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PARKINSON DISEASE
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Step by Step®
Treatment of
PARKINSON DISEASE

PV Rai MD FANP
Consultant Neurophysician and Epileptologist
Nord 28, 9428 Walzenhausen, Switzerland
Formerly Medical Chief Polyclinic
Swiss Epilepsy Centre, Zürich, Switzerland
Step by Step® Treatment of Parkinson Disease

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To
A long time friend,
a great psychiatrist and philosopher

Prof Dr Christian Scharfetter
Professor Emeritus
Psychiatric University Hospital
Zürich, Switzerland
Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

James Parkinson, 1817
Almost two centuries after the original description of cardinal symptoms by James Parkinson, the idiopathic Parkinson disease remains even today a challenging problem in the clinical neurology. The neurology, however, as a specialized discipline has made great advances over the last 6-7 decades, not only in the field of diagnosis but also in the treatment of chronic and intractable diseases. Several major neurological diseases such as multiple sclerosis, epilepsy, myasthenia gravis and giant cell artheritis can be treated with specific drugs and corticosteroids, thus reducing the suffering of patients. The idiopathic Parkinson disease can be treated to a considerable extent through such drugs as Levodopa, Dopamine-receptor agonists and other drugs. A series of factors which are responsible for the neuronal degeneration and cell death in the region of basal ganglia have been identified. Because of this, a fund of knowledge is available from the basic brain research regarding the pathophysiology of basal ganglia. As in the case of many other progressive neurological diseases, definite etiological factors which are responsible for the occurrence of Parkinson disease are not known. Accordingly, the medical profession is not in a position to advise the population at risk regarding the preventive measures. It is now more or less settled that Parkinson disease is preceded by a long preclinical phase consisting of nonmotoric phenomena characterized by neurovegetative disturbances and mood changes. However, it is almost impossible at this stage to make even a suspected diagnosis of future Parkinson disease, as the changes are far too unspecific. By the time
the disease is clinically manifested with the known cardinal symptoms, there is almost 60 percent loss of melanized nigral neurons.

Hence, the diagnosis and treatment of idiopathic Parkinson disease (IPD) remains still a clinical procedure without being able to arrest the further process of this neurological disorder. However, with the development of potential drugs such as Levodopa and Dopamine-receptor agonists, the physician is in a position to reduce the symptoms to improve the quality of life for the patient. With the introduction of further new drugs, perhaps, one has the possibility to improve the general condition of the patient also in view of prevention of late cognitive disturbances leading to dementia. For the diagnosis of IPD, being predominantly a clinical method, every attempt must be made to arrive at an early diagnosis also for the purpose of initiating early drug treatment. One has the possibility today to take help of such methods as cerebrocranial MRI and PET in the event of difficulties in clinical diagnosis.

This book is the result of over 35 years of neurological practice involving also patients of Parkinson disease and gives practical hints for the general medical practitioners and students of neurology. Attempts have been made to give details regarding the interrogation of patients and the management of various clinical aspects of the disease. As there is no proper standardization in the drug treatment of IPD, other than the use of Levodopa, suggestions are made for the proper combination of drugs during different phases of the illness. Management of such problems as late dyskinesias, akinesia crisis and late phase of Parkinson disease have been referred to. Short mention has been made regarding the supplementary treatment and deep-brain stimulation.
I would like to thank my long-range patients of Parkinson disease, who have given me an opportunity to treat them for years. For any physician, who is attached to the profession, the patients are the real living libraries. My special thanks are due and hereby offered to my part-time secretary Mrs Silvia Kürsteiner, who has taken great pains to write this manuscript in spite of repeated corrections. I am thankful to my wife Nirmala, my sons Vijay, Vinay and Anil as well as for my daughters-in-law Rekha, Sheela and Bhavana for their tremendous moral support during my medical and my non-medical publications. Finally, I am highly thankful to the publishers M/s Jaypee Brothers Medical Publishers (P) Ltd, New Delhi and Bengaluru for their cooperation and help.

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## Contents

1. Historical Aspects .......................... 1
2. Clinical Findings .......................... 11
3. Epidemiological Aspects ................. 29
4. Differential Diagnosis ..................... 39
5. Diagnostic Procedure ........................ 49
6. Pathology of Basal Ganglia in IPD .......... 61
7. Mechanism of Pathogenesis in IPD .......... 83
8. The Concept of Therapy in Idiopathic Parkinson Disease ............. 105
    • Anticholinergic Drugs .................. 110
    • Levodopa .......................... 111
    • Dopamine Agonists .................. 123
    • NMDA-Antagonists .................. 136
    • MAO (Monoamino-Oxidase)-inhibitors ...... 140
    • COMT-inhibitors .................. 142
10. Neurosurgery in IPD ........................ 171
11. Parkinson Syndrome and Dementia ........... 179
12. Other Forms of Treatment for Parkinson Disease ............. 205
13. The Environment of the Patient .......... 211
14. Case Histories of Patients ................. 217

References .................................. 231
Index ........................................ 235
Chapter 1

Historical Aspects
Parkinson syndromes are common neurological disorders occurring in all ethnic groups throughout the world. Around one percent of the population after the middle age seems to suffer from this condition which generally takes a chronic, progressive clinical course leading to different grades of motoric and cognitive disturbances. These syndromes are named after James Parkinson, an English physician and palaeontologist (1755 - 1824), who practiced in Hoxton-Square, Shoreditch, London. Parkinson is today known in the medical circles for his original description of the clinical cases on the Shaking Palsy published by Sherwood, Neely and Jones in London 1817. He was however a multitalented personality whose earlier publications involved several scientific papers on palaeontology. In addition to that, over several years James Parkinson was actively involved in the English politics particularly during the spread of French Revolution in England. He published several articles under the pen-name of Old Hubert. James Parkinson was born on 11th April 1755 as the son of John Parkinson, a surgeon and an apothecary who practiced in Hoxton-Square, London, which practice was later taken over by James Parkinson. Before the famous Essay on Shaking Palsy was published in 1817, Parkinson was politically advocating the causes of the under-privileged. During one such instance he had to be even examined on oath before the Privy Council in connection with the plot of treachery to King George III. In the field of general medicine and surgery before the publication of the Essay on Shaking Palsy, Parkinson described an original case of appendicitis which he operated along with his son and showed that perforation was the cause of death.\(^3\)
3HISTORICAL ASPECTS

Medicine those days was a science involved mostly with clinical observation, examination and management through medical and surgical methods. What is today practiced as neurology was then a part of internal medicine. At the beginning of 19th Century several English physicians made brilliant contributions towards the description of ailments involving the central nervous system. Major contributions were done by John Hughlings Jackson and William A. Gowers regarding the phenomenology and pathophysiology of Epilepsy as also by James Parkinson about the movement disorders. These were the stepping stones for the later development of neurology as a speciality of the nervous system. The original essay described by James Parkinson on the Shaking Palsy in 1817 covers around twenty pages involving six detailed case-histories. Parkinson mentioned
in the preface of the essay: “The disease is of long duration: To connect, therefore, the symptoms which occur in later stages with those which mark its commencement, requires a continuance of observation of the same case, or at least a correct history of its symptoms, even for several years.” He mentions further: “By these repeated observations (the author) hoped that he had been led to a probable conjuncture as to the nature of the malady, and that their analogy had suggested such means as might be productive of relief, and perhaps even of cure, if employed before the disease had been too long established. He (the author) therefore considered it to be a duty to submit his opinions to the examination of others, even in their present state of immaturity and imperfection.”

Parkinson describes the clinical picture in six patients, all men, between the ages of fifty and seventy-two years on the basis of his observations in his practice but also on the streets. The cardinal symptoms described by Parkinson are:
- Involuntary tremulous motion
- Lessened muscular power
- A propensity to bend the trunk forwards.

The movement disorders associated with the symptoms of Parkinson Syndrome, cannot be a new disease. Even Parkinson mentions shaking limbs described by the antic Greek physician Galen and later by such celebrated physicians like Cullen. There is mention of hemiplegia and similar disorders in the ancient Indian medicine Ayurveda in the Charaka Samhita (500 BC). The paralytic symptoms there, are classified as Vata disorders. However, the description of the cardinal symptoms as related to the present concept of Parkinson syndrome started with the original essay by James Parkinson. It was however five decades later Jean-Martin Charcot who added rigidity to the group of symptoms and called the condition as malady of Parkinson.
Considering the life history and professional activities of James Parkinson, it can be inferred that Parkinson during his lifetime did not expect much recognition for his description of the six clinical cases. In addition to his medical practice he was the author of several geological publications during the years 1797 – 1811. Along with other scientists Parkinson founded the Geological Society of London and authored a study “Observations on Some of the Strata in the Neighborhood of London, and on the Fossil Remains Contained in Them.” It is stated that during his life time Parkinson received little attention from his English speaking colleagues until an American JG Rowntree made a publication in the Bulletin of the Johns Hopkins Hospital “English born, English bred, forgotten...”
by the English and the world at large, such was the fate of James Parkinson.\textsuperscript{3}

The original paper on Shaking Palsy (Paralysis agitans) by James Parkinson was based on the keen observation of the patients involving a mastery of history taking. Parkinson writes: “So slight and nearly imperceptible are the first inroads of this malady, and so extremely slow its progress, that it rarely happens, that the patient can form any recollection of the precise period of its commencement. The first symptoms perceived are, a slight sense of weakness, with a proneness to trembling in some particular part; sometimes in the head, but most commonly in one of the hands and arms.”\textsuperscript{1} It is interesting to note that even today while taking clinical history it is difficult to estimate the actual period of the beginning of the symptoms as the milder symptoms were not taken seriously by the patients until tremor and akinesia became clearly manifest. Even the unilateral involvement of the extremities has been noted by Parkinson. The age group of six patients, all men, described by Parkinson holds good even today as in majority of cases the symptoms begin after the age of fifty years. Even the progression of clinical course has been mentioned by Parkinson in the following sentence: “As the debility increases and the influence of the will over the muscles fades away, the tremulous agitation becomes more vehement. It now seldom leaves him (the patient) for a moment; but even when exhausted nature seizes a small portion of sleep, the motion becomes so violent as not only to shake the bed-hangings, but even the floor and sashes of the room. The chin is now almost immovably bent down upon the sternum. The slops with which he (the patient) is attempted to be fed, with the saliva, are continually trickling from the mouth. The power of articulation is lost.”\textsuperscript{1}
The clinical description of the cases by James Parkinson refers mostly to our present concept of idiopathic Parkinson disease; one case however could also speak for a multisystem atrophy. For the last 150 years, particularly after the syndrome was named after Parkinson by Jean-Martin Charcot, much clinical and scientific knowledge has been added to the understanding of this disease. However the original description of James Parkinson holds good to a considerable extent even today. In his case history VI Parkinson writes: “At present he (the patient) is almost constantly troubled with the agitation, which he describes as generally commencing in a slight degree, and gradually increasing, until it arises to such a height as to shake the room, when, by a sudden and somewhat violent change of posture, he (the patient) is almost always able to stop it. But very soon afterwards it will commence in some other limb, in a small degree, and gradually increase in violence.”1 The above description could partly suit for our present observation of dyskinesias in patients with long history of Parkinson disease who are also on Levodopa treatment.

It can be noted that neuromuscular disorders involving the motor system such as hemiplegia, paraplegia are known for longer time in the medical literature and even movement disorders such as tremor is also mentioned since hundreds of years. The movement disorders mentioned in the form of a syndrome however has been an original contribution of James Parkinson and later by the succeeding authors such as Charcot. Even Parkinson considers tremor and other conditions of shaking as different than his conception of shaking palsy. At present we know however that paralysis does not occur in the idiopathic form of the Parkinson syndrome. There is also some reference in the Essay by Parkinson on the possible
etiological factors related to the syndrome which do not have much relevance at the present stage of development in neurology. He tries to emphasize however that no clear etiology was found in his cases. Parkinson mentioned that: “all that has been ventured to assume here, has been that the disease depends on a disordered state of the part of the medulla which is contained in the cervical vertebrae. But of what nature that morbid change is and whether originating in the medulla itself in its membranes, or in the containing theca is at present the subject of doubt and conjecture.” In his reference to the methods of cure Parkinson writes: “There appears to be sufficient reason for hoping that some remedial process may long be discovered by which at least, the progress of the disease may be stopped. It seldom happens that the agitation extends beyond the arms within the first two years, which period therefore, if we are disposed to divide the disease into stages, might be said to comprise the first stage. In this period it is very probable that remedial means might be employed with success.” He further mentioned: “It is obvious that the chance of obtaining relief will depend in a great measure on the period at which the means are employed. As in every other disease, so here the earlier the remedies are resorted to, the greater will be the probability of success.” 1 However, the means of therapy mentioned are inadequate as it was the case in most of the diseases two hundred years ago. During the past one hundred years the drugs used to control tremor involved in the Parkinson disease were various Belladonna-preparations in the form of anticholinergic drugs. Some of these drugs are given even today which will be discussed in the later pages of the book. In addition to these drugs attempts were made during the first half of the twentieth century with such treatment as arsenic drugs, ephedrine
as well as different kinds of physical treatments. Already in the second half of the nineteenth century attempts were made to treat Parkinson patients also with surgical operations which sometimes caused severe injuries to the nervous system resulting even in hemiplegias.\(^4\)

Jean Martin Charcot described 1873 in Paris the clinical picture of Parkinson syndrome as maladies de Parkinson.\(^2\) Around twenty years later a major contribution to the pathophysiology of Parkinson syndrome was made by Blocq and Marinesco in 1893 also in Paris.\(^5\) They described for the first time about the pathophysiology related to substantia Nigra which was a major milestone in understanding the disease. A comprehensive presentation of the anatomy, pathophysiology and clinical course of Parkinson syndrome was made by Trétiakoff in 1919.\(^6\)

Drug treatments in different forms were tried already at the second half of nineteenth century. To begin with there were crude extracts of Belladonna, only much later in the 1940s synthetic anticolinergic drugs were produced. The real clinical and research oriented developments related to the Parkinson syndrome began to appear in the form of different studies only around the second half of the twentieth century. Consequently basic researches concerning the pathophysiology of Parkinson syndrome and drug research are being conducted throughout the world for the last fifty years. Parkinson syndrome today is a major neurological disease comparable to such diseases like multiple sclerosis, epilepsy and cerebrovascular disorders. Even though several aspects regarding the etiology and pathophysiology are not known, much can be done to help the patients with the wider availability of anti-Parkinson drugs as also with surgical methods. A significant milestone in the development of drug therapy was the research related to the deficit and substitution of...
Dopamine. Kathleen Montagu identified Dopamine as neurotransmitter in central nervous system for the first time in 1957. Ehringer and Hornykiewicz as well as Birkmayer and Hornykiewicz recognized Dopamine deficit as the cause for Parkinson syndrome and administered Levodopa as a break through in 1960 and 1961.

The first fifty years after the publication of the famous essay by James Parkinson, the clinical condition remained without much attention by the then medical circles in Europe and elsewhere. It was the study of Charcot in 1873 which brought the syndrome into the mainstream of the medical profession. Charcot described rigidity as an important clinical feature in presenting his concept of Parkinson syndrome. In the original essay on six patients, Parkinson did not mention rigidity specifically probably because of the small number of patients, three of whom he had observed only on the streets. Charcot made further examinations of the clinical conditions as well as autopsy of his patients but could not find a convincing brain lesion as an etiological substrate. However, he tried for the first time some Belladonna preparations for treating the patients. Further progress regarding better understanding of the disease was made after the studies of Trétiakoff 1919 who established substantia Nigra as morphological substrate in the etiology of Parkinson disease. However, the advancement in the drug therapy is the result of several clinicians and researchers only around 1960 beginning with the studies of Ehringer, Hornykiewicz, Birkmayer and others.
Clinical Findings
There are some terminological differences regarding the Parkinson syndromes. These syndromes are disorders of the extrapyramidal system which are characterized by different movement disorders involving the pathophysiology of basal ganglia. The extrapyramidal system (basal ganglia) consists of the following structures which however must be considered as a functional entity (Fig. 2.1).

- Corpus striatum (nucleus caudatus and putamen)
- Nucleus lentiformis (putamen and globus pallidus)
- Corpus luysi (nucleus subthalamicus)
- Substantia nigra and nucleus ruber
These structures are intensely connected to one another as well as with thalamus, cortex and midbrain, through ascending and descending fibers. A dysfunction of the extrapyramidal system can lead mainly to:

- An akinetic rigid syndrome which causes reduced spontaneous movements, increase of muscle tone and involuntary movements as characterized by Parkinson syndrome.

- A hyperkinetic hypotone syndrome causing involuntary arrhythmic movements, reduced muscle tone characterized by such disorders as chorea, athetosis, hemiballismus and dystonia.

The classification of Parkinson syndromes or Parkinsonism is somewhat different in different regions of America and Europe which is also because of the influence of such languages as English, German and French. What is generally understood in the medical literature about Parkinson syndrome refers to the Parkinson disease characterized by such cardinal symptoms as akinesia, tremor, rigidity and disturbance of gait. At least three of these cardinal symptoms have been referred clearly by James Parkinson in his description of the original six cases. A clear differentiation of the various forms of the extrapyramidal disorders into specific diagnostic criteria is necessary for a proper diagnosis and treatment. The syndrome must also be differentiated clinically from cerebellar disorders as well as from other neurological conditions involving upper and lower motor neuronal lesions. As extrapyramidal disorders including Parkinson syndrome are mainly a clinical diagnosis much care must be taken to make a differentiation regarding the different forms of syndromes which include the following:

- Atypical Parkinson syndromes:
  - multisystem atrophies:
- progressive supranuclear paresis including Steel-Richardson-Olszewski syndrome
- cortico basal degeneration
- subcortical arteriosclerotic encephalopathy

Other extrapyramidal disorders:
- chorea
- athetosis
- hemiballismus
- dystonia
- essential tremor

It can be assumed therefore that it is not always easy in the clinical practice to diagnose a Parkinson disease or the idiopathic Parkinson syndrome during the early phases of clinical course when the cardinal symptoms are not fully manifest. Some of the syndromes will be mentioned here in short form for the purpose of differential diagnosis.

Multisystem Atrophies

These are rather rare diseases compared to the Parkinson syndrome. Some of these syndromes may show a clinical crossover from one type to the other and as such a clear differentiation during the early clinical course is not always possible. In general most of these syndromes begin somewhat earlier in life, already around the age of thirty years and comparatively earlier than idiopathic Parkinson syndrome which generally begins around midlife. However, there are variations even with Parkinson syndrome where cases are seen in earlier age group and also after the age of seventy years. Even in the cases described originally by James Parkinson he mentioned patients in the age group of fifty to seventy years.
Orthostatic Hypotonia Shy-Drager Disease
The clinical symptoms are characterised by giddiness, orthostatic syncope with reduced blood pressure by altered position, particularly when the patient is standing. Several neurovegetative disturbances are seen such as loss of sweating, impotence, incontinence and fasciculation of muscles also with muscle atrophy. A predominant feature is the ophthalmic paresis including iris atrophy. The extrapyramidal symptoms are tremor, rigidity and akinesia. The disease begins generally after mid-age and the predominance is considerably more in men than in women. The clinical condition is progressive mostly without symptoms of dementia but the life expectancy is reduced as the mortality can occur within a few years after the clinical diagnosis of the condition.

Striatonigral Degeneration
The disease can show earlier symptoms associated with Parkinson disease, later during the course of the illness the symptom complex may be dominated by neurovegetative disturbances such as hypotension, syncope and incontinence. The symptoms do not respond to a medication of Levodopa. The clinical course may show during the later stages of the disease pyramidal and cerebellar symptoms.

