

MAIN THEME: MILESTONES IN NEUROLOGY IN THE LAST 50 YEARS

PARKINSON'S DISEASE IN THE LAST 50 YEARS

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Parkinson's disease is a condition that has been known about since ancient times. It is referred to in the ancient Indian medical system of Ayurveda under the name *Kampavata*. However, it was not until 1817 that a detailed medical essay: "An Essay on the Shaking Palsy" published by James Parkinson first formally described the disease in modern times. About 60 years after the essay was published, a French neurologist Jean Martin Charcot recognized the importance of Parkinson's work and named the disease after him in early 1860s. In 1867 Charcot introduced a treatment with the alkaloid drug hyoscine (or scopolamine) derived from the *Datura* plant, an anticholinergic drug. Anticholinergic drugs are still used in treatment of Parkinson's disease even today.

In the 1950s, Arvid Carlsson demonstrated that dopamine was a neurotransmitter in the brain and not just a precursor for norepinephrine, as had been previously believed. He found that dopamine levels in the basal ganglia were particularly high. He then showed that giving animals the drug reserpine caused a decrease in dopamine levels and a loss of movement control, the effects similar to the symptoms of Parkinson's disease. Arvid Carlsson subsequently won the Nobel Prize in Physiology or Medicine in 2000 along with co-recipients Eric Kandel and Paul Greengard.

In 1961, levodopa was first tried in PD patients, but throughout most of the 1960s the results were inconsistent. In 1967, questions about the effectiveness of levodopa in PD were finally set aside when Cotzias and

colleagues reported dramatic improvement in PD patients with oral administration of levodopa in increasing amounts over long periods. The first study reporting improvements in patients with Parkinson's disease resulting from treatment with L-dopa was published in 1968, and levodopa therapy became the standard treatment for Parkinson's disease. Even today levodopa is the "gold standard" for Parkinson's disease therapy, and it has even some diagnostic value, i.e. if a patient does not respond to levodopa therapy, most probably he does not have idiopathic Parkinson's disease.

In the early 1970s, the advantages of adding a dopa decarboxylase inhibitor to treatment were discovered—reducing side effects and gaining better symptom control, and the first levodopa combinations, carbidopa/levodopa, and benserazide/levodopa, became commercially available in mid 1970s. Afterwards, long-acting, slow-release and continuous-release levodopa combinations became available.

A dopamine agonist, apomorphine, was used in 1970 as a means to overcome side effects and loss of levodopa efficacy. However, side effects and difficulty of administration limited its use. Dopamine agonists began to find a place in routine treatment of PD after the discovery of bromocriptine's benefits in PD in 1974. Afterwards the other dopaminergic drugs also became available, especially non-ergot dopaminergic agents such as ropinirole and pramipexole.

Selegiline was discovered in Hungary in the 1960s. The first publication on selegiline in Hungary

ian appeared in 1964, followed by a paper in English in 1965. In 1971 it was shown that selegiline selectively inhibits the B-isoform of monoamine oxidase (MAO-B), and a few years later it was realized that selegiline could be useful in Parkinson's disease. Since then selegiline is used in pharmacotherapy of Parkinson's disease either as a monotherapy in early stages, or as add-on therapy in later stages of disease. In recent years, a new MAO-B inhibitor, rasagiline, was introduced in Parkinson's disease therapy.

Amantadine was approved by the U.S. Food and Drug Administration in 1966 as a prophylactic agent against Asian influenza. However, in 1969, by accident it was discovered that amantadine help reduce symptoms of Parkinson's disease, and it is used in early stages of Parkinson's disease, and for temporary alleviation of levodopa induce dyskinesias.

In late 1990s catechol-O-methyltransferase (COMT) inhibitors: tolcapone and entacapone have been approved for treatment of Parkinson's disease, mainly as an adjunctive therapy to levodopa. Later, tolcapone was removed because of liver toxicity.

In the 1940s and 1950s, neurosurgeons began to perform surgery on the basal ganglia of the brain that resulted in improvements in Parkinson's disease symptoms. This surgery was effective, but it was risky, with high percent of patients dying as a result of the operation. On the other hand, with introduction of levodopa in therapy, the enthusiasm for neurosurgical approach temporarily vanished. However, because

of the problems associated with long-term levodopa treatment, in the eighties and nineties, the surgical approach was once again investigated. Various neurosurgical procedures were tested, mostly destruction of the ventrolateral part of the thalamic nucleus – thalamotomy, or of the globus pallidus – pallidotomy. Pallidotomy became very popular, until it became obvious that good postoperative effects did not last long, so it was mainly abandoned. In recent years deep brain stimulation (DBS) is used. It uses small programmable implanted electrodes surgically inserted into the thalamus, pallidum or subthalamic structures.

Diagnosis of Parkinson's disease is still based on clinical ground. However, in recent years single photon emission tomography (SPECT) and positron emission tomography (PET) using special radiotracers are used for confirmation of Parkinson's disease diagnosis showing reduced striatal radiotracer uptake. Transcranial sonography of brain parenchyma showing the hyperechogenicity of substantia nigra is also used in diagnosis of Parkinson's disease. A number of specific genetic mutations causing rare familial forms of Parkinson's disease have been discovered.

In the last fifty years we witnessed huge progress in Parkinson's disease. Many projects are underway researching new possibilities in etiology, pathogenesis, genetics, diagnosis and treatment of Parkinson's disease. Therefore, the outlook for Parkinson's disease look bright.