is converted to its toxic active cation MPP+. MPP+ is then released by the astrocytes into extracellular space and taken up by dopaminergic neurons and terminals. Once transported into the dopaminergic neurons and terminals it becomes neurotoxic by inhibiting the mitochondrial electron transport chain resulting in ATP depletion and increased oxidative stress (17).

The MPTP model of PD has been successfully used in sheep, dogs, cats, mice, rats, monkeys and guinea pigs. However, most rat studies have demonstrated that a large number rat strains are resistant (less toxicity) to the effects of MPTP. The MPTP model of PD mimics some of the clinical PD symptoms in human such as oxidative stress, reactive oxidative species (ROS), energy failure and inflammation. Some studies have reported intra-neuronal inclusions mimicking Lewy bodies while other investigators have not confirmed their presence. Slow infusion of low doses of MPTP into mice has demonstrated inclusions immunoreactive for both alpha synuclein and ubiquitin (18,19, 20). PD like symptoms are better reproduced in monkeys (for a review see 21), however due to cost, limited lab facilities and trained personnel, the number of studies conducted is limited. Initially MPTP monkey studies were given a single high dose of MPTP, however current protocols use lower doses delivered over extended time periods.

N,N'-dimethyl-4-4'-bipiridinium

N,N'-dimethyl-4-4'-bipiridinium (Paraquat) is a herbicide and similar to MPP+. However it demonstrates different transport properties and toxicity. Paraquat has the ability to cross the blood brain barrier in contrast to MPP+ and it is assumed that it exerts its effects through oxidative stress mediated by redox cycling producing ROS. Production of hydrogen peroxide and hydroxyl radicals leads to damage of DNA, RNA, lipids and proteins. In rat studies Paraquat appears to be age dependent with the highest levels detected in the brain of very young and old rats suggesting a blood brain barrier role. Paraquat causes motor deficits in an age dependent manner, however damage to the dopaminergic cell bodies and nerve terminals consistently have not been observed. When Paraquat is given with Maneb (manganese ethylenebisdithiocarbamate) a loss of approximately 20% of striatal dopamine occurred while when paraquat was injected weekly for 24 weeks approximately 30% reduction in rat dopamine levels was observed. Paraquat also causes pulmonary toxicity, which may account for decreased motor performance and the presence of Lewy body like structures have also been reported in the SNpc. To date there have been less than 100 cases of PD reported that can be linked to Parquat toxicity in humans, however Paraquat plus Maneb allows researchers to look for a link to environmental factors as a cause of PD (22,23,24 25).

Rotenone

Rotenone is both an insecticide and herbicide, is widely used, occurs naturally in tropical plants, is lipophilic and crosses the blood brain barrier. Rotenone has a half -life of less than 5 days and chronic exposure of low doses of rotenone results in inhibition of the mitochondrial transport system in the rat

brain. Administered orally, rotenone causes very little neurotoxicity, however in the Lewis rat strain chronic systemic administration via osmotic pumps has demonstrated neurotoxicity, while intravenous injection causes damage to the nigrostriatal neurons with Lewy body-like formations, oxidative stress, and intestinal problems mimicking symptoms of PD. However, in animal studies the mortality is high and rotenone not only affects the dopaminergic system, it also reduces serotonin, noradrenergic, and cholinergic levels in the rat brain. An additional problem of the rotenone model is controversial findings, in which some studies have reported depletion of DA in the nigrostriatal system when using mice while other studies have shown no significant depletion. Likewise, to date, there are no reported human cases involving rotenone induced PD in humans (26,27,28).

Other Nigrostriatal Dopamine Animal Models

While MPTP, 6-OHDA, Paraquat and Rotenone are the most widely used animal models to study PD other animal models have been/are used to study the progression of PD. These include Reserpine, alpha-methyl-Para-Tyrosone, amphetamines, Isoquinoline, and Lipopolysaccharide.

Reserpine

In 1957 Carlsson et al demonstrated that rats treated with reserpine developed akinesia-like behaviors, which could be reversed by treatment with L-dopa (29). Reserpine is believed to act on the storage synaptic vesicles by temporarily blocking the storage of catecholamines via the magnesium and ATP-dependent pathways. The problem of using reserpine as a model for PD is reserpine's effect are short lasting and non-specific for dopamine and do not affect the nigrostriatal pathways (non-neurotoxic).

Alpha-Methyl-Para-Tyrosine

Alpha-methyl-p-tyrosine is an inhibitor of tyrosine hydroxylase and was/is used to deplete dopamine. However like reserpine the effects are short lived and not neurotoxic to DA neurons or pathways.

Isoquinoline Derivatives

Isoquinoline deriivatives can cross the blood brain barrier and are found in plants, food, and are derived from dopamine and dopamine metabolites, hence they are found in higher concentrations in areas of the brain containing dopamine. Structurally, isoquinolones are similar to MPTP and MPP+. However various researchers have reported conflicting results when using isoquinoline and its derivatives (1,2,3,4-tetrahydroisoquinoline or 1,2,3,4-tetrahydroisoquinoline) (30).

Amphetamines

Methamphetamine is a widely used stimulant that is neurotoxic in monkeys, rats and mice to both serotoninergic and dopaminergic synaptic terminals in the nucleus accumbens, striatum and frontal cortex. Methamphetamine however is not neurotoxic to the neurons of SNpc, but causes dopamine to be released from the synaptic vesicles into the cytosol. This release causes increased motor activity within one hour after systemic injection. Using an amphetamine model for PD, Lewy body-like structures have not been observed.