Olivopontocerebellar Atrophy
This disease could appear with or without genetic predisposition. There is an autosomal dominant genetic form involving chromosome six. As the name indicates the predominant symptoms are associated with cerebellum, whereas Parkinson symptoms may appear during the later clinical course of the disease. They may be associated also with pyramidal symptoms and the
patient may develop dementia during the course of the disease. The main neurological symptoms are tremor and ataxia as well as speech disturbances. There may be akinesia, rigidity and urine incontinence. The diagnosis can be done through cranio-cerebral MRI which would show atrophy of the cerebellum and pons. The prognosis is bad as the disease generally leads to mortality within a period of one to four years.

**Progressive Supranuclear Paralysis**

This progressive disease is more often seen in men and may show different Parkinson related symptoms and often mistaken for a real Parkinson disease. It is also known under the terminology of Steel-Richardson-Olszewsky syndrome. The disease manifests between the age of fifty to seventy years and shows to begin with most of the symptoms associated with an idiopathic Parkinson syndrome. A significant difference however is that the patients do not show a posture of bending the head forwards but because of the hypertonic neck muscle the head is rather bent backwards. The patients may have akinesia, rigidity, dysarthria and even drop attacks. They may show during the course of the disease difficulty of swallowing and also ophtalmic disturbances. During the further course of the disease the patient may develop a sub cortical dementia sometimes the dementia may be even an early symptom. There may be disturbances of the pyramidal system. The prognosis is bad because the mortality occurs within few years after the beginning of the disease.

**Cortico-basal Degeneration**

This illness is characterised by progressive Parkinson like syndrome with akinesia and rigidity as well as disturbance
Clinical Findings

of gait and speech. The disease can be mistaken for a genuine Parkinson syndrome because of the predominant symptoms, as in this case mostly unilateral motoric disturbances are seen. In addition the syndrome may be characterized by the presence of cortical neuropsychological deficits as well as predominant gait disturbances which is sometimes called “alien-limb-syndrome”.

Dementia with Lewy-bodies

This clinical syndrome presents itself with several of the characteristics associated with a genuine Parkinson disease however with the marked difference of a progressive dementia. The patients have increased gait disturbances and tend to fall during walking. Within a few years after the commencement of disease the patients show increasing tendency to neuropsychological deficits as well as a fast progression to dementia so that the clinical picture resembles one of Alzheimer disease. The patients are oversensitive to neuroleptics drugs and the prognosis is bad.

Parkinson Syndrome (Disease)

The Parkinson syndrome is a major disorder of the extrapyramidal system and is one of the common clinical conditions seen in the general population. Almost one percent of the population above the age of sixty years suffer from this disease. Even though Parkinson syndrome is not necessarily a disease of old age, it generally begins around midlife mostly in the late forties or early fifties. There are however patients who develop the disease somewhat earlier and others much later after seventy. Both sexes are more or less equally involved. The commencement of the disease is mild with insignificant motor symptoms such
as unilateral tremor, general slowing of the motor function associated with tiredness and gait disturbances. In many cases however tremor is not present as a cardinal symptom but akinesia followed by rigidity and walking problems. It is known in the clinical practice that before a Parkinson syndrome is diagnosed it generally takes one to two years. Even after the diagnosis is made, there may be considerable lapse of time before the drug treatment is commenced as not only the patients but even the physicians may be reluctant to begin with a medication. As the diagnosis of a Parkinson syndrome is even today mostly the result of clinical examination and evaluation, it is understandable that most physicians take time before the pronouncement of the actual diagnosis. On the other hand in the initial stages of the clinical condition a clear diagnosis is not always easy. Similar is the case when the disease commences with atypical symptoms as in the case of certain associated conditions presenting symptoms of a Parkinson syndrome as shown below:

- **Hereditary forms:**
  - Parkinson disease of the type of paralysis agitans
  - Parkinson dementia complex
- **Other forms:**
  - Parkinson symptoms in other degenerative diseases
  - Post encephalitic parkinsonism
  - Arteriosclerotic parkinsonism
  - Rare forms:
    - Parkinson as the result of multiple trauma for example by boxing
    - Carbon dioxide intoxication
    - Manganin intoxication
    - Other intoxications
- Side effect of drugs such as neuroleptics and anti-emetics
- Tumors and other cerebral conditions.

**Idiopathic Parkinson Disease (Syndrome) IPD**

What is commonly seen in the medical practice is the idiopathic Parkinson disease which can also be called as a genuine Parkinson syndrome. This is a major neurological disorder seen throughout the world. It is this syndrome which has been originally described by James Parkinson and the cardinal symptoms of the syndrome described by Parkinson and later by Charcot hold good to a considerable extent even today. The clinical symptoms can be broadly classified as follows:

- **Disturbed automatic motoric functions**
  - akinesia
  - reduced movements
  - pro- and retropulsion
- **Increased extrapyramidal muscle tone**
  - rigidity
  - increased postural tone
  - increase of antagonistic tone
  - Cogwheel or clasp knife phenomena
  - Postural instability
- **Tremor (in the beginning mostly unilateral)**
  - Further somatic symptoms
  - Micrography
  - Speech disturbance
  - Breathing disturbance
  - Motoric weakness
  - Vegetative symptoms such as masked face, increase of saliva and sweating
  - Dystonic movement disorders
20 Step by Step Treatment of Parkinson Disease

• Psychic symptoms
  - Slowing of cognitive functions particularly of thinking
  - Mood instability
  - Dementia
• Late symptoms also associated with L-Dopa-Treatment
  - On-off-phenomena
  - Drug related dyskinesia
  - Hallucination and psychosis.

Akinesia

It can be understood from the above mentioned symptom complex that not all the signs and symptoms are necessary to make a diagnosis of an idiopathic Parkinson disease. Some of the most important symptoms are the disturbance associated with the normal automatic movements. The patients particularly in the early stages of the disease can not describe these movement disorders properly but mention that their movements are blocked or reduced. This reduction of spontaneous movement leads to the condition akinesia which is characterised by different signs and symptoms such as masked face, reduction of eye movement particularly the eyelids and the reduction of entire automatic bodily movements. The patients give the impression of moving en bloc, particularly the movements of extremities of one side being reduced. This leads again to further disorders such as altered gait leading to small steps. There is a change of posture of the patient while standing and walking where the body is bent forwards and moved with reduced dynamic which gives the impression of even younger patients looking much older. When the patients start walking they are unable to control their gait properly and give the impression of either going
too fast or losing control. As a consequence the patients tend to fall down while walking particularly when they start to walk. On the other hand it can be seen that during the examination the patients can develop higher emotion and suddenly go faster. Similar is the case related to speech. The speech is reduced and becomes lower which sometimes during emotion can become rather high. Otherwise there is almost always a change of the voice and the writing becomes smaller during the clinical course of the Parkinson disease.

**Rigidity**

The increased resistance to passive movement is called rigidity. The rigidity in case of Parkinson disease is a cardinal symptom as also akinesia and tremor. During the clinical examination the rigidity seen in Parkinson patients must be differentiated from the pyramidal disturbances mainly the spasticity. The rigidity can be examined by passive bending of the elbow during the neurological examination. Generally in case of idiopathic Parkinson disease only unilateral rigidity is seen which can be compared during the examination with the contralateral side. In examining the rigidity one should try to assess the so called cogwheel or clasp knife phenomena. There is an increase of muscle tone particularly when the patients are standing so that they give the impression of bending forwards. This altered posture is an important factor in the diagnosis of an idiopathic Parkinson disease.

**Tremor**

The tremor at rest is a cardinal symptom in Parkinson disease but is not obligatory for the diagnosis even though
for the patients and environment it could be a very disturbing factor. The tremor is generally unilateral at least during the early stages of the disease. It is a rhythmic regular distal tremor at rest which by activity of the patients gets reduced. The tremor has a frequency of 4 to 6 per second and shows changing intensity. During the examination for example of Romberg test or Finger Nose test the tremor can considerably reduce or disappear. On the other hand when the patient is being observed by others the rest tremor can increase in intensity. The increase of tremor is generally seen in patients during blood pressure check up of the arm with unilateral tremor. During the course of disease the tremor can increase and show the component of “pill rolling” or “coin counting”. Emotions increase Parkinson tremor and the tremor generally disappears in sleep. The tremor is generally embarrassing for the patients and the relatives; however the suffering of the patients due to tremor is less compared to the other symptoms such as akinesia and rigidity. In most cases however the patients go to the physician because of the appearance of tremor which is socially a disturbing factor and accordingly a reason for medical consultation. Some of the progressive cases of Parkinson disease show considerably less tremor, whereas milder cases may show initially more tremor which may remain also somewhat drug resistant particularly to classical drugs such as L-Dopa or some Dopamine-antagonists. Tremor however dramatic it looks, can never be the only symptom associated with Parkinson disease. The essential tremor for example is much more common in the general population.
Abnormal Gait and Posture

The abnormal posture of trunk bending forwards in Parkinson disease is also a prominent feature. In progressive clinical condition the patient is often stooped forwards and has difficulty when starting to walk. The patient finds it difficult to get up from bed or a chair and while standing shows a flexed posture. The patient may lean forwards while starting to walk before one is able to advance. The gait shows small shuffling steps and absence of the swinging of arms. While testing the gait the patient may show to begin with small steps, often increasing the gait until the patient is almost running. The reduced arm swinging particularly of one side is a typical characteristic of the gait in Parkinson syndrome. In advanced cases the patient tends to walk with increasing speed to prevent a fall which is termed as festinating gait and is the result of altered center of gravity (Figs 2.2A to C).

Figs 2.2A to C: Posture of patients with IPD
The Other Clinical Features

Even though Parkinson disease is mostly a disturbance of the motor system as the result of extrapyramidal disorders, during the course of illness the patients show further somatic, neurovegetative and psychic disturbances. Because of the motor dysfunction there is a tendency to fall down which the patients prevent by their altered posture. The voice is of low volume or hypophonia and is generally less modulated. The patients speak in a low voice and sometimes seem to have no control about their vocabulary. There is micrography or small tremulous handwriting which must be tested during the clinical examination of a patient. Sometimes it is useful to compare the handwriting of the patient during the examination with earlier writings if such ones are available. If the patients have a tendency to write in capital letters, they must be encouraged to write in a normal style. There is often fluttering of the closed eyelids associated with mask-like face and infrequent blinking.

During the examination of a patient one has sometimes the impression that the patients have a weakness of the muscle functions which however on further examination may disappear and show a normal muscle tone. Probably this motoric weakness associated with tremor which gave James Parkinson the impression of a “shaking palsy”. Several patients complain of back pain particularly on waking up in the morning probably because of the disturbed sleep due to akinesia and rigidity. There are several neuro vegetative disturbances which the patients complain, such as high perspiration, urge incontinence, sexual disturbances and depressive mood changes. Depression seems to be fairly common among Parkinson patients. In the clinical practice one sees that many patients
with idiopathic Parkinson disease under good medication however live an intact family and professional life for many years. Serious personality changes leading to dementia occur in a smaller percentage of the patients during longer course of the disease or with other complications such as Lewy-body Dementia or other forms of Parkinson disease. Some recent studies show however that even an idiopathic Parkinson syndrome may have a complex pathophysiology which would lead to the hypothesis that even such a syndrome may be considered as a progressive multisystem disorder. For the purpose of clinical management it is therefore necessary to evaluate the different clinical forms related to the less progressive idiopathic forms and the other severe forms showing faster progression of motoric and other symptoms, even if the etiology of Parkinson disease has not been established.

The Preclinical Phase of Idiopathic Parkinson Disease (IPD)

Even though several basic mechanisms leading to the clinical manifestation of an idiopathic Parkinson disease have been understood, the basic pathology has not been clearly identified. The main clinical features namely akinesia, rigidity and tremor associated also with postural changes form the diagnostic criteria of IPD. The response to drug therapy particularly to Levodopa but also to the Levodopa agonists speaks also for an assumption of the diagnosis of an IPD. The differentiation of an idiopathic form should be considered mostly on the basis of lack of specific etiological factors. A progressive and irreversible degeneration of the pigmented dopaminergic neurons in substantia Nigra as also the projection of such neurons to dorsal striatum has been considered as the cause for clinical
manifestation. In the clinical practice it is important to evaluate if there are any factors predictable in an otherwise healthy individual as a risk factor for the later manifestation of Parkinson disease. It is not possible to examine a healthy population for the evaluation of such preclinical assumptions. Only retrospective studies of the Parkinson patients may give us some inference about the possibility of premorbid factors which however remain diffuse and questionable. Through such retrospective studies certain common factors have been collected such as constipation with less than one bowel motion per day. Reduced ferritin levels have been recorded in a good percentage of Parkinson patients. Slight disturbance of motor functions and several neurovegetative disturbances in patients have been seen in the preclinical studies. Some studies have discussed the possibility of a “Parkinson personality” with increased tendency to depression before the clinical manifestation of the disease. It must however not be forgotten that most of the symptoms can be present in the general population particularly in the middle age and later.

**Depression in Patients of IPD**

Community based epidemiological studies have shown that depression is an important feature also in the preclinical phase of idiopathic Parkinson syndrome. One study with 245 patients of idiopathic Parkinson disease found that 8% had major depression while a further 45% showed milder grades of depressive symptoms. On the whole 25% of the total collective had milder to severe grades of depression which was much higher compared to the prevalence of depression in the general population. Such studies postulate that depression may be the first preclinical phase of a Parkinson disease, much before the
motoric disturbances are manifest. Some such studies show that almost 15% had developed a moderate to severe depressive illness sometimes between 6 months to 8 years before the diagnosis of IPD was ever made. In the clinical practice one sees depressive symptoms in a good number of patients with IPD. Some studies estimate as high as 50% of the patients with Parkinson disease as having depression which needs treatment. This is understandable to a certain extent as Parkinson disease is a chronic condition creating problems in daily life for the patient, which under normal circumstances must lead to depressive mood changes, unlike other paroxysmal disorders such as epilepsy or migraine where a patient during the interval is free of symptoms. The Parkinson patients are reminded of their problems on every wakeful hour. Considering this factor one can consider depression also as a reactive illness resulting from the day-to-day problems. Some studies including the above mentioned consider however depression as a factor associated with the Parkinson disease in the same way as other motoric and neurovegetative disturbances.
Chapter 3

Epidemiological Aspects
Among the positive factors which have been evaluated in the prevention of Parkinson disease are strangely studies related to smoking and coffee drinking. These studies have shown the reduced risk of developing Parkinson disease in people who drank several cups of coffee daily associated with smoking. The study could however only partly establish the effect of coffee or the intake of caffeine as a preventive effect without the associated smoking of tobacco. It is presumed that the neuroprotective effects of caffeine and tobacco may be mediated through the adenosine receptor antagonism to improve the motor deficits. Whatever be the preventive aspects of such a method, it would not be possible in the clinical practice to advise any person to take up to smoking for the possible prevention of a Parkinson disease which is prevalent in only around 1% of the population above middle age. Coffee drinking has been a common practice in the majority of the population in many countries of the world. It could however be interesting to know about these factors during the history taking and treatment of patients with idiopathic Parkinson disease.

There have been several population based studies for the assessment of epidemiology of Parkinson syndrome. In a large European study involving more than 16,000 participants, there were 252 patients with Parkinson syndrome. In this study particularly the relative risk of death associated with Parkinson disease has been evaluated. It showed a slightly higher risk of death rate for men with 2.3 compared to women. The age group of patients was between 55 and 84 years where co-morbidity may be expected independent of Parkinson disease. Moreover, the study is nearly ten years old and the situation regarding the development of drugs for Parkinson disease has improved in this period of time. In
general different epidemiological studies show that around 1% of the population above the age of 60 years may have an idiopathic Parkinson disease. The yearly incidence has been considered to be 0.1:1’000 of the general population. There seems to be a prevalence for people beyond the age of 55, 1.2% for men and 1.5% for women. The other studies however mention that there may be a slightly higher prevalence for men above the age of 60. In the further age group of 75 to 84 years a prevalence of 3.1% has been recorded whereas in case of people in the age group of 95 to 99 years a higher prevalence of 3.2 to 5% was seen.

Genetic factors seem to play a considerably higher role in the etiology of IDP. Several single gene defects have been associated in the etiology of Parkinson disease particularly in people with young age onset. However, even in the case of people who develop the disease after middle age a genetic factor as a possible etiological factor has been discussed. Abnormalities in the parkin gene were associated with recessive juvenile Parkinson syndrome. Further in families where at least one member under the age of 45 years developed IDP the risk of offspring or siblings developing the disease was considerably higher. The studies conclude that parkin gene mutations are a major cause for the development of juvenile or early age Parkinson disease.

From some of the studies it cannot be properly assessed whether the patients had really idiopathic Parkinson disease or other Parkinson syndromes which could not be differentiated during the period of epidemiological study. As has been seen from the earlier chapters the differentiation of the clinical picture of certain subtypes of Parkinson syndrome is not always easy particularly during the early stages of the Parkinson syndrome. During history taking and clinical examination it is, however, important
to evaluate the possibility of a genetic predisposition particularly in patients who develop the disease before the middle age.

Over the last 25 years there have been reports about the possibility of toxic effects of pesticide use in the etiology of Parkinson disease. Again there were other reports bringing the association of different environmental factors also in the etiology of IPD. However, such studies have their own limitations because of the lack of clear identification of any of these factors. It is known that several environmental factors may have a negative influence over the general health of the population not only in respect of neurological but also other diseases. Clear community based studies involving a particular region or a country which was more exposed to such environmental risk factors have probably not been done. Moreover Parkinson disease is not known to occur in epidemic or in endemic proportions in any region or country and as such the influence of negative environmental factors remains mostly a hypothesis. Probably several factors are responsible for the occurrence of Parkinson disease as in the case of many other chronic diseases as well. It can be more or less clearly accepted that there is a long preclinical phase in any individual before the idiopathic Parkinson disease is actually manifest. A prevention therefore is not possible with any specific methods. It would, however, be interesting to plan epidemiological studies regarding the prevalence and incidence of Parkinson disease in such countries where coffee drinking is a pronounced social factor or where the population is specially exposed to definite environmental toxins. As in the case of several other neurological diseases the idiopathic Parkinson syndrome must be considered as an unpredictable event in the life of an individual. Different studies have, however,
recognized latent phases or the presymptomatic stages before the actual manifestation of the IPD, which could be as long as five and forty years. It is assumed that during this long phase of latency, there may be a slow but continuous loss of pigmented, neurons in the substantia Nigra and the other structures of basal ganglia. The retrospective studies have shown that the patients had during this preclinical phase such symptoms as olfactory dysfunction, various neurovegetative disturbances and mood changes leading to a clinical depression. There have been attempts to develop different diagnostic questionnaire to assess the possibility of a later manifestation of IPD. In the clinical practice however these methods have not been established as it is not sensible to examine a patient unless there has been a clinical question for the diagnosis of a particular disease. We do not have a proper tool in the clinical neurological practice for the proper assessment of a person for example the offspring or the sibling of a known patient of IPD. In case of epilepsy with familial tendency, it should be possible to evaluate the risk of future epilepsy for example in an offspring or sibling through an EEG-examination. Because of these limitations the Parkinson disease can be diagnosed only when the symptoms are clearly manifest. Expensive methods such as PET may be rarely employed in suspected cases of IPD.

