Exercise Is Not Optional, It Is Mandatory.

SPRING Times No 40. Page 14-16.

The World Parkinson Congress[1], the first of its kind, took place from February 22nd to 26th, 2006 at Washington Convention Centre, USA, attracting some 3,200 participants, 1,100 of whom were patients or caregivers.

The Congress supported by the Movement Disorder Society, the National Institute of Health, U.S. Army Medical Research Acquisition and over 100 professional and patient organizations from all over the world, was unique not only in size and scope but also in that it brought together patients, caregivers and many of the world's leading Parkinson's experts, doctors and scientists.

Michael Kelly, a SPRING member, who attended the Congress, has written this article for SPRING Times.

With almost 200 papers to choose from, it was not an easy task for me to select those that might be of special interest to patients. In taking the subject of exercise as being worthy of special attention, I have singled out three papers for comment based on the following criteria:

- Scientific importance of medical information
- Originality of content
- Immediate relevance for patients

The three papers are supplemented by an addendum, based on work currently in progress at the University of Frankfurt. Taken together, the material presented provides good grounds for a **major re-evaluation of the role of exercise in patient therapy.**

In the first talk entitled **how exercise affects the brain: Towards a rationale for exercise-induced protection,** Dr Michael Zigmond from the University of Pennsylvania spoke about the benefits of exercise, pointing out that it has been accepted for a long time that exercise is recommended for people suffering from numerous conditions, including cardiovascular problems and diabetes. He referred to the fact that studies carried out showed that the incidence of Alzheimer's disease, stroke and PD **was lower for those who exercised regularly compared to control groups**.

The question is: **What is it about exercise that confers a benefit?** The work of Dr Greeno at the University of Illinois was referred to. He has been testing, a) animals walking fast or running, b) animals having to balance on a tightrope to obtain food, and c) couch potato animals relaxing all day. It has been found that **running** very significantly increases blood vessel density in the brain, with enhanced flows of blood improving the supply of nutrients and facilitating removal of waste. Furthermore, the tightrope group showed an increase in the number of synapses and overall, exercise increased the supply of survival or trophic factors. Running or fast walking had no effect on synapses and tightrope walking had no effect on blood supply. So, the type of exercise taken; needs to be considered, when designing a program. Reference was made to the work of Dr Carl Cotman at the University of California, showing that there is **an increase in survival factors in the brain with exercise.**

The question then becomes: **what kind of exercise is needed and how much?** The answer is: **"lots of different types of exercise".**

Dr Zigmond then went on to talk about an animal model using the 60HDA neurotoxin (6 hydroxy dopamine). In a series of elegantly designed experiments using rats (referred to by Dr Zigmond as animals with front-wheel-drive) with individual forelimbs immobilized in casts and thus with the rat being forced to use a particular limb, it could be shown that forced exercise prior to or immediately after lesioning, with 6OHDA and continued for 7 days, **could completely counteract the toxic effects of 6OHDA.** Video clips of this phenomenon were shown for various configurations and provided an impressive demonstration of the benefits of exercise. If exercise was initiated seven days after lesioning, no beneficial effects occurred. Dr Zigmond could give no precise data on how long the effects lasted and how intensive the exercise had to be. This aspect will be referred to later.

The second talk with the somewhat unwieldy title: **The effect of high-intensity exercise using body-weight supported treadmill training on neuroplasticity and functional recovery in individuals with Pd** was given by Dr Beth Fisher from the University of Southern California. Dr Fisher has been involved for some years in translating over animal movement research for use in human applications. She spoke about the re-modeling that the brain is capable of, pointing out that, in recent years, a much greater degree of plasticity has been found to exist than was formerly thought to be the case. This applies not only to animal models but also to stroke and spinal injury models.

Dr Fisher reported on studies of mice using MPTP (a neurotoxin, causing immediate damage to dopaminergic neurons) in which one group receiving MPTP was exercised intensively for 30 days, a second group receiving MPTP did no exercise and a third group exercised without receiving MPTP. **It was found that the MPTP group, which was forced to exercise, caught up with the non-MPTP exercise group and, in terms of speed and endurance, could match them after 30 days. This provides powerful evidence of the benefits of exercise in an animal model.**

For exercise-testing of patients, use was made of a treadmill with an overhead bodyweight-support suspension harness to allow high-intensity exercise without any danger of falling or injury. Patients were divided into three groups: a high-intensity exercise group with MET 3.5 and above, a low-

[1] http://spring.parkinsons.org.uk/images/stories/SpringDigest/2006/40_3_ExerciseIsNotOptional.pdf

intensity group with MET below 3.0 and a no-exercise control group (1 MET=1kcal/kg, h). Testing was carried out in 24 sessions, each of 60 minutes duration, over a period of 8 weeks.