Genetic Models of PD

Animal models of genetic mutations include alpha synuclein, LRRK2 (Leucine rich repeat kinase 2, autosomal dominant PD) and PINK1/Parkin and DJ-1 (PTEN induced putative kinase, (PARK7 Parkinson disease early onset autosomal recessive PD). However in human PD, genetic mutations account for less than 10% of reported PD cases. There is a considerable volume of literature concerning genetic models of PD and it is beyond the

scope of this discussion to attempt to summarize this area of PD research. However, it must be noted that in studies using genetically altered mice where alpha–synuclein (A53T, A30P) was knocked out, DA maintenance and development was not affected. However, in similar studies using Drosphilia, dopaminergic cell loss, inclusions, and some motor deficits were produced.

Leucine rich repeat kinase 2 (LRRK2) is localized to membranes and knocking out LRRK2 had no effect on DA maintenance or development. Likewise, in mice, knocking out parkin, DJ1 or PINK1 caused no DA cell loss, nigrostriatal degeneration, or behavioral deficits (31,32).

Non-Vertebrate PD Models

In addition to subhuman primates, mice, rats, cats, dogs, guinea pigs and rabbits other non-vertebrate species have been used to study PD. These include zebrafish, fruitflies and earthworms. Zebrafish have the advantage of small size, are easy to maintain, have short generation time, are transparent into early adulthood, DA neurons that are well characterized and affected by 6-OHDA or MPTP (induces DA loss). Advantages of using fruit flies include a short life span (approximately 30 days), production of a large number of offspring, complete sequencing of Drosophilia genome, large number of mutant strains and comparable biological pathways to humans. In addition research using fruit flies has well-defined biological, genetic and pharmacological techniques. Earthworms likewise have a short life span, high offspring output, well-defined neuronal cells, (8 bilateral DA neurons), and are easily administered environmental substances or novel drugs. The cost of conducting studies using fruit flies, earthworms or zebrafish is minimal when compared to the cost of using monkeys, rats or mice.

Many animal models have been developed for the study of PD and each has its own advantages and disadvantages. With increasing research and understanding of the mechanisms and underlying factors causing PD, a cure is hopefully in the not too distant future.

Biography

Brian H. Hallas, Ph.D. (brian830@optonline.net) received his BA in Psychology and his BS in Biology from University of Hartford, his MS in Biology and his Ph.D. in Neurobiology from Purdue University in 1979. He has been awarded numerous research grants and has authored over 75 peer -reviewed articles, several book chapters, and published over 250 abstracts. Dr. Hallas received the New York Institute of Technology Presidential service award twice and was a Heritage Foundation Health Policy Fellow in 2004. At the New York College of Osteopathic Medicine Dr. Hallas served as Associate Dean of Research, Chair and Professor of Neuroscience and Director of Graduate Studies. He retired from the New York Institute of Technology College of Osteopathic Medicine in 2014. He currently serves on the AOA Council of Research, and is a board member of Sigma Sigma Phi and the Long Island Chapter of the Parkinson Disease Foundation.

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Editor's Column

It is almost time for the big neuroscience event of the year, the Society for Neuroscience meetings. This year, the event will take place in Chicago on October 17-21 at the McCormick Place. Hopefully, the windy city will not be too windy or chilly then. As usual, David Kopf Instruments will have a full booth displaying their wide variety of stereotaxic and related products. Please stop by the booth (1025) and say hello to the Kopf Instrument representatives and look over the best and most widely used stereotaxic instruments in the world.

We also invite you to attend the David Kopf Lecture on Neuroethics. This widely anticipated lecture will be delivered by Joseph J. Fins, MD of the Weill Medical College, Cornell University and is titled "Giving Voice to Consciousness: Neuroethics, Human Rights and the Indispensability of Neuroscience." It will be delivered in Hall B1 on Monday, October 19 from 10-11:10 am. This lecture series has been very well received over the years, and this year's lecture promises to be exceptional. We hope to see you there.

Also of note is the International Neuroethics Society (INS) meeting that will be held in conjunction with and just before the SFN meetings. The INS has been an expanding voice in the neuroscience community in highlighting the role that ethics must play in our thinking about how neuroscience is done and data interpreted. As scientists, we must play a role in how our data are used, and the moral imperatives and moral choices that we are beginning to realize we face. The INS is working to prepare young neuroscientists and scientists-in-training to realize their role in ethical research and data interpretation. We urge you to plan to attend this meeting on October 15 and 16. The public lecture will be a discussion on the topic "Is Professional Football Safe? Could We Make it Safer? Perspectives from Neuroscience, Law and Ethics" f rom 5-6:30 October 15.The main meeting will be at the Art Institute of Chicago all day on October 16. Please go to www.neuroethicssociety.org for more information.

This issue of the *Carrier*, #85, was written by Brian Hallas, Ph.D. Brian is a neuroscientist who was for many years at the NYIT osteopathic school until his retirement last year. He has been a frequent contributor to the Carrier. This article, an overview of the current status of research and treatment of Parkinson's disease follows an article in Carrier #69 (2010) that looked at the status of deep brain stimulation in Parkinson's disease. His summary here will provide updated information and summaries of various aspects of treatment and research in the area. Remember that all past Carrier issues are available at the Kopf website (www.kopfinstruments.com)

On the home front, we have spent the summer in our condo in Dublin, OH, visiting both sets of grandchildren and doing some traveling through the Midwest. We will be going back to our permanent home in Florida, just outside Ft. Lauderdale very soon. The second hurricane of this season that seemed to threaten us there is now dissipating well out in the Atlantic, so most likely will not be a problem. We hope that again this hurricane season will be a calm one and that we will not have to keep the hurricane shutters up all the time.

I hope to see many of you in Chicago at the SFN meetings and invite you to stop by the Kopf booth to say hello. If you want to pen an article for the *Carrier*, please contact me at the email below, or stop by the booth to discuss it with me.

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