In the epidemiological survey of Parkinson disease, it is necessary to consider the differential diagnosis of various extrapyramidal disorders particularly the essential tremor. It is a common experience in the neurological practice that some patients who are referred for the diagnosis of suspected Parkinson disease have essential tremor. Sometimes as high as 25% of patients diagnosed as having idiopathic Parkinson disease had later a confirmed
diagnosis of essential tremor. The clinical differentiation of essential tremor from IPD will be referred later. In addition several other extrapyramidal disorders such as multisystem atrophy, chorea-Huntington, hemiballism and cerebellar diseases must be differentiated from an idiopathic Parkinson disease. Even though some conditions may be clinically fairly well differentiated, the others may require such methods as positron emission tomography (PET) and single photon emission computer tomography (SPECT). It is therefore necessary to consider the differential diagnosis not only for the epidemiological survey of IPD but also before beginning a drug therapy. Some of the common extrapyramidal as well as cerebellar and cortico-basal disorders already mentioned are: multiple system atrophy, progressive supranuclear palsy, cerebellar ataxia, cortico-basal degeneration and other neurodegenerative conditions. Any neurological disease with symptoms of Parkinson disease but showing fast progressive cognitive degeneration must be clearly differentiated from IPD. A genuine Parkinson disease generally shows a slow progressive clinical course also without considerable reduction in the life expectancy of a patient.

**Clinical Exploration**

Several diseases of the central nervous system begin with a preclinical phase, but it is so insignificant that the patients and the environment do not consider the discrete personal changes as the early symptoms of a serious disease. Such is the case with multiple Sclerosis, Parkinson syndrome and some cerebral tumors. Only retrospectively during the later history taking one can collect information regarding the early symptoms which the patients generally did not
consider as serious. Different is the situation regarding paroxysmal disorders such as Epilepsy, migraine, transient ischemic attacks or cerebral insults, where the early symptoms are so clear for the patients and the environment that generally a diagnosis is done soon after the beginning of the first symptoms. In case of serious neurological diseases which begin in early or later adult age the approach to diagnosis and treatment must be considered not only from the medical but also from psychosocial and philosophical points of view. In these cases the patients generally had an intact family and professional life and the occurrence of a disease is for them a blow of destiny. Attempts must therefore be made during the clinical examinations not only to arrive at a clear diagnosis to the extent possible, but also to consider the sensitivity of the patient carefully during the history taking. Even though it is necessary to get the maximum information regarding the clinical signs and symptoms, one must be careful with questions to the patients for example about one’s inability to write, speak or eat with fork and knife and such other daily functions. It is known in the clinical practice that some very sensitive patients then avoid going to a neurologist or to a physician which would mean a preventable delay in the diagnosis and treatment. It is therefore useful to hold two consultations with the patient in short intervals before the diagnosis is pronounced. Actually it is not possible to make a clear diagnosis of idiopathic Parkinson disease in the early stages as akinesia and rigidity may be less pronounced and tremor may be totally absent. If tremor is present it must be differentiated from the essential tremor. The tremor in case of Parkinson patients is a rest tremor and mostly unilateral, has a frequency of 4 to 6/sec sometimes at rest even slower 3 to 5/sec. The tremor disappears during certain active examinations such as the
finger-nose-test but at rest and during emotions it may increase. In case of an essential tremor it is mostly bilateral and increases on intention. At rest the bilateral tremor may be less significant and on activity the tremor generally does not reduce. It is important to question the patients with essential tremor whether they have experienced that the tremor reduces when they take alcoholic drinks. Parkinson tremor is not influenced by the use of alcohol. People with essential tremor do not have associated rigidity or akinesia and have no postural changes. From the psychiatric point of view most of the patients with idiopathic Parkinson syndrome show even during the earlier phases mood changes related to depression whereas patients with essential tremor are somewhat nervous but generally not depressive. The neurological status in case of patients with essential tremor is otherwise generally normal. A corresponding familial disposition is, however, possible in both cases of essential tremor as well as in Parkinson disease. The essential tremor belongs to the physiological postural tremor which is enhanced and more or less continuous in patients, with a frequency of 8 to 12/sec. However, postural tremor may be present in case of patients with Wilson’s disease or cerebellar disorders. Some serious cases of essential tremor show the characteristic of a flapping tremor where the patients almost in a paroxysmal way shake both their hands like the wings of a flying bird. Most of these essential tremors however disappear at rest or when the patient is sleeping.

The rest tremor is mostly suggestive of a Parkinson syndrome whether the problem is related to idiopathic Parkinson disease or other kinds of extrapyramidal disorders leading to any of the Parkinson syndromes. The frequency is slower, 4 to 6/sec and in case of longer clinical course these tremors may show the characteristic of pill
rolling in a rhythmic manner, opposing circular movements of the thumb and index finger of one hand. The further clinical examinations would show whether the rest tremor seen in a patient belongs to the diagnosis of an idiopathic Parkinson syndrome or to other disorders associated with the extrapyramidal system.
Differential Diagnosis
Chorea

Chorea belongs to a group of extrapyramidal disorders characterized by hyperkinetic and hypotonic symptoms. Chorea shows rapid asymmetric muscle movements which occur involuntarily and somewhat unpredictably in different parts of the body. They could be sometimes discrete movements as in case of embarrassing situations or may show pronounced movement disorders of distal parts associated with facial grimacing and tongue movements. The gait of the patients becomes irregular and unsteady, moving from one side to another showing such movements of a “dancing gait”. The speech becomes also irregular and may sometimes show an explosive character. In advanced stages the patient may also show an athetotic character of movement. The severe movement disorders may reduce somewhat during sleep. The movements can be both sided or predominantly unilateral. During the clinical examination the muscle tone in patients with chorea is reduced, otherwise the patients may show a normal neurological status. The clear pathology of chorea has not been properly established, the autopsy reports have shown however that in many patients there has been a considerable loss of neurons in caudate nucleus and putamen. The clinical condition can be provoked by the use of dopaminergic agonist drugs.

There are different forms of chorea associated with heredity such as Huntington’s disease, benign hereditary chorea, Wilson’s disease and other kinds of chorea associated with perinatal encephalopathy as well as various other forms as follows:
- Pseudonyms chorea
- Chorea gravidarum
- Chorea due to drug toxicity such as by Levodopa, Lithium, Phenytoin and oral contraceptives
- Chorea due to various medical disorders such as thyreotoxicosis, Edison’s disease, systemic lupus erythematoses, encephalitis lethargica
- Chorea due to cerebrovascular disorders such as vasculitis, following stroke
- Chorea due to lesions of the subthalamic regions

**Hemiballism**

Hemiballismus is characterized by unilateral chorea like movements, however, with violent pushing movement disorders of the proximal parts of the limbs. Ballism and hemiballism are associated with lesions of corpus subthalamicus luysi particularly because of ischemic disorders. It could be sometimes due to other kinds of cerebral disorders or as a complication of thalamectomy. Depending upon the etiology and clinical situation the movement disorder may recede after several weeks of onset. If the etiology of chorea and hemiballism is known the treatment should be directed at the cause of disorder for example withdrawal of the provoking drugs or treatment of thyreotoxicosis.

**Athetosis**

Athetosis is characterized by mostly distal abnormal movements which are slow, sinuous and sliding, which look rather like disturbed postures than actually a movement disorder. In this case the joints are overflexed and hyperextended with a strong antagonistic movement. Because of this, the movements take a bizarre form which may be static for a few seconds. Particularly the movements of the hands are characteristic of athetosis which give the
impression of “bayonet finger”. Because of these movement disorders, the gait is also changed and shows an automatic robot-like form. Often the athetosis may be accompanied by chorea-like movement disorders which then give the impression of “worm-like” movements. Athetosis may be caused by various disorders such as cerebral palsy, Wilson’s disease, Huntington’s disease and even later course of Parkinson disease. In the pathophysiology there is generally a loss of neurons in putamen and nucleus caudatus. Under the subgroup of athetosis there are such syndromes known as status marmoratus, status dysmyelini and Hallervorden-Spatz disease. These syndromes begin already in early childhood because of cerebral damage.

**Dystonia**

The terminology of dystonia can be used for such conditions where the movement disorders are characterized by abnormal postures in which single groups of muscles are involved with tonic contraction. There is a disturbed relationship between the agonistic and antagonistic muscles with the result of some muscle groups getting involved as in the case of torticollis spasticus or in writing spasm. In other cases the muscle disturbances can be more or less generalized as in the case of torsio dystonia. In this case one or more of the limbs are affected leading to segmented dystonia or the disorder may be restricted to localized muscle group leading to focal dystonia. The abnormal movements involving dystonia are not present during sleep but may be enhanced by emotion, stress and activity. In some cases however the abnormal movements may be seen only during voluntary activity as in the case of writing, chewing or speaking, leading to spasms.
Perinatal brain damage because of anoxia, birth injury, kernicterus are generally the etiological factors. In such cases the disorder begins already in the childhood before the age of five years and the children may show intellectual retardation. There may be other kinds of brain disorders as well, where pyramidal structures may be involved. Torso dystonia may be due to such conditions as Wilson’s disease or Huntington’s disease. Acute attacks of dystonia may happen also due to the side effect of several drugs including Levodopa, neuroleptics even Dopamine-antagonistic drugs.

**Huntington's Disease**

Huntington’s disease or Huntington’s chorea is a serious disorder traced to a single gene defect on the short arm of chromosome 4. It is inherited in an autosomal dominant manner, with the age of clinical manifestation depending upon the gene carrier whether it is of father or mother. In case of father being the carrier of the pathological gene, the disease could manifest before the 10th year of life. If the mother is the gene carrier the first manifestation of the disease may be somewhat later. In general the offspring of affected parents have a 50% risk of developing the disorder. Huntington’s disease occurs in all ethnic groups throughout the world. Its prevalence has been rated as 5 per 100,000 population. The first manifestation occurs between the age of thirty and fifty years, before which time most of the people getting this disease are already married or even having children so that the pathological gene may be transmitted further. The symptoms are progressive with abnormal movement disorders associated with cognitive changes. There are severe mood changes with irritability, depression and asocial behavior which gradually lead to
dementia. The motoric symptoms are characterized by chorea which may show during the clinical course severe disorders. The patients may have over the years psychosis, hallucinations and irreversible dementia. The prognosis is bad as patients usually do not survive ten years after beginning of the disease. A differentiation from Parkinson syndrome is here not difficult because of the symptoms which are mostly characterized by chorea like movements and severe cognitive disorders.

**Myoclonus**

Myoclonic jerks are muscle contractions which occur as sudden and rapid jerks. They may be of physiological character in many healthy individuals which happen while going to sleep or on awakening. Generally the myoclonic jerks have a generalized distribution or may be restricted to a particular part of the body in the form of segmental myoclonus. The myoclonus may be provoked by sensory stimulation particularly in case of generalized myoclonus. The myoclonic jerks which are bilateral, can be asymmetric but are entirely different from the symptomatology of tremor and akinesia. Myoclonics may be epileptic or non-epileptic in origin and may be easily differentiated from the cardinal symptoms of a Parkinson’s syndrome.

**Tics**

Tics are abnormal movements characterized by sudden and recurrent movements in different parts of the body mostly of hands and face. The movements are repeated in short intervals as a result of anxiety or in some cases even to suppress fear. It may increase on stress and decrease during concentrated work and disappears in sleep. Tics
can be common among children with some neurotic problems but may be associated with the condition of Gilles de la Tourette’s syndrome. Tics may be differentiated easily from Parkinson syndrome but may cause some difficulty in differentiating from chorea like disturbances.

**Wilson’s Disease**

Wilson’s disease is an autosomal recessive disorder associated with copper metabolism. The defect involves the long arm of chromosome 13. The condition produces neurological symptoms and hepatic disorders. It seems to be associated with the decreased binding of copper to the transport protein ceruloplasmin, because of which large amounts of unbound copper enter the circulation and are pathologically deposited in tissues, including brain, liver, kidneys and cornea. The average age of onset is about 10 to 11 years for patients with hepatic disorder and 19 to 20 years for those with early neurological symptoms. But the disease may begin also much later in life. The symptoms may be associated with joint disease, fever, hemolytic anemia or even behavioral problems. In the pathophysiology there is involvement of caudate nucleus, putamen, cerebral cortex and cerebellum. There may be postural tremor, chorea like movements of the limbs, grimacing of face, rigidity, dysarthria and dysphagia as well as ataxia. In the differential diagnosis of Parkinson’s syndrome with unusual clinical features Wilson’s disease must be considered.

**Restless Legs Syndrome**

Restless legs syndrome is a common disorder in the general population characterized by unpleasant sensation and
abnormal movements of the legs particularly while going to sleep or during sleep. It can occur sometimes when the patients are relaxed, in positions of sitting comfortably or in laying to rest. The patients feel a kind of unpleasant sensation deep within the legs and rarely also in the arms. The symptoms are almost always disturbing in sleep as the patients have to get up and walk a few steps or massage their legs before they go to bed again. Several patients suffer chronic sleeplessness because of the disorder. The condition can be diagnosed in a sleep laboratory and can be treated with Levodopa or Dopamine agonist drugs. The etiology is not known and the condition does not seem to be associated with Parkinson syndrome.

Normal-Pressure Hydrocephalus

The clinical picture of normal-pressure hydrocephalus may sometimes imitate a Parkinson syndrome particularly because of gait disturbances followed by such conditions as urinary incontinence and cognitive disturbances leading to dementia. However, contrary to Parkinson syndrome in case of normal-pressure hydrocephalus the patients have urinary incontinence right from the beginning of the clinical course and the progressive cognitive disturbances leading to dementia are also seen much earlier in hydrocephalus than in the case of IPD. The cranial Computed tomography and the MRI will give a clearer picture of normal-pressure hydrocephalus showing the dilatation of the ventricle system but without cortical atrophy. This disorder may be the result of head injury, intracranial hemorrhage or meningoencephalitis but sometimes the etiology may be completely unknown. Surgical shunting procedure with bypass is useful in most of the cases.
Creutzfeldt-Jakob Disease

The Creutzfeldt-Jakob disease may show some features of a progressive Parkinson disease but on clinical observation several of the symptoms are different. There is a dementia right from the beginning of the disease associated with myoclonic jerks and ataxia. There may be some pyramidal symptoms and visual disturbances. The disease is caused by Pryons infection and is a very fast progressive condition which may lead to death within a few months after the diagnosis. The EEG shows a clearer diagnosis of the Creutzfeldt-Jakob disease.

Alzheimer’s Disease

The Alzheimer’s disease is characterized by dementia which may show different neurological findings during the clinical course particularly some extrapyramidal symptoms. The clinical course is characterized right from the beginning by progressive cognitive disturbances leading to dementia. The other form of Lewy-body dementia with Parkinson symptomatic will resemble Alzheimer’s disease much more than the IPD. However, patients of Alzheimer’s disease have often extrapyramidal symptoms particularly tremor which is however not the type of rest tremor as seen in IPD. Some of the patients with Parkinson disease may show some characteristics of an Alzheimer’s disease with the exception of a pronounced dementia.
Chapter 5

Diagnostic Procedure
It has been already referred that the diagnosis of Parkinson disease is made even today only on the basis of detailed clinical examination and longer periods of observation of the patient. A majority of neurological societies worldwide accept the concept of diagnosis on the basis of clinical neurological examination only. Some further examinations such as cranial MRI or other neuroradiological methods such as PET and SPECT may be useful also to exclude the possibilities of other diseases but are not obligatory for the diagnosis of an IPD. As in the case of many neurological and other diseases it is of utmost importance to make a detailed history taking. Along with the usual questioning of the family predisposition and cerebral infections, one should try to explore the risk of different environmental factors. The patients may be exposed to such risks through their profession or by accident. It is necessary to question about the comorbidity and the medication the patient is taking for such diseases. In particular one has to find out about the neuroleptics and such drugs as Resarpin and Lithium. The beginning of the symptoms experienced by the patients and the family members must be taken into account. As mentioned earlier one must take care in putting sensitive questions about the deficits felt by the patients in one’s daily life. However, all details are necessary regarding the daily performance within the family circle as well as in professional field. Changes experienced by the family members in the motoric functions of the patient must be considered. In the clinical practice one sees that only some of the symptoms which bother the patient and the environment are mentioned ignoring the other aspects. The first symptoms noticed by the patients and the family are generally tremor and the psychomotor slowing of the patient in view of gait, speech and writing. The patients and the dependants must be encouraged to talk freely
about every minor detail in the lifestyle of the patient. One makes the experience that the patients of their own choice rarely mention about the urinary incontinence or motoric difficulties while eating with fork and knife.

The examination of the patient begins when the patient enters the consulting room. In case of idiopathic Parkinson disease the patients have a slow and typical gait characterized by stooping head and shoulder and reduced swinging of the arms. This gait may not be very pronounced during the early stages of the disease but later in the clinical course practically every patient with IPD shows these postural changes. The mood of the patient is also important as the majority of the patients show depressive mood changes. It is rare that a patient begins to smile and show spontaneity in one’s behavior. Patients for example with essential tremor do not have gait changes or the mood changes which are generally observed in IPD.

During the history taking, primarily the patient must be interrogated and only in the event of uncertainty the accompanying dependents can be consulted, for not offending the patient. The physician should not give the patient the impression that he or she is already disabled because of the IPD. As in case of all other neurological disorders, the clinical exploration should include also a general medical examination of the patient followed by a detailed neurological clinical examination. The cardinal symptoms associated with IPD must be considered in the order of tremor, akinesia, rigidity and posture. Tremor should be observed particularly for the presence of rest tremor which is usually unilateral at least in the beginning of IPD and in many cases for several years. The frequency of the tremor is 4 to 6/sec. A faster tremor is not characteristic of IPD but of other conditions particularly essential tremor. The tremor should be examined during
different phases of examination. Generally the tremor in IPD disappears when the patient carries motoric activities. On the other hand as mentioned earlier the tremor can increase on such situations as blood pressure examination particularly on the same arm having tremor or during emotions of the patients. Sometimes the tremor can increase in such intensity during a blood pressure examination that a further examination may be difficult. On the other hand in the same patient the tremor may disappear on Rhomberg test or finger-nose test.

The **akinesia** can be seen on the face of the patient because of the reduced mimic which gives the impression of a mask like facies associated with infrequent blinking and a certain fixed facial expression. If the patient smiles it begins mildly and fades away slowly without proper dynamic. Further there may be skin changes in the face in the form of a seborrhea. The voice is of reduced volume in the form of hypophonia and is generally poorly modulated. The handwriting should always be examined as it shows small and tremulous script which is difficult to read. The pronounced features of akinesia which is also called hypokinesia is a general slowing of voluntary movements particularly in respect of automatic movements such as swinging of the arms while walking.

The **rigidity** refers to increased tone in respect of increased resistance to passive movements which is very characteristic of IPD and is also a disabling condition for the patient. The resistance is generally unilateral and affects both agonist and antagonist muscles alike. The rigidity must be differentiated from such conditions as in cases of spasticity where the resistance can be more marked in some muscles than in others. The rigidity should be examined in respect of all muscles of the neck and the extremities.
In the arms the rigidity can be best examined in the joints of the hands by making rigorous movements of the hand joints. One must observe the possibility of cogwheel phenomena while examining the rigidity. The increased tone and the disturbance related with that is responsible for the flexed posture of majority of the patients with IPD.

Abnormal gait and posture are seen in most of the patients of Parkinson syndrome who find it difficult to get up from bed or from a chair because of the rigidity and akinesia. The patients have their own strategies to overcome this difficulty in that they prepare a while before they actually get up from bed so that they may lean further and forward and take help of their arms. This is similar as in the case of patients suffering from chronic back pain. The posture as has been mentioned is flexed and rather unsteady. The gait is characterized by small shuffling steps without proper swinging of the arms particularly of one arm. The patients have difficulty in turning and stopping at will. In longer clinical course the patients try to walk with increasing speed and find it difficult to control their gait properly. During the neurological examination the motoric and coordination must be carefully examined in view of diadochokinesia of the extremities. It is useful to examine the fine motoric by asking the patient to open and close the buttons.