The outcomes of the exercise were measured in terms of changes in disease severity, functional performance (stair climbing, stand/sit movements) and brain function testing. This latter test, carried out using Trans-cranial Magnetic Stimulation (TMS) techniques, provided the most significant indications of the benefits of exercise. At various levels of stimulation, TMS was used to provide a Motor Evoked Potential (MEP) response, with peak-to-peak maximum amplitude and cortical-spinal rest time (Silent Period Duration, SPD) being measured independently in both brain hemispheres. This enabled a comparison to be made between the more the less affected sides in Pd patients and between Pd patients and healthy controls. SPD tends to be shortened and MEP shows higher peak-to-peak rest values (hyper excitability) in Pd.

Comparison between pre- and post-exercise readings showed that exercise led to a convergence to normal values in Pd patients, with the higher intensity exercises having the greatest effect.

A third very engaging talk entitled, '**People with Pd should have weekly Parkinson exercise classes for the rest of their lives',** was given by John Argue from San Francisco. John is a former actor and, for the past 23 years, a physical therapist, working with People with Pd.

His approach to exercise and movement is a very practical one, using the activities of everyday life to counteract the restrictions imposed by Parkinson's. A book he published in 2000 has sold over 20 000 copies and he now has a DVD out containing details of this program.

As an actor, John is able to slip into the role of a Person with Pd (PwP) and gave a completely convincing performance in terms of posture and movement. His somewhat unconventional approach to physical therapy involves three main headings: **Stretching** – as a preventive measure, countering foreshortening and restrictions of movement, **Strength** – to prevent muscle atrophication and to maintain ability to perform movement, along the lines of 'use it or lose it', **Movement strategy** – managing movement such that one is mindful of the sequence of actions required to complete the execution of a task. Examples shown included motion sequences associated with sitting down on a chair, rising from a supine position etc. Such sequences are executed automatically, when a person is healthy, but can pose severe problems for a PwP.

John's program involves 10 lessons, the first 5 of which are performed lying or sitting. Video clips with examples of straight stretch, rotational stretch, tilt side stretch etc. were shown.

Very early on in therapy, PwPs are given fall training, long before falls become a factor in disease progression. Patients are shown how to protect their face and head and how to mitigate the effects of falling.

John emphasized the importance of group therapy, not only in terms of the fellowship created among patients and benefits accruing from getting a sense of **control over the disease**, but also in as far as it gives caregivers time to rest and recuperate.

Addendum: As a spin-off from programs developed for performance improvement of top-class athletes, the University of Frankfurt has been carrying out extensive testing on the effects of various types of motion stimuli. One such program has been aimed at off-season training supplementation for downhill alpine skiers. This has led to development of the so-called Zeptor, a treadmill-like device with two oscillating footplates. This has been in use for past 2-3 years in specialized Parkinson clinics in Germany. Extensive tests in Germany and in Spain have shown it to have positive effects due to interactions between variable-intensity semi-stochastic (random) oscillations and neuro-muscle systems.

Dr Haas, a researcher in the Institute of Sport Medicine in Frankfurt University, has reported on tests showing that exercise/movement of a particular type can lead to nerve growth factors (NGF) being released by nerve cells (through activation of muscle sensors referred to as spindles). NGF initiates a cycle leading to enhanced formation of proteins, thereby assisting in **neuron survival and growth**. Increased physical activity is thus found to protect nerves but NGF release is dependent on the type and range of movement. Exercise carried out while standing have little or no effect on NGF, swimming has a small effect and treadmill exercises give good results. To achieve the best results, exercises should meet the following criteria:

- Be quasi-rhythmic but with a stochastic element (a degree of randomness)
- have a frequency of 1-10 Hz, about 5 Hz is optimal
- involve a learning situation (complexity) and, if possible,
- have an element of spatial variability.