The other clinical features include blepharoclonus (flattering of the closed eyelids) and sometimes blepharospasm (involuntary closure of the eyelids). Some patients may have difficulty of swallowing and may have hoarseness of voice. The neurological findings in respect of tendon and plantar reflexes may be normal.

In the psychiatric exploration it is useful to observe the mood changes in the patients. Even though several
patients show a tendency to depressive mood change, this is not always obligatory in case of IPD. Some patients manage to accept their condition in a philosophical manner and continue to be active in their professional and family lives. However, some other patients may show cognitive disturbances particularly word finding difficulties and such other cognitive problems. These aspects must be considered in view of not only IPD but also of the age of the patient. It is useful to conduct wherever necessary the minimental test to evaluate such cognitive problems however after discussion with the patients. During the course of the disease several patients with IPD develop cognitive problems which they sometimes mention spontaneously and the others rather reluctantly. Exploration could include also the situation regarding sexuality. Many patients seem to have libido disturbances and erectile dysfunction. Only a minority of patients may show hypersexuality which may also be caused by some of the anti-Parkinson drugs particularly the Dopamine-agonists. As IPD is a chronic neurological disorder leading also to emotional and psychiatric problems long range control of patients is useful also based on certain testing scales. In the meantime several rating scales are available for the assessment of the patients with idiopathic Parkinson disease. Even though such rating scales are not always necessary for the diagnosis of a Parkinson disease, the assessment may be useful for comparing the clinical course. The rating scales however need some experience for the physician who examines and the findings may be influenced through the personal assessment depending upon one’s own judgement. One of the popular scales is the rating scale of Webster from the year 1968 which is still popular and shown in the next page.
**Webster Rating Scale**

**I. Bradykinesia of hands, related to writing**

0 No impairment  
1 Discrete slowing of supinations and pronations rate, beginning difficulties of working with instruments, closing of buttons and writing  
2 Moderate slowing of supinations and pronations rate of one or both sides, moderate impairment of functions of the hand, writing clearly impaired, micrography is present  
3 Severe slowing of supinations and pronations rate. Incapable to write or open and close the buttons. Clear difficulties in handling objects.

**II. Rigidity**

0 Normal tone  
1 Discrete rigidity in neck and shoulders. Activations phenomena is present. One arm or both arms show slightly negative lasting rigidity.  
2 Moderate rigidity in neck and shoulders. Lasting rigidity when the patient is not under medication  
3 Severe rigidity of neck and shoulders. Rigidity lasts even in the presence of medication.

**III. Posture**

0 Normal posture. Head lesser than 10 cm flexed to the front  
1 Beginning poker-spine. Head bent to front to 12.5 cm  
2 Beginning arm flexion. Head flexed to front to 15 cm. One arm or both arms flexed but still under the waist line  
3 Beginning simian-posture. Head more than 15 cm flexed to front. One arm or both arms are flexed...
above the waist line. Severe flexion of the hand with beginning interphalangeal extension. Beginning flexion of knees.

IV. Swinging of upper extremities
- 0 Both arms swing properly
- 1 One arm’s swinging is reduced
- 2 One arm is not swinging
- 3 Both arms are not swinging

V. Gait
- 0 Normal gait with 45 to 105 cm steps, turning around is without problem
- 1 Gait is shortened to 30 to 45 cm steps, beginning to turn up the heels. Slower turning. Needs more steps
- 2 Steps are moderately shortened now 15 to 30 cm. Both heels strike the ground severely
- 3 Beginning of shuffling steps, steps lesser than 7.5 cm. Rarely “stotter-steps” and blocked gait. Walking on toes. Turning around is very slow.

VI. Tremor
- 0 No tremor
- 1 Less than 2.5 cm peak-to-peak-tremor in the extremities or in head or in the hands during finger-nose-test
- 2 Maximum tremor amplitude does not exceed 10 cm. Tremor is heavy but not constant. Patient maintains certain control over his hands
- 3 The dimension of tremor exceeds 10 cm, tremor is constant and heavy. Patient does not get free from tremor as long as one is wakeful, the exception being the tremor of cerebellar type. Writing and eating independently is not possible.
VII. Facies
0 Normal, active mimic; no starring
1 Discrete immobility, the mouth remains closed. Early symptoms of anxiety and depression
2 Moderate immobility. Emotions appear by much higher threshold. Lips are sometimes half open. Moderate signs of anxiety and depression. There may be flow of saliva
3 “Frozen face” (frozen facies). Mouth 0.6 cm or more open. Eventually flow of saliva.

VIII. Seborrhea
0 No seborrhea
1 Increased perspiration, the secretion is thin
2 Clearly oily skin. Secretion is much thicker
3 Clear seborrhea. The whole of face and head are covered with thick secretion.

IX. Speech
0 Clear, loud, with resonance and easily understandable
1 Beginning of hoarseness with reduced modulation and resonance. Good speech volume is still easily understandable
2 Moderate hoarseness and dysphonia. Constant monotonous unchanged tone. Early signs of dysarthria. Delayed and stammering speaking, difficulties to understand
3 Clearly rough and week speech.

X Personal independence
0 No deficits
1 Still practically completely independent, but changing of cloths is somewhat difficult
2. Needs help in some situations for example by lying down in bed or staying up from a chair. Longer time to start an action. Manages certain things but needs lots of time.
3. Completely disabled. Incapable of changing cloths or taking food by oneself or walking alone.

Clinical Symptoms of IPD—Reevaluated

The cardinal symptoms of Parkinson disease have been known since the description of the syndrome originally by James Parkinson and later by Jean-Martin Charcot. Over the last five to six decades several other symptoms have been added to the clinical picture of IPD, which involves not only the motoric deficits but other functional disturbances experienced by the patients during the course of illness. Table 5.1 shows a list of such symptoms.

<table>
<thead>
<tr>
<th>Table 5.1: Clinical symptoms of IPD</th>
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<tr>
<td><strong>Cardinal symptoms</strong></td>
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<tr>
<td>- Tremor</td>
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<tr>
<td>- Rigidity</td>
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<tr>
<td>- Akinesia</td>
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<tr>
<td>- Abnormal gait and posture</td>
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<tr>
<td><strong>Neurovegetative symptoms</strong></td>
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<tr>
<td>- Hypersalivation</td>
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<td>- Seborrhea</td>
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<tr>
<td>- Orthostatic hypotonia</td>
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<td>- Gastrointestinal disturbances</td>
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<td>- Breathing difficulties</td>
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<tr>
<td>- Sleep disorders</td>
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<tr>
<td>- Urinary incontinence</td>
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<tr>
<td>- Sexual disturbances</td>
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<tr>
<td><strong>Psychic symptoms</strong></td>
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<tr>
<td>- Frequent mood changes and depression</td>
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<tr>
<td>- Cognitive disturbances leading to dementia</td>
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Contd...
In addition to these complex symptoms the patients of IPD develop over the years other problems such as “freezing”, “on-off phenomena” and severe movement disorders characterized by dyskinesia. There is not sufficient clarity as how much of these later symptoms are associated directly with the Parkinson disease and to what percentage these symptoms are caused by the drugs particularly Levodopa. Probably both factors play a role, the long range side effect of higher dosage of Levodopa leading to severe dyskinesia has been established. In some cases of IPD which has been caused by severe cerebral trauma, dyskinesia is seen even with the lower doses of Levodopa. Some authors consider that if an IPD does not show dyskinesia after a duration of 10 to 15 years, irrespective of the medication, the diagnosis of IPD must be reconsidered. In the clinical practice, however, one practically does not see an IPD patient without a medication of Levodopa over the periods of 10 to 15 years. The association of other symptoms which are not cardinal may also show individual variation in patients of IPD. Depression for example as a medical problem can be seen only in around 40 to 50% of patients. The others even though have mood changes seem to manage fairly well without much psychic problems. The neurovegetative disturbances seem to occur in most of the patients even in the earlier stage of the disease. The cognitive changes again
seem to show much variability depending upon the personality structure of the patients. Accordingly one must be careful in making a global assessment of a person with IPD in respect of prognosis. There are patients who continue with their professional activities for several years in spite of motor and vegetative deficits, the others may have to reduce their professional activities already 3-4 years after the commencement of the clinical symptoms. It will be useful to test the patients every two years or so with psychological rating scales such as minimental tests or the already mentioned rating scale of Webster or neuropsychological tests. Several neurologists over the recent years consider IPD not only as a motoric disorder associated with only the extrapyramidal system but as a complicated clinical condition associated also with psychiatric conditions because of the cognitive disturbances seen in a majority of Parkinson patients.
Pathology of Basal Ganglia in IPD
Parkinson disease is the result of progressive neuronal loss in the nigrostriatal system which causes a dopaminergic denervation of the striatum and related structures. The basal ganglia are not a clearly defined anatomical structure. Also the functioning of basal ganglia has not been clearly understood. As the famous Wilson mentioned in his paper in 1925 the ganglia situated in the base of the brainstem, to a large extent, retain the characteristic of basement—namely darkness. Over the last 80 years the darkness related to the basal ganglia has not been completely cleared. However, it is known that these ganglia play an important role in the motor function. The structures which belong to basal ganglia are striatum (nuclear caudatus and putamen), pallidum, nucleus subthalamicus and substantia nigra. As it has been mentioned earlier the structures are closely connected to one another and to the cortex through ascending and descending pathways. The afferent pathways are connected primarily with the cortical areas, thalamic structures, dopaminergic neurons of the zona compacta of substantia nigra and the structures of midbrain. From the substantia nigra there are pathways connecting the limbic system. There has been increasing knowledge over the last 3 to 4 decades regarding the neurotransmitter substances in the basal ganglia which play an important role in the pathophysiology of idiopathic Parkinson disease. The progressive degeneration of dopaminergic neurons of the substantia nigra pars compacta (SNC) and the striatum as well as the presence of Lewy-bodies in SNC make the essential pathological factors of IPD. The Lewy-bodies are characterized by the eosinophilic intraneural granules which are present in the basal ganglia but may be present also in the brain stem. These Lewy-bodies are generally not seen in post encephalitic Parkinson syndrome but the neuronal loss in
the substantia nigra and other structures of basal ganglia are present also in the post-encephalitic form of Parkinson syndrome (Figs 6.1A and B).
The neurotransmitter **Dopamine** is a catecholamine which occurs predominantly in the basal ganglia. Around 80% of the entire content of cerebral Dopamine is present in the substantia nigra pars compacta and striatum. Dopamine is predominantly an inhibitory neurotransmitter whereas acetylcholine and glutamate are excitatory neurotransmitters. Dopamine can however not cross the blood brain barrier which is then accomplished by its precursor dihydroxyphenylalanine. Phenylalanine and thyroxin exit the blood barrier and enter the neurons where they are in the end phase as Dopamine decarboxylated. Dopamine is then deposited in the vasiculs of neuronal ends and preserved for transformation to the synaptic exchange. The discharge of Dopamine is converted partly to monoaminoxidase (MAO) and to catecholomethyltransferase (COMT). A part of it is taken over again by the synaptic neuronal ends. Apomorphine and other dopaminergic agonists stimulate the Dopamine receptors, whereas the receptors will be blocked through phenothiacine, butyrophenone and pimozid. Amphetamine can provoke the release of Dopamine from the neuronal ends. Monoaminoxidase-inhibitor can reduce the reduction of Dopamine.

Beginning with the publication of Tréttia污水1919 it is known with increasing knowledge that the important pathological changes leading to Parkinson syndrome occur in the demelanization of neurons particularly in the substantia nigra par compacta and in the striatum. Over the years the further studies have shown that there may be a disturbance of the neuronal activity also in the neighboring structures in thalamus, limbic system and brainstem. Histologically the neurons of substantia nigra pars compacta show the clear demelanization which is characterized by the loss of neurons. Some authors have...
mentioned in the autopsy reports that the patients of Parkinson disease have slightly reduced weight of brain with an average of 1281 g compared to 1365 g of control subjects. They have also noticed a 35% loss of smaller neurons and 50% of the larger neurons in the region of basal ganglia (Fig. 6.2). Their report shows a loss of 60 to 80% of pigmented neurons in the substantia nigra pars compacta compared to control subjects. Along with the loss of nigronal neurons there is a corresponding deposit of Lewy-bodies in patients of IPD. It has been reported that the presence of Lewy-bodies however is not characteristic for the pathophysiology of Parkinson syndrome as these bodies can be found in other forms of dementia, such as Lewy-body dementia and Alzheimer disease. Some authors have reported that 7 to 10% of the healthy subjects above the age of 60 years could also show the presence of Lewy-bodies however without recognizable clinical and pathological changes in these
individuals. The Lewy-bodies may occur in the cytoplasm or in the neuritis of pigmented cells. They consist of a protein, are of round or oval shape with a radius of 5 to 25 \( \mu \text{m} \). It is believed that the occurrence of Lewy-bodies is related to the disturbance in proteins synthesis.

Figs 6.3A and B: Substantia nigra. A. Normal finding with pigmentation, B. without pigmentation
It is therefore necessary to consider in the pathophysiology of idiopathic Parkinson disease that not only the deficiency of Dopamine due to the cellular loss in the substantia nigra pars compacta and other neighboring regions, is the cause for IPD but also the occurrence of Lewy-bodies which appear in larger quantities in the neurons of substantia nigra. The Lewy-bodies were described by the neuropathologist FM Lewy in 1912. The presence of Lewy-bodies therefore is a necessary component in the pathology of IPD. This is of particular significance for researchers and pathologists for the diagnosis and differential diagnosis of IPD in respect of such syndromes as multisystem atrophy, progressive supranuclear paralysis and cortico-basal degeneration. In these conditions the typical presence of Lewy-bodies in the nigral neurons are not found. The two conditions namely an irreversible degeneration and loss of pigmented dopaminergic neurons in the region of substantia nigra pars compacta (SNC) and the dorsal striatum accompanied by the occurrence of Lewy-bodies in the SNC can be considered as the essential pathological factors of IPD (Fig. 6.4).

Fig. 6.4: Lewy-bodies
In the pathophysiology of IPD: It is customary to divide the clinical stages into two phases namely preclinical stage and a stage of clear clinical manifestation. The concept of considering preclinical or presymptomatic phase is rather arbitrary as it is only after the clinical manifestation of IPD the presymptomatic phase can be retrospectively evaluated. However, most authors accept this division as patients report the occurrence of some symptoms related with the later clinical condition of IPD, which started years before the patients came for a consultation of their symptoms. The extent of the preclinical phase has been estimated to have large margins depending upon the experience of the patients and the concept of describing the earlier phases. Some of the early symptoms experienced by the patients are not always of motoric nature. Olfactory dysfunction for example has been experienced by several patients as an accompanying condition over several years, without this problem leading to a severe deficit. Depression as has already been mentioned is being experienced by a large percentage of patients, according to different studies from 40 to 50% much before the manifestation of motoric symptoms. Autonomic functional disturbances are also being mentioned by several patients. On the one hand these symptoms could be the beginning of functional disturbances of a brain organic nature but on the other hand they are too unspecific for considering the later predominantly motor disturbance of IPD. The clearer organic findings are examined by neuropathologists and researchers in the autopsy studies which are the end stage of the clinical IPD. Accordingly the authors describe a selective degeneration of the pigmented dopaminergic cells of the basal ganglia with particular reference to the loss of neurons in SNC (almost 70%) followed by considerable loss in the substantia nigra lateralis (30%). It is believed
that at least 60% of the neurons of the substantia nigra pars compacta are lost before the IPD is clinically manifest. The neuronal loss has been mentioned by the authors referred above as highly selective with maximum loss in the ventral areas of SNC than in the dorsal areas. Along with the irreversible loss of pigmented neurons of SNC, the pathophysiology of IPD is characterized as has already been mentioned, by the presence of Lewy-bodies in the SNC and in the neighboring structures particularly the limbic system but also in the cerebral cortex. It is mentioned that all major structures in the limbic system, including deeper layers, hypocampus and the portion of singulate gyrus projecting to the amygdala are all afflicted with the occurrence of Lewy-bodies. These pathophysiological considerations would give us some idea about the clinical picture of IPD which during the course of the illness leads not only to motor disabilities but also to other multiple symptoms as well. The authors mention that it is not clear whether the changes of the neuronal loss in SNC precede the changes in other brain regions or whether the changes in the basal ganglion are in themselves sufficient to explain the clinical picture of IPD.

As mentioned earlier the Lewy-bodies are first identified in the brainstem by Lewy in 1912. It is considered to be the result of altered metabolism or transport in the neurofilament. It is however not clear whether the Lewy-bodies are the result of neuronal damage and degeneration in the substantia nigra pars compacta and related structures or whether they are the cause for the neuronal damage and subsequently for the loss of pigmented neurons. The brainstem in patients with IPD consist of a dense mass of Lewy-bodies, whereas in the cortex they appear similar but with less density. It is known that Lewy-bodies occur only in neuronal cells either of
substantia nigra and related structures or in the cortex but not in the glial cells. It is also mentioned that Lewy-bodies have not been definitely identified in any other species other than human beings. The similar structures called “pale-bodies” have been however identified in experimental monkeys. Such pale-bodies have also been identified in human beings, the pathophysiology of which is rather uncertain. As mentioned earlier the Lewy-bodies are seen in 5 to 10% of the normal individuals above the age of 60 years who may not develop an idiopathic Parkinson disease at all. Some authors consider this as “incidental Lewy-bodies” and connect their significance sometimes with the preclinical phase of IPD. On the other hand, there is mention about the presence of “diffuse
cortical Lewy bodies” in conditions which resemble Alzheimer-type of dementia. This only shows that not every thing is known yet regarding the presence of Lewy-bodies even though their presence has been established in the pathophysiology of IPD.

Etiological Factors

The etiology of idiopathic Parkinson disease is still very unclear. It has been established in the clinical diagnosis of IPD that age is an important etiological factor, as the disease rarely commences before the middle age, that is 40 to 50 years, even though some rare forms of juvenile Parkinson syndromes are known. There seems to be no significance regarding the incidence related to gender. Even though some factors have been considered such as the heredity and environment, none of these have been established as playing a single role in the etiology of IPD. Genetic factors seem to play an important role accounting for about 10% of all cases of IPD. Some cluster-like occurrence of the disease has been noticed even though the clinical manifestation is generally of a sporadic nature. Some kind of toxin-induced oxidative stress has been considered as a possible etiological factor through the toxic effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its MAO-B metabolite. In humans MPTP provokes progressive parkinsonism with similar clinical features of IPD. It is assumed that exited generation of free radicals leading to oxidative damage to the cell structure related to substantia nigra may be an important aspect in the etiology. Even though several aspects of the etiology are not known it was significant that single toxic provocation could lead to clinical symptoms similar to the picture of IPD. It is believed that free radicals damage essential
components of the dopaminergic neurons including DNA, resulting in the disruption of function and ultimately loss of neuronal cells. This has been an important theme of research over the past years particularly in respect of oxidative stress related to Dopamine deficiency. There have been rather contradictory reports about the possibility of L-dopa inducing oxidative stress but also about the possibilities of neuro-protection through L-dopa in certain quantities. Similar are the reports involving iron levels in the substantia nigra in the generation of free radical reaction. The source of the increased iron levels in IPD is unclear, is presumed to be caused either by reduced ferritin levels or by increased cellular uptake of iron. Even though increased ferritin levels in the striatum of patients with IPD have been reported, in the clinical practice patients show rather reduced ferritin blood levels. Foley and Riederer\(^8\) considered from their experiments that iron is not involved in the earlier pathogenesis of IPD but its ability to generate free radicals might mean that it plays an important role in the progression of the disease. Reduced glutathione levels in substantia nigra pars compacta have also been attributed to be an etiological factor in the IPD. Foley and Riederer\(^8\) summarize the etiological factors as follows:

- Evidence of oxidative damage to proteins, lipids, DNA
- Reduced glutathione levels
- Increased superoxide dismutase (SOD) levels
- Increased iron levels in the absence of increased ferritin levels
- Increased aluminium levels

Over the past 3 to 4 decades there has been intensive research regarding the etiological factors involved in the clinical manifestation of IPD. Several possibilities have
been discussed such as mitochondrial disturbances associated with the generation of free radicals, disturbance of intracellular calcium-homeostasis, toxicity resulting in impaired energy metabolism at the mitochondria level and other factors. In addition, the possibility of cell death due to age related pathological factors as well as genetic factors have been discussed by many researchers. A number of pathological processes have been recognized in the etiology of IPD but the actual interrelationship among these different phenomena has not been clearly established. The problem could be associated among other factors with the slow development of IPD over years, because of which the actual causative factors cannot be clearly identified. Actually such is the case in many of the other brain diseases such as multiple sclerosis, amyotropen-lateral-sclerosis, Alzheimer disease and even epilepsy. It has been asked by researchers who advocate the theory of age-related etiology as to how the neuronal maintenance and cell death including in the region of substantia nigra and striatum differ from that of a normal aging process. There are others who consider the possibility of not a natural but “programmed” cell death in IPD. Foley and Riederer again postulate the possibility of following factors:

- Oxidative stress based on the free radical hypothesis, possibly due to failure of antioxidant defences
- Mitochondrial defects especially an impairment of the activity of complex I
- An endogenous or exogenous toxin
- Age-related pathology in normal cell maintenance
- Excitotoxic injury of specific neuronal populations
- Disturbance of intracellular calcium homeostasis
- A genetic cause for the disease due to a genetically determined predisposition
In spite of the intensive search for the etiological factors leading to IPD, no definite cause has yet been established. Several authors think that more than one factor may be involved in the etiology as it is the case in many other diseases as well. It is however clear that due to factors which have not been definitely established, there is a slow death of melanised cells in the region of substantia nigra, striatum and other structures of basal ganglia with the additional formation of Lewy-bodies which then subsequently lead to the clinical condition of IPD. Genetic predisposition and age may be possible etiological factors but other possibility such as the toxic influences can be suspected, even though no specific toxic factor has been properly established as yet. Some authors consider that the toxic factor influence of the etiology of IPD is more or less of universal nature as the disease occurs in all regions of the world and in all ethnic groups. Further it is assumed that at least two basic mechanisms in the etiology of IPD is possible namely a triggering factor which might provoke a series of still unidentified brainorganic events which may over the years lead to the progression of cellular degeneration. The trigger may be responsible to unleash a chain of factors leading to the later degenerative process which again may remain latent over years or decades until the IPD is clinically manifest. It can be understood that whatever be the triggering factors are, they may be beyond the control of the medical profession as the later patient of IPD may still be individuals of normal population who are mysteriously undergoing the changes in the region of basal ganglia. It would therefore be necessary not only to identify the triggering factors but also the process of later degenerative changes still during the preclinical phase, for the purpose of finding a strategy of neuroprotection. An intervention during the preclinical phase with any kind of
preventive therapy should allow the medical profession better plasticity in managing the problem with IPD at preclinical and clinical levels. Even though several studies have shown that almost 60% of the loss of pigmented cells in the SNC occurs even before the IPD is clinically manifest, it has become possible now to detect the loss of neurons even at the stage of 20% through PET investigation. However, it is doubtful whether a sensible intervention at this stage is possible to prevent the further process of cellular degeneration. Several researchers believe that the process of degeneration of neurons cannot be reversed even if the detection is possible at the stage of 20% of cell loss through PET investigation, which is an expensive method. It should be clear for students of neurology that the neuronal loss in the substantia nigra and in the striatum cannot be regenerated but it remains rather uncertain whether the surviving neurons can be encouraged to regrow and compensate functionally for the lost neurons. The question arises as to how one can intervene at the preclinical phase of a future clinical IPD patient even if some strategy of intervention is possible.

From the patient studies available in the recent years particularly from the urban population, it is known that the clinical condition of the idiopathic Parkinson disease can be detected some what earlier, that is already through the earlier yeas which are considered as a preclinical phase. Accordingly when the symptoms are not fully suggestive of an IPD a PET examination may detect, as it has already been mentioned even 20% of loss of neurons in substantia nigra and striatum. Even though the diagnosis of an IPD may be possible at this stage to a large extent, the question remains still open whether a neuroprotection is possible in one or other way. The aim of such a neuroprotection would be to stop the disease process at this point which
would mean a good preventive measure. It is doubtful whether the disease process which has been triggered off earlier and probably has been provoked through undetermined brain factors can be intercepted through some drugs or other therapeutic measures. Several clinical neurologists find the option of examining the patients with suspected history through PET investigation as not only expensive but also impracticable. As the diagnosis of IPD is still a clinical procedure, it is doubtful whether by insufficient symptoms the loss of around 20% pigmented neurons in the region of substantia nigra would give sufficient ethical evidence for a diagnosis or for beginning of a therapy. From the neurophysiological point of view it is also not clear whether the disease process which has started in the region of basal ganglia can be intercepted because of the possibility of affected neurons in “provoking” healthy neighboring cells. In this degenerative process the question of even a transplantation of healthy neurons over striatum may not bring the desired benefits. Whatever therefore the etiological factors are whether they are of an intrinsic origin as in the case of genetic predisposition or due to external factors such as toxins, prevention is sensible only if the triggering and further provocative mechanisms are understood. The different investigations in the basic research have thrown some light into the possible mechanisms of cell death in association also with Lewy-bodies but have not been able to answer why it comes to this kind of degenerative process. Summarizing one could assume that a multifactorial etiology is probably the reason for the clinical occurrence of an IPD. There may be two or more components such as the trigger factor, the provocation and other unknown processes playing a role in the etiology. In the pathophysiology of cellular strategy it can be assumed
that a problem which is generally handled well by a healthy cell becomes critical because of lower cellular defence, on the one hand because of the aging of the cell but on the other hand also due to factors mentioned in this chapter.

Further Clinical Aspects of IPD

The question of considering idiopathic Parkinson disease as a nosological entity fulfilling the criteria of “a disease” must be discussed further. There has been some confusion regarding the definition of this condition as a disease entity or as a syndrome consisting of several related clinical factors. With the addition of scientific information available from fundamental research, one gets the conviction that IPD is much more than a single clinical condition defined on the basis of cardinal symptoms associated with the pathophysiology of substantia nigra only. Scientists from basic research have identified that more cerebral structures are involved in the pathophysiology of Parkinson syndrome even though basal ganglia still remain the central point of attention. Accordingly several authors\(^8,9\) are of the opinion that IPD is much more than a disease and can be associated with a multisystem pathology. For the definition of a disease as a nosological entity, there must be a clinical picture and an etiology based on the pathogenesis and pathological factors. This is not an established method in defining IPD, because of which not only the clinical entity becomes unclear but also the possibility of finding a definite treatment. From the academic point of view it remains therefore unclear whether the clinical condition should be termed as an “idiopathic Parkinson disease” or which other factors contribute for defining it as a syndrome. In the clinical
practice we are confronted also with such conditions which begin after a brain trauma, cerebro-vascular insult, intoxication, infection and such other factors which lead to the clinical condition of a Parkinson syndrome. For the purpose of treatment one has to differentiate between Parkinsonism seen in different neurological or even psychiatric conditions showing the clinical picture of a Parkinson syndrome and IPD. For the purpose of drug treatment we have to make sure whether the clinical picture shows more factors associated with an idiopathic Parkinson disease, even in the presence of traumatic or other toxic factors. The following shows the accepted criterion for the clinical diagnosis of an idiopathic Parkinson disease:

**Definition of IPD**

- A preclinical phase with unclearly defined symptoms
- An adult onset with slow progression of the symptoms
- At least three of the cardinal symptoms namely rest tremor, akinesia, rigidity and postural instability
- Associated symptoms related to mood changes, cognitive deficits and neurovegetative disturbances
- Good response to Levodopa

A symptom complex of the above mentioned clinical features should enable us to make the diagnosis of IPD which should also be sufficient for starting a specific drug treatment. A diagnosis of IPD can be done in such cases even in the presence of traumatic or toxic etiology. It will be interesting however to find out whether these patients irrespective of their mentioned etiology show some genetic predisposition which can be considered as a latent factor for the occurrence of IPD. Before starting with the drug
treatment it is necessary however to rule out the possibilities of other Parkinson syndromes, which may show different clinical pictures. Description of such syndromes given below:

Other Syndromes with Parkinsonism

- Multisystem atrophy
- Progressive supranuclear paralysis
- Normal pressure hydrocephalus
- Cortico-basal degeneration
- Huntington’s disease
- Wilson’s disease
- Alzheimer’s disease with Parkinson symptoms
- Lewy-body dementia
- Hallervorden-Spatz disease

During the further clinical course it is necessary to reevaluate the clinical diagnosis, particularly in case of Levodopa resistance and the resistance to other Dopamine-agonists. The diagnosis of an IPD must be doubted if the patient shows already during the early clinical course increased instability of gait with falls which may also be associated with cerebellar signs and symptoms. A fast progression of the cognitive deficits leading to dementia, should also make us to reconsider the diagnosis. The concept of diagnosis based on the response to Levodopa must be carefully analyzed. The response to Levodopa may be obligatory for the diagnosis of an IPD, however, the clinical response could be somewhat weak during the early stages of IPD. On the other hand patients with other Parkinson syndromes may also respond somewhat for the medication of Levodopa. This may be the case regarding multisystem atrophy and progressive supranuclear palsy.
Some authors suggest that the concept of diagnosing a Parkinson disease as “idiopathic” may be incorrect, as a condition cannot be called a disease unless the etiology has been established. This is more of an academic discussion and in the clinical practice we have to stick on to the present practice of differentiating the idiopathic Parkinson disease from other Parkinson syndromes.

In the clinical assessment of the diagnosis, it is more useful to depend upon the cardinal symptoms and the clinical course of the disease rather than on the basis of Levodopa response. There may be some confusion if the emphasis is given on the response to Levodopa as the cardinal symptoms of IPD may respond sometimes poorly to Levodopa whereas the other syndromes may show even a better response. On the whole the response to Levodopa in all syndromes seems to involve the improvement of akinesia and rigidity and less of tremor. Some of the red flags associated with the doubtful diagnosis of IPD during the clinical course must be carefully considered. The fast progression of cognitive deficits leading to dementia is not associated with the clinical course of IPD as some patients manage to maintain intact cognitive condition for a period of 10 to 15 years. Similar is the case involving dyskinesias after a period of 10 to 15 years which is generally common but not seen in all patients having IPD at least not in a pronounced manner. A clinical differentiation of idiopathic Parkinson disease and the Lewy body dementia is not always easy particularly during the early stages of the disease. However, the early occurrence of a dementia associated with extrapyramidal deficits would speak against the diagnosis of an idiopathic Parkinson disease, but more for Lewy-body disease.
Juvenile Parkinson Syndrome

Even though idiopathic Parkinson syndrome is basically associated with age-related onset, beginning mostly around middle age, a juvenile form of the disease is seen sometimes in the clinical practice. This syndrome has been reported in the literature mainly in the Japanese population but sometimes also in the other Asian population and described as an autosomal recessive form of juvenile Parkinson syndrome. It is a Levodopa responsive Parkinson disease whereas the pathology and pathophysiology are a selective degeneration of dopaminergic neurons in the substantia nigra zona compacta. These cases show clinical manifestation much before the age of forty years with a familial tendency to occurrence of this syndrome. Clinical features are similar to the IPD of adult onset with resting tremor, akinesia and rigidity as well as postural instability. The clinical condition shows also a similar slow progression but with good response to Levodopa medication. The patients show a faster tendency for the development of the dyskinesias under the Levodopa medication. There may be betterment of symptoms after sleep and the patients show often mild dystonia of feet. In contrast to the IPD of adult onset the juvenile type of Parkinson disease does not show the formation of Lewy-bodies as reported by neuropathological findings. The management of patients with juvenile Parkinson syndrome is similar to that of IPD of adult onset. However, considering the possibility of earlier onset of dyskinesias one has to be careful in giving higher dosage of Levodopa in the long range drug treatment.
Mechanism of Pathogenesis in IPD
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The pathogenesis of idiopathic Parkinson disease is based partly on the available scientific information up to date and partly on the basis of hypothesis depending upon different pathophysiological factors. Some of these factors have found an established place in the pathophysiology of IPD, the others are still very speculative. However, it is of great importance to search for further definite factors as the future of therapy would depend upon a clearer pathogenesis. The different factors postulated as a possible cause for the occurrence of IPD is listed here below. The adequate functioning related to dopamine metabolism at the cellular level depends upon a proper synaptic neurotransmission of dopamine at the region of pre- and postsynaptic neurons. Figure 7.1 shows the general principle of dopamine neurotransmission.

**Possible Causative Factors**

- Aging process
- Premorbid personality
- Disturbed metabolism in the region of substantia nigra
- Inflammatory process in substantia nigra
- Unknown programmed cell death in the region of basal ganglia
- Genetic factors leading to metabolic disturbances such as alpha-synuclein-mutation, mitochondrial defect of DNA
- MPTP-like toxicity
- Oxidative stress

**Cell Aging**

It has been recognized that with the aging process several of the neurons in substantia nigra are lost even among
normal individuals. However, the normal process of aging of neurons also in the region of basal ganglia is not considered pathological. In spite of this, it should be recognized that the aging of an individual as it has been the case with the present generation of people, should increase the risk for IPD. The situation leading to normal aging and pathological aging process cannot be clearly differentiated when an individual lives far too long, in regard to cell pathophysiology.

The premorbid personality structure as an etiological factor in IPD is a debated matter. Even though during the
clinical course the patients of Parkinson disease show certain general characteristics which are typical for this predominantly motoric disease condition, the presence of a premorbid personality structure can not be properly estimated. The presence of associated non-motoric signs and symptoms do not help us to analyze the situation better as some of these problems may be of a reactive nature.

**Programmed Cell Death**

This is based on the hypothesis that there may be an unknown kind of programmed cell death leading to the occurrence of IPD. It is believed that the cell population in the basal ganglia of Parkinson patients is destined to die under an unknown program of cell death, which may be the result of certain mechanisms related to the immune system. This may also be related to the trigger factor which has been mentioned in the earlier pages as a possible cause in the pathophysiology of IPD. It is called as the apoptotic reaction of the cell population meaning a “programmed suicide”.

**The Oxidative Stress**

Over the past several years oxidative stress has been considered as an important pathophysiological factor in the idiopathic Parkinson disease. One considers under oxidative stress a potential “disturbance of the pro-oxidant-antioxidant balance in favor of pro-oxidants, which cause potential damage”. Certain biochemical processes may be responsible for the damage of dopaminergic neurons in the substantia nigra pars compacta. It is believed that there is a deficit of a complex-I-activity which may lead to the damage of mitochondria related to the neurons of basal
MECHANISM OF PATHOGENESIS IN IPD

Consequently oxidative stress is considered one of the main reasons for the mitochondrial damage involving the pathophysiology of IPD.

**Endogenous and Exogenous Toxic Factors**

The different toxic factors have been considered as a possible etiology in the occurrence of IPD. Experiments in the year 1979 in California based on the clinical experience of patients who were injecting heroin showed that they developed a Parkinson-like syndrome after the injection of high dosages of synthetic heroin. It was seen that these patients under the influence of heroin developed over night a symptomatic Parkinson syndrome similar to the clinical form of IPD. During the analysis of heroin the toxin MPTP was found responsible for the occurrence of the clinical condition. As MPTP is not a natural molecule, one considers the possibility of exogenous toxin resembling MPTP as a possible cause also for endogenous toxic nature of the substance.

In addition other exogenous factors such as the exposure to different toxic substances including chloral hydrate or trichloroethylene and lead could also play a role in the etiology of IPD.

**Genetic Factors**

In the clinical practice it is often seen that there is a familial tendency to Parkinson disease particularly in respect of parents and siblings. The actual mechanism of transmission has not been properly understood even though some polygenetic factors have been suspected. Certain genes which are responsible for the synthesis of alpha-synuclein may be responsible for the transmission mechanisms. The possibility of the so called Parkin-gene
has already been mentioned. On the whole the genetic factors seem to play an important role in the occurrence of IPD even though other associated factors cannot be ruled out as in the case of many other diseases.

Neuropathological Aspects

It is well known from the anatomical studies that in the region of basal ganglia there is a pronounced dark color involving the substantia nigra pars compacta, where the neurotransmitter catecholamine dopamine as well as noradrenaline are synthesized. The reason for the dark color of the substantia nigra is the presence of neuromelanin. This neuromelanin is present only in certain regions of the human brain and particularly around substantia nigra. It is believed that neuromelanin is produced because of an auto-oxidative process involving dopamine and noradrenaline in the form of an exudative product. This is however one of the hypotheses involving the production of neuromelanin. It has been however established that the loss of this pigment neuromelanin with the cell loss in the region of midbrain and the occurrence of Lewy-bodies in substantia nigra are the main neuropathological factors for the clinical manifestation of idiopathic Parkinson syndrome. The paleness of substantia nigra seen in the autopsy findings of patients of Parkinson disease is a diagnostic criterion in the neuropathology of IPD. The Lewy-bodies on the other hand even though are present mostly in the dopaminergic cells which are dying, may however be present also in the normal cell population. As mentioned the Lewy-bodies have been seen in the autopsy findings of individuals who never suffered from Parkinson disease during their lifetime. There is however a difference in the form of the
Lewy-bodies seen in the region of substantia nigra when compared with those of other parts of the brain particularly in the cortical regions. In case of Parkinson patients they are seen in larger numbers not only in substantia nigra but also in the related structures including limbic system which involves hippocampus, amygdala, gyrus singuli and hypothalamus.

**Discussion of Findings**

It is not clear whether the occurrence of Lewy-bodies is responsible for the damage of neurons or whether it is a defensive mechanism which may be a rescue for the other normal cell population. There are some neuropathologists who even believe that the beginning of neuropathological process may not be directly related to the region of substantia nigra but much more on the other structures of brainstem. However, these are still academic discussions and programmed for further research and at present have less clinical consequences. The basic research in the field of neuropathology gives however some hints that the beginning of IPD may involve the neurons of glosso pharingeous and vagus as well as certain specific neurons of the cortex which could mean, that the preclinical phase of the disease may begin because of the involvement of vagus nerve even in the region of intestinal tract, as also such neurons involving the olfactory system. This would lead to a hypothesis that the absorption of certain toxins through the gastrointestinal system may play a considerable role in the etiology in Parkinson disease. However, in the present stage of scientific development we have to consider the loss of Dopamine in the region of striatum-substantia nigra as the main pathophysiology of IPD. In spite of different known and unknown factors, one
can believe depending on the long phase of preclinical latency, that the brain has a tremendous capacity to compensate the slow deficits of Dopamine. Only when there is a reduced concentration of 50 to 70% of Dopamine in the striatal region that the disease gets clinically manifest. From the clinical and neurological point of view this phenomena can be accepted for the management of Parkinson patients. As long as we do not know the clear etiology of IPD, there is only the possibility of symptomatic treatment particularly on the basis of L-Dopa and Dopamine-agonists. At the same time we should be aware of the situation that with the available drug treatment we are not able to stop the progression of the disease not only from the clinical point of view but also involving the pathophysiology. Irrespective of the success of drug treatment, the progression related to the loss of pigmented neuronal cells seems to go uncontrolled during the course of the disease. The question whether with the loss of Dopamine the GABA neurons also degenerate remains unclear. Several studies indicate that the balance of GABA-neurons remains undisturbed even during the progression of Dopamine deficits.