Swimming is apparently too slow to be of major benefit but jogging/walking fast* (over uneven ground) would seem to come close to the ideal. Completely rhythmic or repetitive movements (such as might arise for example when holding a pneumatic tool) lead only to fatigue, with no beneficial effects on the nervous system. **To get maximum physiological and neurological benefit, it would appear to be important to exercise on a regular basis because muscular degeneration begins within some days of stopping exercise**.

The exercise sessions should involve a challenging degree of intensity, duration and complexity, factors that will vary widely depending on the abilities and impairment status of the individual.

Summary: While the benefit of exercise has been appreciated for many years, only in recent times has research begun to unravel the mechanisms underlying this phenomenon and to provide a differential evaluation of what different kinds of exercise can do. Findings that exercise can counteract the effects of neurotoxins and can lead to increases in nerve growth factors are especially encouraging. **By establishing a solid basis for the benefits of exercise, it is hoped that patients on a wider front will be encouraged to include it as an integral part of their daily routine**.

Articles supplied by Northwest Parkinson's Foundation Post:

Potential for exercise to Slow Parkinson's Progression

23 October 2009

New results, presented at the Society for Neuroscience's annual meeting in Chicago this week point towards the profound effects that exercise may have on the brain. In studies conducted by researchers at the University of Pittsburgh in the US, exercise is able to protect the brains of monkeys against chemicals that researchers usually use to mimic Parkinson's.

Testing exercise for Parkinson's

Over a period of 3 months, monkeys were divided into groups that either ran, jogged or sat on a treadmill for an hour every day, 5 days a week. After this training period, all the monkeys were given MPTP, a chemical which attacks the nerve cells that are lost in Parkinson's. These nerve cells produce dopamine, a chemical messenger that helps regulate movements. The MPTP successfully killed dopamine producing nerve cells in the monkeys that sat still. They developed a slowness of movement that is typical of Parkinson's. But in the brains of monkeys that had been running, MPTP had almost no effect. Their dopamine-producing nerve cells survived and the monkeys were protected from the Parkinson's symptoms that normally occur. Even after another 6 weeks, brain scans showed that exercising animals had virtually normal levels of dopamine in their brains.

What does this mean?

Dr Kieran Breen, Director of Research and Development at the Parkinson's disease Society, comments: "These new studies provide tantalising glimpses of the potential exercise has to slow the progression of Parkinson's – something no current treatment can." Now, further studies are crucial to understand exactly how exercise affects the brain, and how we can harness the power of exercise, to develop better treatments and therapies for people with Parkinson's."

The Story Surrounding GDNF

The existence of GDNF has been known for well over twenty years. Only in 2006, at the World Parkinson's Congress held in Washington DC, was it first announced that GDNF is produced in the brain, by the glial cells, and that ***GDNF repairs the damaged brain cells***.

If everybody in the Parkinson's world knew about GDNF in 2006, why do only a few people, outside of the medical profession, know anything about it yet?

If the medical profession do know about GDNF then they should have jumped onto the bandwagon, in 2006, and made every effort to tell their patients about it!

That has not happened, at least not in my neck of the woods. Does this mean that this vital information is not being disseminated amongst all the players in the medical world? If so,

Why would that be?

At that World Congress, we were told that ***energetic walking*** is the best way to go about producing GDNF in the brain. Patients should all be shown that they are capable of ***walking,*** at least most of them can. Whatever walking they do manage to do would be better than nothing.

Getting better, even by a little bit is better than continuing to get worse.

As far as I know, scientists knew about the existence of GDNF, long before 1993, when the first clinical test was performed in England. If they knew about it so long ago, why did ***we all*** not know about it?

1. I assume that It must have been found first inside the brain of a human being.
2. The purpose of GDNF must have been known, otherwise, why would Amgen have made an artificial version of it?
3. When the 1993 trials were started, they must have known that GDNF repairs the damaged brain cells, and they were conducting these trials to see how effective it is!
4. I must therefore assume that because GDNF - a natural cure, which is produced in the brain - does not generate income for anybody; it was more important to do trials using artificial GDNF, rather than getting some pd patients to do some walking and then measure how much they managed to improve over a period of time.