**Clinical Picture**

Idiopathic Parkinson disease is a major neurological disorder which occurs worldwide nearly in one percent of the population above the age of 60 years. The disease begins generally in the middle age around 50 years and shows a progressive clinical deterioration. Only in a small number of people a juvenile type of Parkinson disease is known. IPD is predominantly a motoric condition however associated with additional symptoms of nonmotoric nature. The cardinal symptoms which are responsible for
the syndrome are akinesia, rigidity, tremor and postural instability. Three of these cardinal symptoms namely akinesia, tremor and postural instability have already been mentioned through the original work of James Parkinson. The occurrence of rigidity was the contribution of Jean-Paul Charcot. At least three of these cardinal symptoms must be clinically present for the diagnosis of an idiopathic Parkinson disease. For the purpose of clinical understanding the signs and symptoms are further clarified also in view of differential diagnosis involving other Parkinson syndromes which are not of idiopathic nature.

Akinesia refers to the loss of movements, hypokinesia or bradykinesia mean accordingly reduced or slow movements. Rigidity refers to increased muscle tone with special phenomena such as clasp knife or cogwheel findings. The tremor associated with IPD is a rest-tremor or a postural tremor. It is slow and shows the frequency of 4-6/sec. Dyskinesia or hyperkinesia are the terms referred to late manifestations of exaggerated movemental disorders associated with the clinical course of IPD particularly in the presence of long range treatment with levodopa. The most disturbing clinical features in IPD are akinesia and rigidity which are responsible for motoric dysfunction involving most of the movements of an individual. Tremor on the other hand is not always present in IPD but when present it seems to be a socially disturbing factor and in most cases the first symptom which brings the patients for medical check-up. The signs and symptoms of IPD begin slowly so that in many cases the patients are not in a position to explain clearly the actual time of beginning of the symptoms. Moreover, there is a long preclinical phase which precedes the clinical manifestation of IPD which may be from a few years up to many years.
In this preclinical phase the patients may have such nonmotoric symptoms as neurovegetative disturbances or mood changes leading to a depressive condition. Some of the frequent problems during this phase are olfactory disturbance, constipation, sleep disorders and reduced vitality. However, these are generally non-specific symptoms except in the case of olfactory dysfunction. Such signs and symptoms may not lead to a disease condition or may be the preclinical phase of other diseases also. A diagnosis of IPD during this preclinical phase is mostly not possible as the patients may not consult a physician or even if they do consult the symptoms may be too unspecific for the diagnosis of any definite clinical condition. Even in other neurological disorders such as multiple sclerosis patients are known to have some preclinical phases particularly in respect of neurovegetative disturbances and mood changes. In the neurological practice however one must consider the possibility of a later clinical manifestation of IPD in people coming for consultation around middle age. It will be useful to make detailed history in view of the possible etiological factors of IPD such as genetic tendency, environmental toxicity and the other related factors. A detailed clinical neurological examination would be useful but the diagnosis of IPD can not be done until the cardinal symptoms are present. One should be careful not to lead the patients to unnecessary anxiety and conduct the examinations in such a way that an avoidable neurosis is not caused in the patients.

**Approach to Diagnosis and Management**

The diagnosis of idiopathic Parkinson disease is done as already mentioned mostly on the basis of clinical examination involving a careful assessment of at least three
of the four cardinal factors known under the symptom complex of IPD. In the majority of cases the symptoms involving tremor and rigidity are unilateral. Postural instability should be examined as also the possibility of akinesia felt by the patients. Most of the patients with IPD coming for the medical examination have mood changes. Even though the diagnosis of Parkinson syndrome is possible in the general medical practice it would be useful in the case of uncertainty to consult a neurologist. The neurologist may then decide according to necessity and upon discussion with the patient the possibility of further evaluation through such neuroradiological examination as positron-emission tomography (PET). Magnetoresonance imaging of the brain is not contributory for the diagnosis of IPD, it may however be useful for the differential diagnosis of a Parkinson syndrome. People with IPD may have normal MRI findings whereas other people with such disorders as multiple system atrophy, normal pressure hydrocephalus may show morphological changes of the brain. During the history taking one must take care about the possibility of patients taking neuroleptic drugs for other diseases particularly psychiatric conditions. Often patients with psychosis who take high dosage of psychopharmaka may show drug induced Parkinson syndrome which must be excluded from the diagnosis of IPD. In some cases however in spite of careful history taking and detailed neurological examination a clear diagnosis of IPD is not easy particularly during the earlier stages when the cardinal symptoms are not clearly manifest. In such cases one has to try the reaction on levodopa as patients of IPD react positively on the medication of L-Dopa. However, some other patients with Parkinson syndrome such as multisystem atrophy or Parkinson with Lewy-body dementia may also react
positively on L-Dopa which factor must be taken into account.

The diagnosis of an IPD cannot be generally done after only one neurological examination because of medical and ethical reasons, except in cases of clearly defined picture of the cardinal symptoms. The examination begins with clear observation of the movements of the patient. The akinesia is characterized by the reduction of spontaneous and voluntary movements which can be seen when the patient is walking. The Parkinson patients show already quite early a posture with head and body bent forwards which involves head, joints of the extremities including shoulder, arm and hands as well as joints of the legs and hip. This is the result of akinesia as well as rigidity with flexion of the joints of the upper extremity. While walking the patient shows reduced swinging of one arm and a disturbed movement of one leg.

The akinesia, depending upon the grade of involvement in patients with IPD seems to be the most disturbing feature for them. The patients have a reduced mimic in the facial muscles in the form of a mask-like face with a kind of fixed facial expression, infrequent blinking and a smile that comes and goes slowly. This reduced facial expression is seen already during the early stages of the disease and should be carefully observed. The voice is of low volume in the sense of hypophonia and is sometimes insufficiently modulated. The handwriting is small and in the later stages of the disease rather hard to read, because of the tremor particularly if the tremor is present in the right hand. The akinesia leads to reduction or loss of automatic movements which are debilitating for the patients. In spite of being a disabling condition many patients have difficulty to explain their symptoms and refer to them in different terms such as “weakness”, “blockage”,...
etc. Even though akinesia is a generalized phenomena in most of the patients with IPD, many of them complain of unilateral problems such as the inability to have control over automatic movements of one-sided extremities. This is the case also involving the other symptoms such as tremor and rigidity. In the majority of patients the tremor begins unilateral also with the presence of rigidity in the affected extremity. The tremor may be pronounced in some patients during the course of the disease and take the form of, as already mentioned, a pill-rolling- or coin-counting-phenomena. At least during the early diagnosis of IPD the unilateral occurrence of tremor and rigidity may be present which however could be bilateral particularly during the later course of the disease. In some rare cases it is also possible that tremor may be present contralaterally in the upper and lower extremities which needs however further careful examination. The rigidity should be examined in the arm, leg and the hand. The presence of clasp-knife-phenomena or cogwheel-phenomena should be evaluated by the examination of rigidity through alternative passive movements of the wrist joints.

The additional signs and symptoms which occur in case of patients with IPD are: hypersalivation, orthostatic hypotonia, urge incontinence, sexual disturbances and sleep disorders. Some of these symptoms may be influenced through the medication taken by the patients. Mood changes and depression are common associated factors in patients of IPD and may need corresponding treatment. Cognitive disturbance leading to dementia is a slow degenerative process in case of IPD which shows variable clinical course. Postural instability leading sometimes to drops are possible in several patients with IPD. In the clinical neurological practice it is necessary to rule out the possibilities of other symptomatic
Parkinson syndromes before the diagnosis of idiopathic Parkinson disease is pronounced to the patients and the dependants.

**Summary of Etiology and Pathophysiology in IPD**

A clinical differentiation of idiopathic Parkinson disease from other syndromes related to parkinsonism is possible to a good extent because of the extensive information available in the clinical neurology from all over the world. Even in cases of doubtful symptoms a further assessment of neuronal loss in substantia nigra and striatum is made possible through neuroradiological methods such as PET. However, not much is known about the etiology of Parkinson disease and whatever information is available is based mostly on hypothesis or indirect evaluation of the possible etiological factors. Different possibilities have been considered in the etiology of IPD such as the genetic factor, oxidative stress, the influence of toxic factors as well as further hypothesis of unknown mechanisms of cell death and age related factors. There are hypothesis of trigger and provocative factors which may lead to a process of specific cell destruction in the region of basal ganglia and related areas. There is however little experimental evidence to evaluate a single or a particular etiological factor. Accordingly the medical profession is left in the dark in view of any prophylactic measures involving the population at risk particularly after midlife. Some of the predominant symptoms during the preclinical phase such as chronic constipation, reduced serum ferritin levels, mood changes leading to depression and other neurovegetative disturbances may all be rather too unspecific for the evaluation of diagnosis of an impending IPD. These signs and symptoms may occur in a
considerable percent of the general population after middle age and may not have further clinical significance involving the possibility of a specific neurological disease such as IPD.

In the pathophysiology of IPD however considerable information is available already after the investigations of Trétiakoff as early as 1919. The basic mechanism leading to the clinical condition of IPD is related to the loss of pigmented neurons of substantia nigra also followed by the occurrence of Lewy-bodies. The loss of Dopamine has been established to be the main factor in the pathophysiology of IPD. There are basically three regions or systems related to the production of Dopamine:

1. The nigrostriatal system consists of substantia nigra pars compacta and the striatum which is subdivided into nucleus caudatus and the putamen. The substantia nigra as mentioned earlier gets it’s name based on the dark color of the regional neurons because of the presence of neuromelanin. These neurons degenerate in patients with IPD which leads to the pathology of demelanization and the loss of Dopamine. The nigrostriatal dopaminergic system is particularly responsible for the functioning of voluntary movements. The importance of this system and mechanism was experimentally shown by the studies of Hornykiewicz.7

2. The mesolimbic and mesocortical system consist of limbic structures as well as connecting areas in the cortex namely corpus amygdala, septum, tractus olfactorium, as also the cortical structures including frontal cortex and gyrus cinguli. The meso-limbic and meso-cortical systems are functionally related to the control of motivation, behavior and probably concentration and memory. Some behavioral pattern
such as the tendency to alcohol and drugs have been suspected to the malfunctioning of this system. An increased functioning of this system may lead to psychotic conditions which then under antipsychotic medication may show a drug-induced Parkinson syndrome.

3. The tubero-infundibulare system. In this unit the dopaminergic neurons of nucleus arcuatus project dopamine into the hypothalamus and regulate the stability of pituitary hormones. The dopamine receptors act in the system for the control of synthesis related to prolactin from the pituitary gland.

The essential aspects of pathophysiology in IPD are as already mentioned the loss of dopamine due to the degeneration of melanized neurons in substantia nigra and related structures such as striatum and limbic system. The occurrence of Lewy-bodies is an associated factor in the pathophysiology, the actual significance of this development has not been properly established. It is not clear whether the Lewy-bodies should be considered as bi-products of neuronal degeneration or whether they are the provocators of a degenerating process in the nigral and striatal structures. They seem to be somehow associated with the cellular age as they have been found in smaller numbers in other age-related disorders and also among normal individuals in the older age-group. It could be inferred that they may be associated with the normal aging process of an individual but may occur extensively in other age-related diseases such as IPD and Alzheimer’s disease. However, a clinical Parkinson disease is possible only after considerable loss of neurons in the region of substantia nigra compacta and striatum. The clinical manifestation of the known cardinal symptoms associated begin only after around 60 to 80% loss of the nigral
melanized neurons. From the therapeutic point of view therefore the clinical condition of IPD remains irreversible once the degenerative process has started in the region of basal ganglia. It has been shown in several studies that the treatment of patients is restricted only for the control of certain symptoms whereas the process of degeneration in the nigral and striatal structures go uncontrolled further, which may explain the slow progression of the condition leading to dementia.

The etiology of Parkinson disease is not known, even though several possible factors have been identified. Without a clear etiology, there is no specific drug to stop the progression of clinical course in IPD. Accordingly there are only substitute therapies for the treatment which are mainly in the form of synthetic L-dopa and L-dopa agonists. The main problem however is the uncontrolled cell death in the region of basal ganglia particularly substantia nigra and striatum. The mechanism leading to progressive cell death in this region is not clearly known even though there are several experimental evidences which lead to the hypothesis of programmed cell death. However, unless there is more clarity about these mechanisms, any sensible treatment seems to be not possible for preventing the progression. From the diagnostic point of view it is possible to suspect the beginning of IPD even at the stage of about 20% loss of melanised neurons in substantia nigra through the help of PET. On the other hand when the disease is clinically manifest there is already a loss of 60 to 80% of neurons in the region of basal ganglia. It is also known that even after the clinical diagnosis of IPD, it is not possible to prevent the further loss of neurons for want of specific knowledge in this regard.
Through the help of animal experiments several possible mechanisms leading to progressive cell death have been postulated. Parkinson disease is pathophysiologically characterized by a specific pathological sensitivity of dopaminergic neurons in the mesencephalon. It has been found that the degeneration of neurons in Parkinson disease is related to the sensitivity of oxidative stress. Accordingly the increased production of oxygen free radicals in Parkinson disease may suggest that oxidative stress may be an important factor in the mechanism of cell death. The denervation in the region of substantia nigra and striatum induces a hyperactivity of the output related to basal ganglia which seems to be directly induced by the hyperactivity of glutamate afferent fibers from the subthalamic nucleus. A reduction in the activity of subthalamic nucleus reduces the symptoms of IPD and restores the activity of the output structures of the basal ganglia. In addition to these mechanisms the genetics and other toxic factors may influence the progression of cell death. Experimental evidence suggests that only certain population of neurons in the mesencephalon degenerate, whereas the others of the population seem to be less susceptible. The neurons which are susceptible to degeneration have been shown to be more sensitive to oxidative stress. Such susceptible neurons also produce more radicals and they are less protected against such oxygen free radicals. Therefore, an active mechanism of oxygen free radicals seems to play a particular role in the progression of cell death in Parkinson disease. Hirsch, speculates the possibility of following factors playing a role in the progressive course of nigrostriatal cell death.

1. Iron which catalyses the formation of hydroxyl radicals accumulates directly within the dopaminergic neurons.
2. Alterations in mitochondrial functions leading to the accumulation of oxygen free radicals have been found in the substantia nigra of patients with IPD.

3. Increased manganese-dependent superoxide dismutase activity has been reported in substantia nigra.

4. Glutathione levels are decreased in substantia nigra of patients with IPD.

5. Nitric oxide levels are probably also increased in substantia nigra leading to toxic form of superoxide.

The above mentioned factors suggest a major change in the metabolism of oxygen free radicals which may be responsible for cell death in substantia nigra and striatum. Oxidative stress leading to an increase in the level of oxygen free radicals may play a role in the pathophysiology of several diseases including brain disorders. They seem to be particularly important in Parkinson disease where the susceptible neurons of basal ganglia are too sensitive to oxidative stress and inflammatory reactions. A further experimental research in this area may be directed on the prevention of oxygen free radicals with incidental prevention of progressive cell death. It is known since the experiment of Hornykiewicz that the loss of melanised neurons in the substantia nigra pars compacta lead to decreased dopamine-concentration in the striatum which then provoke a chain of reactions in the basal ganglia which also seem to be responsible for the development of the clinical condition IPD. It is therefore of great importance to advance the basic knowledge about the mechanism of progressive cell death in Parkinson disease for the purpose of new drug development. Hirsch suggest therefore that along with L-dopa and dopamin-agonists, antioxidants, anti-inflammatory and anti-glutamate drugs may be useful for the treatment of IPD.
Milestones in Parkinson Syndrome

1817 An Essay on Shaking Palsy by James Parkinson
1873 Charcot Jean-Martin describes the syndrome and names it after James Parkinson
1912 Lewy F H, describes autopsy findings of Parkinson patients having concentrated zytoplasmic bodies
1919 Trétiakoff C recognizes substantia nigra as morphological substrate of Parkinson Syndrome
1951 Schwab R S recognizes the beneficial effects of apomorphin on Parkinson syndrome
1954 Cooper IS tries pallidotomy in the treatment of Parkinson Syndrome
1954 Hassler R, Riechert T try thalamotomy in the treatment of Parkinson tremor
1957 Montague K identifies Dopamine as neurotransmitter in CNS
1960 Ehringer H Hornykiewicz O recognize dopamin defizit as biochemical substrat in PS
1961 Birkmayer W, Hornykiewicz O administer 20 Parkinson patients with intravenous injections of levodopa
1967 Cotzias G administers levodopa in oral form
1967 Birkmayer W, Mentasti M combine levodopa and decarboxylase-inhibitors
1975 Birkmayer W administers MAO-B-inhibitors in PS
1976 Lieberman A. introduces Bromocriptine in the medication of PS
1989/90 Introduction of COMT inhibitors
1990 and later Introduction of further drugs for Parkinson syndrome
Milestones in the Treatment of IPD

1867  Introduction of belladonna extract
1946  Introduction of synthetic anticholinergica
1949  Stereotactic pallidotomy
1961  First trials with L-dopa
1967  Combination of L-dopa and Bensarizide
1969  Trials with combinations of L-dopa and decarboxylase inhibitors
1969-70 Introduction of Amantadine
1974  Trials with Bromocriptine
1975  Introduction of Madopar
1982  Trials with Pergolide
1987  Concept of deep brain stimulation
1990  Introduction of COMT-inhibitors
1991  Introduction of Ropinirolee
1992  Introduction of Pramipaxole
2003  Introduction of Stalevo
2005  Introduction of further drugs
The Concept of Therapy in Idiopathic Parkinson Disease
The diagnosis of any disease based on the etiology and pathophysiology is directed at prevention and treatment of the disease concerned. In several diseases in the internal medicine and neurology, it is difficult to arrive at a proper diagnosis particularly the nosological diagnosis for lack of etiological factors. Accordingly a correct treatment is not possible for want of proper understanding of the basic factors involved in the mechanism of a disease. Similar is the case regarding the idiopathic Parkinson disease which is characterized clinically as a syndrome consisting of cardinal symptoms akinesia, tremor, rigidity and postural instability. Scientists in the field of fundamental brain research are trying to show brain organic correlate related to the above mentioned clinical symptoms. It has been shown that akinesia probably arises from the underfunctioning of the frontal areas receiving major input from the basal ganglia. This underfunctioning seems to be reversible when dopaminergic drugs are administered or when brain surgery is performed with pallidotomy or implantation of subthalamic stimulator. The slow characteristic rest tremor of IPD results from a combination of abnormal overactivity of cerebellar-thalamic connections and loss of dopaminergic projections. The late manifestation of dyskinesia occurs when striatal overactivity leads to increased opioid neurotransmission allowing release of unwanted movements. It is believed that dyskinesias appear when basal ganglia opioid neurotransmission becomes deranged due to a combination involving the progression of disease as well as due to a chronic influence of levodopa. In the pathophysiology of IPD, the chronic loss of Dopamine due to the progressive cell death in the region of substantia nigra and striatum have been established. The reasons for
such a progressive cell death may be multiple and are still a subject of hypothesis.

The present concept of treatment of IPD is based mostly on the replacement of Dopamine in the form of a substitute therapy. This is achieved by the administration of levodopa and decarboxylase inhibitors as well as levodopa agonists. Through the substitution therapy, the patients are helped to reduce their suffering by controlling the symptoms to the extent possible. However, it has not been possible to stop the progression of cell death in spite of several at present available anti Parkinson drugs. Without the use of these drugs, it can be presumed that the patients will have higher rate of suffering and probably faster progression of the disease leading to dementia, even though not many clinical studies are available in this regard. The most potential drug up to date is however levodopa without which a patient with IPD can not manage for a longer duration of years. There is a convention in the clinical practice of starting with levodopa agonists particularly in people of the younger age group and go forwards to the use of levodopa only later when the clinical condition makes the addition of levodopa necessary. This generally happens after a clinical course of two to three years which however is variable in different patients. There seem to be certain individual compensatory mechanisms which help the patients to manage their problems better than the others. However, a definite prevention of progressive symptoms is not seen in any patients, which makes the management of this disease also difficult for the medical profession. Apart from the idea of starting with a levodopa agonist or directly with a levodopa preparation, depending upon the clinical situation of the patient, not much is known about the principle of proper combinations of drugs. It is therefore somewhat understandable when some
physicians directly begin with a levodopa preparation irrespective of the clinical picture involving the patient as levodopa remains the basic therapy sooner or later in all patients of IPD. It must however not be forgotten that the duration and the dosage of treatment with levodopa may have serious consequences involving the development of dyskinesias in the later course of Parkinson disease. The treatment becomes then considerably difficult once a patient has developed dyskinesia. Hence at the beginning of a treatment, this aspect should be taken into consideration and must be discussed with the patients.

In case of patients where the clinical picture is not clearly diagnosed as idiopathic Parkinson disease there are some possible strategies. Either one tries to bring more clarity in the diagnosis of IPD through PET examination or through the drug test with levodopa, or one takes time to observe the clinical condition before beginning a treatment. These aspects should also be clearly discussed with the patient and the dependents taking them into confidence about the procedure. This should not be considered as an uncertainty of the consulting physician but as a useful hint involved in the later disease process.

In the following pages the list of drugs available for the treatment of IPD will be shown followed by drug introduction depending upon the clinical picture of the patient. Most of the important drugs used today are available for the last 50-60 years and there seems to be an active fundamental research also in view of the development of newer drugs. Even though many aspects on etiology and pathophysiology of IPD have been discussed, there is not sufficient clarity regarding these issues. A correct treatment therefore with drugs or surgery may not be possible until the basic research makes the road
clear for such a development. A list of the antiparkinson drugs is shown here also with registered trade names.

**AntiParkinson Drugs: As available in Switzerland and Europe**

<table>
<thead>
<tr>
<th>Basic drugs</th>
<th>Trade name</th>
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<tbody>
<tr>
<td>Amantadine-HCl</td>
<td>Symmetrel 100 mg</td>
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<tr>
<td>Amantadine sulphate</td>
<td>PK-Merz 100 mg</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Subcutan. injections</td>
</tr>
<tr>
<td>Biperiden-HCl</td>
<td>Akineton 2 mg, 4 mg</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Parlodel 5 mg, 10 mg</td>
</tr>
<tr>
<td>Budipin</td>
<td>Parkinsan 10 mg</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>Cabaser 1 mg, 2 mg, 4 mg</td>
</tr>
<tr>
<td>Dihydroergocriptin mesilas</td>
<td>Cripar 20 mg</td>
</tr>
<tr>
<td>Entacapone</td>
<td>Comtan 200 mg</td>
</tr>
<tr>
<td>Entacapone-Levodopa-Carbidopa</td>
<td>Stalevo 50 mg, 100 mg, 150 mg</td>
</tr>
<tr>
<td>Levodopa-Benzarizide</td>
<td>Madopar 62.5 mg, 125 mg, 250 mg</td>
</tr>
<tr>
<td>Levodopa-Carbidopa</td>
<td>Sinemet 100 mg, 250 mg</td>
</tr>
<tr>
<td>Pergolide mesilas</td>
<td>Permax 0.25 mg, 1 mg, 0.05 mg</td>
</tr>
<tr>
<td>Pramipaxole</td>
<td>Sifrol 0.125 mg, 0.25 mg, 0.5 mg, 1 mg</td>
</tr>
<tr>
<td>Procyclidine-HCl</td>
<td>Kemadrin 5 mg</td>
</tr>
<tr>
<td>Rasagiline mesilas</td>
<td>Azilect 1 mg</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Requip 0.25 mg, 1 mg, 2 mg, 4 mg</td>
</tr>
<tr>
<td>Ropinirole-HCl</td>
<td>Adartrel 0.25 mg, 0.5 mg, 2 mg</td>
</tr>
<tr>
<td>Rotigotin</td>
<td>Neupro-Plaster 2 mg, 4 mg, 6 mg, 8 mg</td>
</tr>
<tr>
<td>Selegiline-HCl</td>
<td>Jumexal 5 mg</td>
</tr>
<tr>
<td>Tiaprid-HCl</td>
<td>Tiapridal 100 mg</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>Tasmar 100 mg</td>
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</table>

The above list shows the trade names of the drugs with the dosage as these are available at present in Switzerland.
Anticholinergic Drugs

Anticholinergic drugs in the treatment of IPD are known already since the second half of 19th century. It is known that Charcot Jean-Martin in Paris used belladonna extract for the treatment of IPD patients against hypersalivation which consequently showed a reduction of tremor in such patients. Much later around 1940 belladonna was synthesized and was made available as an anticholinergic drug. The principle of treatment with the anticholinergic drugs is based on the pathophysiology of IPD in which Dopamine, glutamate and acetylcholine are known as important neurotransmitters in the region of striatum. Because of the reduction of Dopamine in IPD patients there is a hyperactivity of acetylcholine which then will be reduced by the use of anticholinergic drugs. Some of the anticholinergic drugs are available even today even though their use has been considerably reduced in the treatment because of the development of further drugs. The use of anticholinergic drugs is mostly for the treatment of tremor whereas rigidity and akinesia are only insignificantly influenced. However, the drugs have a useful effect against excessive sweating and overproduction of saliva. Because of the anticholinergic activity there are however several side effects such as increase of cardiac rhythm, bronchodilatation and reduced gastrointestinal motility. Other than that, they can also cause dysfunction of bladder and increase of ophthalmic pressure. Rarely there may be side effects such as hallucinations and cognitive disturbances. It has also been noted that a combination of anticholinergic drugs with levodopa may have long-range side effects leading to the increased occurrence of dyskinesias. Therefore there are several contraindications for the use of anticholinergic drugs such as glaucoma, prostate
The concept of therapy in IPD

hyperplasia, constipation and tachycardia. Other contraindications are the development of a dementia, epilepsy and myasthenia gravis. The clinical side effects are dryness of mouth, tachycardia, visual disturbance and constipation. Therefore it is advisable not to use these drugs in IPD of long duration particularly in patients of older age group. However, the drug is being used in many countries particularly in younger people getting the first symptoms of IPD or in cases of juvenile Parkinson disease with dominance of tremor. In case of such usage a smaller dosage of the drug is indicated beginning with 1 mg of Biperiden (Akineton) per day with slow increase of dosage up to 3 – 4 mg per day in dosage intervals of three times per day, or as a tablet in retard form.

Levodopa

Levodopa (L-Dopa) is the most important drug in the treatment of idiopathic Parkinson disease. During the course of illness every patient with IPD needs this drug for controlling the symptoms and improving the quality of life even though levodopa also can not arrest the progress of IPD. The drug was introduced in the years of 1961 and 1962 by Birkmayer and Hornykiewicz, who also made clinical trials with the drug. Since then it has been used extensively worldwide in the treatment of IPD and sometimes also in associated disorders. Levodopa is a L-3,4-dihydroxy-phenylalanine and is synthesised from L-tyrosine. L-Dopa is converted into Dopamine in the organism and administered as a synthetic drug. If only Dopamine is directly administered into the human body it is not able to cross the blood brain barrier and therefore L-dopa is used as a combination drug, with dopa-decarboxylase-inhibitors such as Carbidopa or Bensarizide.
This helps to prevent the synthesis of Dopamine in peripheral tissues so that maximum availability is made possible in the brain. The basic principle of administering L-dopa is to make good the loss of Dopamine in the striatum caused by the cell death in the region of substantia Nigra and striatum leading consequently to the depletion of Dopamine. The reduction of Dopamine in the basal ganglia leads to the cardinal symptoms of Parkinson disease such as tremor, akinesia and rigidity.

During the clinical trials of Birkmayer, Hornykiewicz and co-workers in the 1960s, they had to administer high dosages of L-dopa which led to serious side-effects in the patients concerned. Even then the bioavailability of the drug for the required regions in brain was minimal. With the combination of decarboxylase-inhibitors to L-Dopa the bioavailability of the drug was considerably better. Since then L-dopa is combined either with Carbidopa or Bensarizide, sometimes also with the addition of COMT-inhibitor to prevent the unwanted metabolization of the drug in the peripheral tissues. There are several preparations with the combination of L-dopa either with Bensarizide or with carbidopa. Even though Bensarizide and Carbidopa are quite different substances, but on the combination with L-Dopa the therapeutic effect in patients of IPD does not seem to be significantly different. Generally about ¼ of the dosage of decarboxylase-inhibitor is combined with one unit of L-dopa which means 100 mg of L-dopa is combined with 25 mg of decarboxylase-inhibitor or in similar dosages. Some pharmaceutical companies along with L-dopa plus decarboxylase-inhibitor or L-dopa and carbidopa a third drug namely a COMT-inhibitor. The L-dopa in combination with the other drugs which crosses the blood brain barrier is metabolized and absorbed at the presynaptic dopaminergic neuronal ends.
and converted into Dopamine. This will be then preserved in the vesicles and released in the form of a natural release of Dopamine in the region of synaptic ends (Fig. 8.1).

The pharmacokinetic of L-dopa shows a rather short half life of 1.5 to 2 hours. The half life could not be increased in spite of the addition of decarboxylase-inhibitors or carbidopa. During the longer duration of illness the half life seems to even further decrease and the patient feels clinically the negative symptoms such as off-on-phenomena. The withdrawal effect of the drug during the early stages of the intake seems to be however not abrupt and last somewhat longer. Accordingly during the early
stages of intake of L-dopa considerably longer therapy effect can be seen. The basic principle of administering L-dopa or for that matter any other antiparkinson drug is the replacement of the loss of Dopamine in the region of striatum. It can be inferred that along with the metabolization of L-dopa by the dopaminergic neurons, a certain portion of L-dopa can also be decarbolized by the gliacells which then consequently may have a preventive effect against degeneration of neurons. The bioavailability of L-dopa occurs through the proximal parts of the intestine which may show the risk of prolonged resorption as well as loss of the substance in the intestinal canal. It is therefore necessary to administer levodopa independent of meals particularly those which are rich in proteins. This aspect should be made clear to the patients already in the beginning of the medication so that they take an L-dopa preparation either one hour before a meal or about 1-1½ hours after a main meal with protein rich food. One sees in the clinical practice that not all patients are sufficiently informed about the necessity of taking L-dopa preparations this way to prevent the unnecessary loss during resorption in the gastrointestinal tract.

Even though the half life of L-dopa is rather short, the therapeutic effect of each dosage seems to be longer and lasts 4 – 5 hours. Further there seems to be an even longer effect related to the Dopamine stored in the vesicles during the longer intake of L-dopa so that the withdrawal effects are seen particularly in the early phase of the disease only after 4 – 5 days. However, the resorption of L-dopa which occurs in proximal parts of the intestine is reduced and the greater part of it is lost in the periphery before reaching the blood brain barrier. With the addition of Bensarizide or Carbidopa it is considerably better as the combination helps a better transportation through blood brain barrier.
However, even the other drugs such as Bensarizide or Carbidopa alone are not capable of crossing the blood brain barrier unless they are combined with levodopa. The proper administration of L-dopa even with other drugs such as Bensarizide or Carbidopa is problematic because of the absorption in the gastrointestinal tract leading to several side effects. This is particularly disturbing for the patients at the beginning of the treatment but also during the further clinical course of drug-intake. Some of the disturbing side effects are the following:

**Gastrointestinal**
- Nausea
- Constipation
- Diarrhea
- Gastritis, rather rarely

**Cardiovascular**
- Tachycardia
- Orthostatic disegulation
- ECG-changes, rarely

**Psychiatric**
- Anxiety and agitation
- Sleep disturbances
- Mood changes, depression
- Hallucinations, rarely

**Other side effects**
- Liver function disturbances
- Hematological changes
- Hypersexuality, rarely

The medication with L-dopa must be monitored carefully particularly during the phase of titration. The
The pharmacokinetic of L-dopa is not linear, so that the bioavailability is not directly proportional to the dosage administered. As the dosage is being increased the serum concentration increases rather unproportionately which may lead to side effects. The therapeutic effect of L-dopa is mostly related to akinesia and rigidity and considerably less against tremor. However, the patients benefit from the allround-betterment through the medication of L-dopa as the most disturbing feature for them is akinesia and rigidity than tremor. In the clinical practice one can notice that not only the motoric functions but also other disturbances such as related to sleep, mood changes and even cognitive functions improve. Because of these factors L-dopa remains even today the basic drug for the treatment of idiopathic Parkinson syndrome. Actually patients who do not react positively on the medication of L-dopa must be reconsidered from the aspect of diagnosis, whether they really have an IPD at all. However, a reduced reaction to L-dopa cannot rule out the possibility of an idiopathic Parkinson disease. On the other hand a questionable reaction to the treatment of L-dopa in the early stages of clinical condition must make us think about the possibility of other Parkinson syndromes related to multisystem atrophy. The difficult phase of the medication with L-dopa is certainly in the earlier stages because of the gastrointestinal reactions. It is therefore very useful to start with a low dosage of L-dopa combined with Bensarizide or Carbidopa and titrate the dosage carefully, if necessary with addition of such antiemetics such as Domperidon (Motilium). It is known in the clinical practice that patients who have serious side effects against L-dopa have a reluctance to take the drug further even in the later stages. This can happen even because of the reactions of the
dependents of the patients who see them suffering after the early dosage of L-dopa. This aspect should be considered during the early phases of treatment as practically all patients need L-dopa sooner or later for the treatment of their symptoms.

**Dosage of Levodopa**

In the clinical practice it is useful to start with a dosage of 50 mg L-Dopa and 12.5 mg of Bensarizide and increase the dosage slowly in intervals of 5-7 days until the desired dosage is reached. Even under such small dosages it is useful to give patients in addition Domperidon to prevent particularly the gastrointestinal side effects which seems to be quite disturbing. As Domperidon is an antagonist to peripheral Dopamine receptors, it seems to be a suitable drug for combination in the early stages which naturally can be slowly stopped after the patients tolerate L-dopa without any serious side effects. It is useful to know that L-dopa given in the early phases of IPD only three times a day can have the therapeutic effect in spite of L-dopa having a short half-life. This is probably related to the mechanism of preserved Dopamine converted from the intake of L-dopa by the presynaptic nigrostriatal nerve-endings. In the clinical practice, it is possible to continue this kind of three times daily medication with L-dopa combined with Bensarizide or Carbidopa for a period of generally 4 – 5 years. Later however the patients need the intake of 4 or more dosages of L-dopa per day which however must be planned according to individual requirements. The early phase of prompt reaction to L-dopa medication is known in the clinical circles as “honeymoon phase”. In this phase the patients feel an
allround-betterment of their motoric functions as well as other disturbances related to IPD. There may be a somewhat hyper-mood in patients in the form of a euphoria which is mostly seen under L-dopa medication.

**Indications for Levodopa and Side Effects**

During the treatment of IPD it is necessary for the physician to know that every patient needs L-dopa as a basic medication but the higher dosages of L-dopa are also responsible in the longer clinical course for the occurrence of dyskinesias. It is also useful to know right from the beginning that the so called honeymoon-phase with L-dopa medication is a rather short lived phenomenon and does not last for long. Even though there are no clear cut guidelines as to when and who should get L-dopa as the medication of first choice, it is necessary to consider some factors. In patients who are comparatively younger belonging to the group of fifties, it is useful not to begin with L-dopa but with other Dopamine-agonists. In case of medication with Dopamine-agonists one does not experience the so called dramatic effect in the form of honeymoon-phase seen with L-dopa medication. However several patients can manage during the early phases of IPD without the addition of L-dopa. On the other hand patients who show the first symptoms of IPD around the age of 70 years, it may be useful to begin with a medication L-dopa, even though also in this age-group there could be individual considerations. The aspect involving the occurrence of late dyskinesia must be considered carefully also in view of the patient information. Even though it is very likely that L-dopa leads to the occurrence of late dyskinesia in most of the patients of IPD, it is not known
with certainty whether the drug alone is responsible for the occurrence of such late complications. As mentioned earlier late dyskinesia may also be related to the disease complex of IPD with or without medication. It is however difficult to estimate this factor properly as practically all the patients after a course of 10 years of IPD have in their medication, some preparation related to L-dopa. During the discussion with the patients therefore one has to be careful in dealing with this matter of dyskinesia associated with L-dopa because of the risk that the patients may get fear of getting dyskinesias and may not agree to take the medication of L-dopa at all. This will be very contraproductive as the patients would suffer many more complications without the medication of L-dopa during their further lifespan. It is however useful for the physician to control the dosage of L-dopa in view of the possible side effects with dyskinesia, but an over-interpretation should be avoided. It is possible that some patients have an increased tendency to get dyskinesia than the others, who may be getting also many other disturbing symptoms motoric or otherwise associated with IPD.

From the different L-dopa preparations available in the market, one has to make individual selection to start a particular drug. Generally it would be better to take a simple drug of L-dopa combined with Bensarizide in a small dosage of 50 and 12.5 mg combination. Depending upon the requirements the dosage may be switched over to the tablets having 125 mg combination. There are retard forms of L-dopa with a dosage of 200 mg L-dopa and 50 mg of Bensarizide. After early trials many neurologists are of the opinion that it would be useful to take the non-retard-forms because of faster effect of these preparations. Only in some patients with extremely disturbing
fluctuations during night the retard- or depot-forms may be useful. Generally however it is better to start with the non-retard-forms to begin with three times daily, then depending upon the requirement 4–5 times daily. Attempts should be made to keep the dosage of L-dopa between 450 and 600 mg per day and combine the drug with other Dopamine-agonists wherever necessary. The highest dosage of L-dopa recommended is around 1000 mg per day which however must be avoided to the extent possible, because of the risk of dyskinesia.

Like any other drug against IPD, even L-dopa looses its efficiency related to the therapeutic effect during the course of disease generally after a period of 4-5 years. This may be probably due to the progression of the disease with further loss of nigral neurons with consequent loss of Dopamine in striatum. The earlier therapeutic effect of L-dopa lasting several hours becomes weaker so that the patients need the drug several times per day. Some patients report a better effect of L-dopa in the mornings whereas the others mention benefits during the day. After a duration of 7-8 years most of the patients experience fluctuations in the form of wearing-off-phenomenon. They begin to take the drugs more often even without the instruction of the physician to compensate this on-off-effect. It becomes then also difficult to decide the dosage depending upon the half-life of the drug as the earlier phase of therapeutic effect is lost leading to a confusion in the management of medication. It may be possible that the earlier capacity of the nigral and striatal neurons to preserve the Dopamine converted form of L-dopa does not function any longer properly. Consequently the patients experience symptoms such as fluctuations related to akinesia, dyskinesia, dystonia and depression. It is known that patients, who begin with the treatment of
L-dopa early, have a tendency to get the later complications particularly fluctuations and dyskinesia also comparatively earlier.