5. That would have cost next to nothing, compared to what that first artificial GDNF trial must have cost.
6. Are we all so powerless that we are unable to take action against this silence on what fast walking can do for us?
7. It makes me think of the fuel crisis. There have been many inventions, over the years, which ***reduced*** the amount of fuel consumed by cars over a given distance. I can remember, when I got my driver's license in 1953 that my little pre-war car did well over thirty miles to the gallon. Today, some cars do maybe fifty percent better than that, but nowhere near the total savings of all those inventions, which all seemed to just disappear off the face of the earth. I know it is not in the interests of the fuel companies to allow cars to use less fuel, but it has become in the interests of the whole world to use less fuel now in 2015. Should that also be allowed to continue?

Artificial GDNF has been produced in the USA by a company named Amgen. This GDNF was first used in the trial mentioned above, carried out by Dr Steven Gill, at the Frenchay hospital in Bristol, England. This was the published result of that trial:

Results: "After one year, there were no serious clinical side effects, a ***39% improvement*** in the off-medication motor sub-score of the Unified Parkinson's Disease Rating Scale (UPDRS) and a ***61% improvement*** in the activities of daily living sub-score. Medication-induced dyskinesias were ***reduced by 64%*** and were not observed off medication during chronic GDNF delivery. PET scans showed a significant ***28% increase*** of dopamine storage after 18 months, **suggesting:**

A direct effect of GDNF on dopamine function."

Methods: A brain autopsy was performed on one of the Bristol, United Kingdom phase I GDNF trial participants, who had died of an unrelated heart attack.

Results: The autopsy analysis revealed re-growth of nerve fibers in the putamen area of the brain. Professor Love, who examined the brain stated that

"This was the first neuropathological evidence that infusion of GDNF in humans causes sprouting of dopamine fibers, in association with a reduction in the severity of Parkinson's Disease."

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Why won't they let Parkinson's sufferers take a life-changing drug?

By NIKKI MURFITT

When Tom Isaacs was 27 he was diagnosed with Parkinson's disease. The condition gradually destroys the brain's ability to control the muscles - there is no cure.

Determined to give himself the best possible prognosis, Tom embarked on a very personal journey to meet leading scientists in the hope of finding new treatments that would help him.

Three years ago it seemed he'd found the answer: a new drug GDNF (glial derived neurotrophic growth factor). A group of Parkinson's patients had been treated with GDNF at Bristol's Frenchay Hospital in 1993 and their transformation had been remarkable: sufferers who'd been trapped in a living hell were suddenly able to walk, talk and smile again.

Parkinson's is caused by a shortage of dopamine, a chemical messenger involved in movement, mood and behaviour. Why this happens is still not known.

GDNF seems to work by stimulating dopamine production and preventing degeneration of the brain cells. The drug is delivered via a catheter permanently implanted in the brain. The catheter is connected to a Jaffa cake-sized pump sewn into the abdomen.

When GDNF was given to the Bristol patients the results were astonishing. 'Men who had been unable to get up out of a chair unaided were walking normally across a room. Their hand co-ordination was unbelievable, in exercises they could move their hand easily from left to right, something that had previously been impossible under the onslaught of Parkinson's,' says Tom.

So impressive were the results that the study was rolled out to North America and by September 2004, 50 patients were receiving the drug. The Parkinson's Disease Society in the UK planned to hand over** £1.2 million to fund further trials in Bristol.

But suddenly, at the end of 2004, and without warning, this lifeline was ***snatched away***. Amgen, the American drug company which holds the patent for manufacturing GDNF, claimed the drug was dangerous as it could cause brain damage and refused to continue prescribing it.

Read more: http://www.dailymail.co.uk/health/article-413634/Why-wont-let-Parkinsons-sufferers-life-changing-drug.html

The below link is to an online book by Anders Bjorkland which discusses some truly interesting aspects of the Bristol study:

http://books.google.com/books?id=ljWYjL2rOo4C&pg=PA4&lpg=PA4&dq=%22bristol%22+%22gdnf%22&source=bl&ots=evmIjieV99&sig=lC9G5zfC4FKlekkhUpmktw66vl8&hl=en&sa=X&ei=abqbT7LiBOaRiAKmzZmWAQ&sqi=2&ved=0CFMQ6AEwBQ#v=onepage&q=%22bristol%22%20%22gdnf%22&f=false

Case Inspires Parkinson's Crusade

Parkinson's patients in the US, who are suing a drugs company for withdrawing a pioneering treatment, say a man treated in Bristol has given them fresh hope.

Amgen halted medical trials of glial cell line-derived neurotrophic (Repair) factor (GDNF) because of side effects. But an autopsy on the brain of Henry Webb, who volunteered to undergo tests at Frenchay Hospital, showed signs that his nerve fibers were re-growing.

The company said it had no plans to restart the trials.

Mr Webb, from Blackwood in South Wales, died from a heart attack last December. He was one of seven patients with advanced Parkinson's Disease involved in the GDNF trials at Frenchay.

He told BBC News in 2003 the drug had given him back his life.

"Mr. Webb's case is important because it shows that GDNF is a safe and effective treatment."

Lower dosage

Kristen Suthers, daughter of one of the US patients fighting to get the medical trials restarted, said: "We believe high doses of GDNF causes lesions. But we've seen the study from Mr. Webb, and that it is not the case, if you give patients a ***lower dosage of GDNF.***

A spokeswoman for Amgen told the BBC: "It is a case of interest, but you have to remember, it was phase one of the study. "In the phase two study, those on placebos did well, sometimes better, than those on the drug."

http://news.bbc.co.uk/2/hi/uk_news/england/bristol/somerset/4695567.stm

Question: Why would this second study come up showing a totally different result, when the first study, held *ten years* previously, showed a highly successful result? This looks so very suspicious to me!

This is an interesting bit from Oxford Journal:

Restorative treatments for brain disorders are rare. In neuroscience research, it is not uncommon to suggest that experimental treatment strategies may have great clinical potential. The rescue or regeneration of a few cultured neurones may be sufficient to entice such optimism. However, the path to a new clinical therapy is typically painstakingly long and difficult to navigate. In our minds, we would like it always to be a straight path starting with tests in cell models and rodents providing us with mechanisms of action and leading to trials in non-human primates. Then open-label tests can be performed in small patient groups and eventually large controlled clinical trials are conducted. In reality, however, the path may be tortuous, filled with detours that set the field back, as well as shortcuts and parallel tracks that yield different strategies which develop at their own speed. The development of glial cell line-derived neurotrophic factor (GDNF) as a treatment for tgciq's disease over the past nine years provides an example of such an interesting journey. Moreover, it illustrates one role of non-human primates in preclinical development of a novel therapy.

In this issue, Grondin and co-workers (Grondin *et al.*, 2002) present evidence for structural and functional benefits of infusions of GDNF in rhesus monkeys previously rendered parkinsonian by unilateral intracarotid injection of 1-methyl-4phenyl-1,2,3,6-tetrahydropyridne (MPTP).

Using mini-pumps, they infused 5–15 μg/day GDNF either into the lateral ventricle or the dopamine-depleted dorsal putamen. Starting during the first month, **there was a**

gradual and marked reduction in parkinsonian symptoms, including bradykinesia and rigidity, without any signs of adverse effects. Post-mortem examination revealed partial restoration of dopamine and its metabolites in the corpus striatum, as well as evidence for an increased number of nigrostriatal dopaminergic fibres and cell bodies in the substantia nigra. Interestingly, there were no significant differences between the intraventricular- and intraputamenal- infusion groups, so the data for both groups were pooled. This is the first demonstration that GDNF infused *directly into* the brain parenchyma of non-human primates is effective in restoring dopaminergic function. The treatment was not initiated until over 3 months after the MPTP lesion, when most of the dopaminergic cells had probably died due to the toxin. Therefore the authors argue that GDNF most likely worked through a neuroregenerative mechanism as opposed to one of acute neuroprotection (Grondin *et al.*, 2002).

Read more on:

http://brain.oxfordjournals.org/content/125/10/2149.full

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This is interesting! It tells why the drug company making GDNF stopped the trial – or the reasons given by them — and the Michael J. Fox Foundation's role in halting the trial:

Trial of New PD Treatment Halted: Some Patients and Advocates Protest

By Robin Elliott

On Friday, February 12, Amgen Inc. announced that, after much internal hand wringing, it was denying a request by participants in trials of a molecule known as GDNF, an experimental Parkinson's treatment, to continue receiving the treatment following termination of the trials.

California-based Amgen, the world's largest biotechnology company, had abruptly concluded its own double-blind trial almost six months earlier, saying that the treatment had not been shown to be effective and citing safety concerns in two areas. In one of these, several subjects were found to have developed antibodies that could potentially attack the body's own GDNF, a naturally occurring product that is essential for the production of dopamine, the chemical messenger that is deficient in Parkinson's.

The other safety concern came out of a separate trial involving monkeys. It turned out that a few of the animals were found to have evidence of lesions in the area of the brain known as the cerebellum.

Several leading scientists and advocacy groups take issue with Amgen's decision

Several of the scientists who had served as investigators in the Amgen trials, including Drs. Michael Hutchinson of New York University, Don Gash and Greg Gerhardt of the University of Kentucky, Richard Penn of the University of Chicago and Steven Gill at the University of Bristol, England, have challenged Amgen's interpretation of both the efficacy and the safety data. As to efficacy, some have argued that the wrong statistical test was used, and that an alternative test would have showed GDNF to be effective. (Amgen, supported by several investigators including Drs. Jay Nutt of the Parkinson Center of Oregon and Anthony Lang of the University of Toronto, has held to its original opinion that the trials failed to show efficacy.)

As to the safety issues, some of the doctors have argued that Amgen has overreacted on both counts. The antibody issue, they say, is frequently seen in such studies and does not necessarily have any adverse effects on the health of the patient. (Indeed, they note that when the antibody findings first surfaced in the spring of 2004, Amgen seemed unconcerned by the data and would have continued with preparations for a larger-scale Phase III trial of GDNF, had the second wave of monkey data not come along.)

As for the monkey data, some of these doctors point to evidence that suggests that the cerebellar damage was caused, not by the toxicity of the intervention, but by its precipitate withdrawal (six months into the trial). They also point out that the dose used for the monkeys was many times the doses used in the human trials.

Michael J. Fox Foundation stages "Scientific Summit" on GDNF

At a meeting in Chicago in early August 2004, where the efficacy data on GDNF were announced, Debi Brooks, President and CEO of the Michael J. Fox Foundation for Parkinson's Research, offered to host a scientific summit on the subject. The summit, which was held in November, drew some 30 scientists from North American and European centers for Parkinson's research and concluded with a broad consensus that while GDNF remained a promising potential treatment, more animal studies should be done to assess the health concerns before any new human trials should be undertaken.

What this discussion did not address was what should be done about the 48 people in the U.S. and the United Kingdom who have participated in one of the Amgen-sponsored trials, several of whom have indicated that they wish to continue receiving the treatment. Most observers believe that the "risk-benefit" calculus for these people is different from what it would be for a new patient because all of them have already undergone the surgery necessary to participate in the trial, and several of them have been on GDNF for as long as three years. Representatives of this group have set up a website - www.GDNF4Parkinsons.org - which has be-come a rallying-point for the Parkinson's community.

Not surprisingly, Amgen's February announcement was especially galling to this group - many of whom had written personal letters to Amgen pleading for reinstatement of GDNF. They were backed by several of the community's advocacy groups, including the Parkinson's Disease Foundation, the Parkinson's Action Network and the Parkinson Pipeline Project.

To understand how GDNF got to this point, we need to look at the scientific history of the molecule.

GDNF - The trials and tribulations of a promising Parkinson's treatment

Glial-cell line-derived neurotrophic factor, or GDNF, is one of the most powerful naturally-occurring human factors known to nourish and foster the growth of dopamine-generating neurons. Soon after GDNF was identified in 1993, Dr. Gash and colleagues at the University of Rochester and later at the University of Kentucky showed that the injection of GDNF protein into both rat and monkey models of parkinsonism showed therapeutic promise.

Dr. Gash's work was soon followed by the first gene therapy trial of GDNF, conducted in a rat model by Dr. Martha C. Bohn and her colleagues at the University of Rochester. This seminal study, which was published in the journal Science in 1997, showed that continuous delivery of GDNF at low levels using a so-called "viral vector" was able to protect dopaminergic neurons from neurotoxin-induced cell death.

Drs. Jeffrey H. Kordower and Marina E. Emborg, along with their colleagues at Rush University Medical Center in Chicago and the University of Lausanne in Switzerland, picked up the ball by conducting the first study of GDNF gene therapy in a monkey model. Their studies showed improved motor performance in the animals which received the GDNF gene (compared with animals that received no treatment). In the treated animals, parkinsonian symptoms were reduced, and, after the animals were sacrificed, the numbers of healthy dopamine neurons were found to be significantly enhanced. A summary of the findings was published in Science in 2000.

The investigation in humans

While the animal studies were continuing, scientists began to examine how GDNF might work in humans. Based on the preliminary results of Dr. Gash's studies in rat and monkey models, Amgen initiated a human, randomized, double-blind trial of GDNF, led by Dr. Nutt. The results, published in a 2003 edition of the journal Neurology, were disappointing; the treatment showed little benefit and several side-effects, confirming that benefit in animals does not necessarily translate to benefit in humans.

Some two years later, a British team conducted a follow-up study that greatly raised world interest in the promise of GDNF. In this study, led by Dr. Gill and his colleagues at Frenchay Hospital in Bristol, scientists implanted catheters in the brains and pumps in the abdominal walls of five people with moderate Parkinson's. The pumps continuously fed GDNF into specific areas of the brain via the catheters at a precise rate of infusion. All five patients showed improvements in "off" states comparable to their "on" states within two months of the onset of the trial. Their motor skills continued to show improvement and even gait difficulties were eased. Brain scans documented the patients' progress while the dosage of anti-Parkinson's medications was steadily reduced. The results showed significant improvement in the functioning of the dopaminergic system.

The Amgen "double-blind" trial

Impressive as the new data appeared to be, the Bristol trial did not provide an answer as to whether GDNF works. The reason is that it was of the so-called "open-label" variety, in which every participant received the treatment and some of them - human nature being what it is - may have imagined that they felt better than they really were. To correct for this factor, known as the "placebo effect," scientists try to confirm early data by conducting what is known as a "double-blind" trial, in which some patients are randomly placed on the treatment and the others are given a sugar pill. To test the validity of the British data, Amgen initiated such a trial for GDNF in 2003 with 34 patients.

As reported by Dr. Lang at a meeting of the American Neurological Association in October, 2004, the study did not prove the efficacy of GDNF. The investigators judged the patients' "off" periods to be somewhat improved, but saw no improvement in "on" periods.

The uncertain future of GDNF

Dr. Clive N. Svendsen of the University of Wisconsin (co-investigator in the Bristol study), as well as other investigators involved in GDNF research, has suggested that the studies' dissimilar results may have been a consequence of the different dosages used, as well as by the different sizes of the catheters used to infuse the treatment.

Dr. Bohn says she is encouraged by the Bristol results but believes that a delivery system utilizing gene therapy rather than infusion via catheter may ultimately be safer (since it does not require the administration of live virus to the brain) and may offer a better long-term outcome for patients. Dr. Svendsen agrees, and suggests that another potential delivery technique might be the implantation of genetically-engineered stem cells that could in turn release GDNF.

Dr. Svendsen also reports that he and other study participants are meeting with Amgen to analyze the differing results of the studies to date and to seek consensus on whether and when there will be further studies of GDNF. Meanwhile, additional animal studies are being pursued.

The reinstatement issue continues

While discussions continue concerning the long-term future of GDNF, the short-term issue of the patients who were in the trials to date remains unresolved. Some have indicated that they would like to go back on GDNF if the opportunity were to be offered, but several have now had their pumps and catheters removed. Voluntary organizations such as PAN and PDF are continuing to explore options of persuading Amgen to reconsider its position. In the words of a recent open letter from leaders of the Parkinson Pipeline Project, a group of patient advocates: "[Reinstatement] is important not only to today's patients but to our prospects of being able to recruit sufficient numbers of people for future trials...[without people to participate] all of us - companies as well as patients - will be the losers."

Robin Elliott is the Executive Director of the Parkinson's Disease Foundation.

If you are keen on reading medical evidence, both for and against GDNF infusion into the brain, then read more:
http://www.pdf.org/en/winter04_05_Trial_of_New_PD_Treatment_Halted

This article discusses the mixed results of the trial, concerns over GDNF, and is a good, brief read:
http://www.zhion.com/drug/GDNF.html