**Duodopa-Pump**

Duodopa-Pump (Fig. 8.2) is a method of treatment with L-dopa for the continuous application of L-dopa for patients in advanced stages of Parkinson disease. The indication for such a method of treatment is a positive reaction to L-dopa in spite of the motoric fluctuations and the dyskinesias in the patients concerned. Such a strategy is necessary because of the short half life of L-dopa which in the oral form does not give sufficient bioavailability of the substance to control the symptoms. The Duodopa-Pump is meant for a direct application of L-dopa combined with Carbidopa in the Duodenum through a percutaneous endoscopic gastro-stomy (PEG). The PEG surgery can be performed with a local anesthesia so that the contents of the Duodopa-Pump can be directly available in the duodenal region. The Duodopa-Pump is made available in a cassette which is normally sufficient for a day that means nearly for 16 hours. The purpose is to make at least temporarily the continuous availability of L-dopa directly through intestinal resorption. The dosage can be adjusted according to requirements and the clinical condition of the patient. This is given in the form of a basis bolus injection and can be monitored through the patient. This method of treatment is rarely used and in only such patients who because of their advanced progression of the disease are not in a position to react to the usual oral treatment with L-dopa and other Dopamine-agonists. This method is available only in certain countries of Europe.
Because of uncertainty during the early phases of idiopathic Parkinson syndrome related to unclear cardinal symptoms, it may be necessary to have more confirmation in the form of Apomorphine-test and L-dopa test. The Apomorphine test seems to be rather less conducted than L-dopa-test as the later shows lesser side effects. The clinical neurologist has to decide as to which test to be used depending on the later strategy of treatment. If from the beginning of the disease a treatment with Dopamine-agonists are considered, then it may be preferable to use Apomorphine-test. If on the other hand a treatment is planned with L-dopa then an L-dopa-test is sensible, which must however be considered with caution. Some scientists from basic research think that if a L-dopa test is carried out without proper considerations it may lead to a kind of “priming” for later dyskinesias. However, these considerations are more hypothesis than proved facts.
Apomorphine Test
The Apomorphine test is carried out with pre-intake of Domperidon. A dosage of 4-8 mg of Apomorphine is given per subcutaneous injection. If there is a fast reaction with the reduction of tremor, rigidity and akinesia then the IPD can be diagnosed as very probable.

L-Dopa Test
The L-dopa test is also carried after pre-intake of Domperidon. Consequently a dosage of 100-300 mg of L-dopa combined with a decarboxylase-inhibitor is given mixed with water. The reaction can be ascertained either clinically or through the unified Parkinson disease rating scale. An improvement of at least 30% gives the probable diagnosis IPD whereas an improvement of over 50% makes the diagnosis fairly certain.

Dopamine Agonists
The treatment of idiopathic Parkinson disease is unsatisfactory because of the progression of the disease irrespective of the medication. The present medication with anti-Parkinson-drugs targets the improvement of symptoms without being able to influence the degenerative process. From what is known about the pathophysiology and etiology it would be sensible to stimulate the postsynaptic receptors in the striatum directly so that a continuous production of Dopamine is made available in spite of the degenerative mechanism in the basal ganglia. However, the present drug-treatment particularly with Levodopa is directed at the substitution of Dopamine and accordingly to reduce the symptoms and improve the quality of life. A new generation of drugs belonging to the
group of Dopamine-agonists claim to stimulate the Dopamine-receptors in the striatum to restore the neuronal signals needed for better functioning of the basal ganglia. At the same time some of these Dopamine-agonists claim to have a neuroprotective function which is however a hypothesis. The use of Dopamine-agonists has become common particularly in the beginning of the IPD, in people of the younger age-group. The Dopamine-agonists can be given as monotherapy or can be combined with the basic drug L-dopa. There are several drugs available in the market and new drugs are appearing over the last few years. Basically there are two groups of Dopamine-agonists namely ergoline and nonergoline, which can be divided as follows:

Ergoline Dopamine-agonists
- Bromocriptine
- Lisuride
- Alpha-Dihydroergocriptin
- Pergolide
- Cabergoline

Nonergoline Dopamine-agonists
- Apomorphine
- Pramipaxole
- Ropinirole
- Pirebedil
- Rotigotin

Some of these agonists such as Apomorphine exist in the market for many years, the others have been introduced during the past years. Apomorphine is given as a subcutaneous injection whereas Rotigotin is available in the form of a 24 hours-Plaster. The present trend is to use
more of nonergoline Dopamine-agonists than the ergolin-agonists because of the side effects. Different kinds of side effects are however known in practically all the Dopamine-agonists.

**Apomorphine**

Apomorphine is an old Dopamine-agonist existing in the market for several years. During the early fifties and later in the sixties the drug was tried in the form of a subcutaneous injection for the treatment of IPD. Because of the serious side-reactions the drug was abandoned and introduced later in the 1980s. It is an Apomorphine-alkaloid and the substance is known to stimulate D1- and D2-receptors. At the present day of Parkinson treatment Apomorphine plays a marginal role and when used, is given even today in the subcutaneous route. It is used as an Apomorphine-pen for the subcutaneous injection along with Domperidon to prevent the side effects. The drug is not suitable for a long-term treatment but is useful during operation, preoperative and postoperative periods in the form of subcutaneous injections with pen. The therapeutic effect reaches in about 1–2 hours. Because of the subcutaneous injections there may be side effects associated with skin-reactions which may lead to ulcer-formations. Further side effects are gastrointestinal and cardiovascular disturbances as well as rarely psychosis. The application of these injections are meant today for temporary situations such as the mentioned above. Other forms of application have been found through nasal and sublingual routes which also create considerable side-reactions particularly allergic reactions.
Bromocriptine

Bromocriptine is an ergoline Dopamine-agonist and the drug is known for the last nearly 40 years. The drug has been tried as a monotherapy and also in combination with L-dopa. It seems to give during the early stages a beneficial therapeutic effect which is lost within the next 3-4 years almost completely or up to a considerable level. The dosage of Bromocriptine was compared to the equivalent dosage of L-dopa which shows a proportion of 1 mg Bromocriptine as equivalent to 12.5 mg L-dopa. It has a half-life of 3-6 hours so that the dosage has to be administered 3-4 times a day in the similar way as L-dopa. The drug being an ergoline Dopamine-agonist is not indicated in coronary heart diseases and it is also known to increase the tendency of cardiac valvular problems. The most common side effect however is nausea and cardiovascular disturbances. It is also known to create in the long run pulmonal, retroperitoneal and cardiac fibrosis. Under the treatment of Bromocriptine it is necessary to make regular hematological examinations as well as X-ray examinations of thorax around once a year. In case of long-range treatment it is also advised to make echocardiography in intervals of 1-2 years. Because of these different short-term and long-term side effects Bromocriptine remains a second choice in the treatment of IPD.

Cabergoline

Cabergoline is also an ergoline Dopamine-agonist and is being used for many years in the treatment of idiopathic Parkinson disease both in the form of monotherapy as well as in combination with L-dopa. Cabergoline has a very
long half-life of 65 hours and accordingly it has to be used only once daily. The increase of dosage is also simple as it can be done in intervals of one week until the desired dosage of 2-6 mg per day is given mostly with breakfast. This is useful particularly in view of better compliance of patients. In milder cases of Parkinson disease beginning in the younger age-group Cabergoline can be given as a monotherapy for a few years so that the medication of L-dopa can be delayed. However, the drug has the common contraindications related to cardiovascular diseases and valvular disease of the heart. It can also create pulmonary problems leading to pulmonary and cardiac fibrosis. During the treatment of Cabergoline it is therefore necessary to make yearly X-ray examination of the thorax and also echocardiographic examinations.

**Alpha-Dihydroergocriptine (Alpha-DHEC)**

The Alpha-dihydroergocriptine is a ergoline Dopamine-agonist which is not being used much in the first line treatment of Parkinson disease. The therapeutic effect is similar to that of Bromocriptine and has similar side effects as well. The half-life of Alpha-DHEC is about 10-16 hours so that the drug can be given twice daily. The dosage ranges between 60-120 mg per day. There is not much information available in the literature about this drug and in the clinical practice it’s not being used often. However, it has the usual therapeutic effects of a Dopamine-antagonist. The side effects are related to liver function and probably the usual long-range side effects connected to pulmonary and cardiovascular systems.
**Lisuride**

Lisuride is an ergolin Dopamine-agonist which is not available in certain countries also in Europe. The substance is similar to Bromocriptine, seems to be however somewhat more effective. Among the beneficial effects of Lisuride are good therapeutic effects against akinesia and rigidity similar to L-dopa. In some studies it has been noted that Lisuride may cause lesser late dyskinesias than L-dopa. The half-life is short around only 2 hours so that the drug has to be taken several times per day. 1 mg of Lisuride has been roughly equated to 100 mg of L-dopa. Lisuride is given as subcutaneous infusion through a pump similar to the injection of Duodopa-Pump. Because of this problem the drug is not frequently used in the treatment of idiopathic Parkinson disease.

**Pergolide**

Pergolide belongs also to the group of ergolin Dopamine-agonists and is known in the market for the last nearly 40 years. It has a somewhat longer half-life and lesser side effects when compared to drugs such as Bromocriptine. Also in case of Pergolide it is known that the later complications of dyskinesia are prolonged in comparison to the treatment of the basic drug L-dopa. The pharmacokinetic of Pergolide seems to be similar to that of L-dopa so that it can be given both in monotherapy as well as in combination. The equivalent dosage of Pergolide is given as 1 mg to 100 mg L-dopa. The maximal dosage is recommended at 4-5 mg per day. The side effects are similar to that of the other ergolin Dopamine-agonists. However, the major short-time side effects are gastrointestinal disturbances. Therefore it is necessary to
introduce this drug along with the Domperidone to prevent the serious short-time side effects. As long-time side effects similar conditions are described related to pulmonal and cardiac fibrosis. Because of these problems the drug has a place of second choice in the treatment of IPD.

**Pramipaxole**

Pramipaxole is a widely used Dopamine-agonist belonging to the group of nonergolin agonists. With the introduction of this drug in the year 1998 it has given a new indicator in the treatment of idiopathic Parkinson disease, a drug of first choice particularly in people of younger generation. But the drug can be used in all age-groups both as monotherapy or also in combination with L-dopa or other drugs. The therapeutic effect is comparable to the longer known drugs belonging to the group of ergolin agonists but Pramipaxole has lesser side effects even though certain side effects are known even for this drug. It is an aminobenzothiazol and stimulates the D2- and D3-receptors. The half-life is between 8-12 hours so that the drug can be administered three times daily. A high Dopamine-receptor effect has been noted in this drug. Through the introduction of Pramipaxole there has been some change in the treatment of IPD particularly as already mentioned in people who get the disease around the age of 50 years. It is possible to give only Pramipaxole as a monotherapy which seems to help several patients at least for the first 2-3 years. This enables the later introduction of L-dopa and accordingly the prevention of late dyskinesias to the extent possible. Along with this, it has been shown that with the addition of Pramipaxole to the existing medication of L-dopa the dosage of L-dopa can
be somewhat reduced. Pramipaxole is therapeutically effective against all the three major cardinal symptoms of IPD namely tremor, akinesia and rigidity. The postural instability is a phenomenon independent of these above mentioned cardinal symptoms however which accompanies the clinical picture of practically every Parkinson patient. Patients report a positive effect of Pramipaxole not only regarding the motoric disturbances but also related to the other non-motoric phenomenon such as anxiety, mood changes and depression. From the experimental studies with Pramipaxole the possibility of neuroprotection has been reported. The dosage has to be given slowly as in case of all other anti-Parkinson drugs. The drug is available in different dosage of 0.125 mg, 0.25 mg, 0.5 mg and 1 mg. It is useful to start with the smallest dosage in the evenings and increase the dosage in intervals of 5-7 days up to a daily dosage of 3 mg per day in the beginning, which can be by necessity increased up to 6 mg total per day. In case of patients already taking L-dopa it may be necessary to give a comparatively smaller dosage but the reverse is also possible, namely that patients who have a monotherapy of Pramipaxole need comparatively lower dosage of L-dopa. The common side effects are nausea and drowsiness. Some patients get edema of the ankles which on correction of dosage is reversible. The patients must however be informed of the possible sudden drowsiness which may be a problem during driving. This kind of drowsiness can appear also with other Dopamine-agonists. In rare cases a tendency to hypersexuality and gambling have been reported which behavior also seem to be reversible. Pramipaxole is also an effective drug in the treatment of restless leg syndrome. In idiopathic Parkinson disease it can be considered as a drug of first choice in the group of Dopamine-agonists.
Ropinirole

Ropinirole is also a nonergolin agonist, is available since 1997 in Europe. It can be used similar to Pramipaxole as monotherapy and in the combination for the treatment of IPD. The indications are similar to that of Pramipaxole so that Ropinirole can be introduced as a mono drug in the treatment of patients who get the disease earlier. It is a dihydro-indol-derivat and is highly selective D2-receptor. The half-life ranges from 3-8 hours so that the drug can be given three times daily. There is a retard-form meant for the intake of only once daily. It is effective against the three cardinal symptoms namely akinesia, rigidity and tremor and seems to possess a relaxing antidepressive effect. The drug is contraindicated in clear cases of renal insufficiency and liver function disturbances. The dosage must be increased slowly so that the daily dosage is maintained between 4-8 mg. Similar to the usage of Pramipaxole, Ropinirole can be given during the first few years of IPD without the use of L-dopa so that the late complications may be reduced even with this medication. Ropinirole is also a widely used drug and can be given in the early stages of IPD and later combined with L-dopa or other drugs. The drug is available in the dosage of 0,25 mg, 1 mg and 2 and 4 mg as retard tablets.

Several studies have been conducted with the monotherapy of Ropinirole in patients with early stages of Parkinson disease. During clinical studies it is shown that the administration of L-dopa could be prolonged for one year or longer under the monotherapy of Ropinirole and the patients show considerably less tendency to dyskinesias after a period of five years. The studies also show that the patients needed lesser dosage of L-dopa under a therapy of Ropinirole. Summarising one can say...
that Ropinirole as monotherapy is effective in the treatment of early Parkinson disease and has advantages of delayed occurrence of dyskinesia also in combination with Levodopa. Ropinirole can also be considered as a drug of first choice in IPD.

Rotigotine

Rotigotine is a nonergoline Dopamine-agonist with selective sensitivity to Dopamine-receptors D3, D2 and D1. It is available in the form of a 24-hours-Plaster for application over the skin and the resorption through the skin has been established. It is available in different dosages of 2 mg, 4 mg, 6 mg and 8 mg so that the dosage titration can be done even under dermal application. The half-life of the drug has been established at 5-7 hours and the plasma-binding has been seen at 92%. The eliminations seem to be mostly through renal route. The drug is absorbed by transdermal application about 45% within 24 hours so that the plasma level remains more or less constant event after a few hours. It can be used as a monotherapy but also in combination with Levodopa or other Dopamine-agonists. Even though there is no other special advantages through the Plaster-application of Rotigotine it may be suitable for patients who want to avoid the oral intake of too many tablets. It may be useful also for patients who have already developed swallowing problems during the course of Parkinson disease. Certain side effects as in the case of other Dopamine-agonists are known even though without serious consequences. There may be some irritation in the skin-region of transdermal application which can be changed from time-to-time. The long-range therapy with this Plaster as monotherapy or in combination has not been properly studied and established.
Ergoline versus Nonergoline Agonists

After the development of newer drugs belonging to the group of nonergoline Dopamine-agonists, the use of ergoline agonists has been somewhat pushed to the place of second choice drugs. However, both groups are being used in the clinical practice and the benefits and side effects must be individually evaluated. One of the main pharmacological considerations is the higher specificity in respect of Dopamine-receptor selection seen in the case of nonergoline agonists. Consequently there are lesser side effects in case of nonergolin agonists when compared to the ergolin derivatives. This is particularly related to the side effects of Ergot-preparations which may have long-range problems related to pulmonary and cardiac systems. In the neurological practice therefore it has become customary to begin with a nonergolin Dopamine-agonist as the drug of first choice and only under clinical and biochemical problems the drug can be changed over to ergoline agonists. Among the two most popular drugs which have already been mentioned are Pramipaxole and Ropinirole which both show in the monotherapy effective therapy-markers particularly in view of reducing the earlier occurrence of dyskinesias. It has been more or less established therefore particularly in the patients getting IPD in the earlier age-group to start with one of the nonergoline Dopamine-agonists particularly the Pramipaxole or Ropinirole in smaller dosage which can be titrated to the adequate daily dosage. The treatment of the patients in the clinical practice becomes somewhat easier under nonergolin Dopamine-agonists as continued care in view of X-ray-examination of thorax and cardiography are not needed. However, it must be taken into account right in the earlier stages of Parkinson disease
whether of early or later onset that the patients need along with the treatment of Dopamine-agonists the addition of L-dopa over the years depending upon the clinical condition.

**Neuroprotection Through Dopamine-agonists**

The pharmaceutical companies which manufacture the Dopamine-agonists particularly the nonergoline agonists mention often about the neuroprotective effect through these agonists. There have been several studies including animal experiments to explain this phenomenon and show the possible effects of a neuroprotection through Dopamine-agonists. The experimental methods as well as the hypothesis relating to neuroprotection have been explained on the basis of Dopamine-receptors particularly D1 and D2 as also the so called receptor-families. It is usual to classify the receptors as D1 and D2. To the first group of receptors belong D1 and D5 and to the second group or family belong the receptors D2, D3 and D4. The actual functioning of these receptors has not been properly understood. It appears the ergoline Dopamine-agonists seem to have an affinity to D2-receptors whereas the nonergoline to D3-receptors. These receptors are seen mostly in the basal ganglia but also in other regions of the brain. In the regions of substantia nigra these receptors are found in the pre- and postsynaptic level. It is known that most of the Dopamine-agonists stimulate D2-receptors with a variable selectivity. Probably the nonergolin agonists are responsible for maximum stimulation of the D2-receptor-system. The principal of neuroprotection seems to be based on the concept of the reduction of possible oxidative stress. It is therefore presumed that the Dopamine-agonists are responsible for the antioxidative
effect in the region of synapses. The possibility of neuro-protection through such phenomenon based on the therapeutic effect of Dopamine-agonists has been studied through PET- and SPECT-examinations.32 There have not been however clear results about the neuroprotection based on the Dopamine-receptors through the Dopamine-agonists, even though a possibility of such effect has been presumed. Among the Dopamine-agonists which seem to possess such a positive action are Pramipaxole and Ropinirole. In the clinical practice it gives us only some hints to begin with these drugs as agonists of first choice. It has been proved through several studies that the occurrence of dyskinesias can be delayed by the use of these nonergoline Dopamine-agonists whatever the neuro-protection through these drugs may be. As dyskinesias appear earlier in case of patients who get the IPD also in the earlier phases of life, it seems to be therefore sensible to begin with Dopamine-agonists than with levodopa and wait for the introduction of Levodopa as long as possible.

**Clinical Side Effects of Dopamine-agonists**

All the antiparkinson drugs have more or less severe side-effects particularly during the early phase of treatment. The major side effects through the Dopamine-agonists are nausea and vomiting. These can be prevented by the parallel use of Domperidon during the titration with agonists. There are other side effects as well, such as the edema of ankles and tendency to sudden sleepiness. The other somewhat less common side effects are psychotic experiences leading to hallucinations, hypersexuality and gambling. It is therefore necessary to monitor in a combination therapy with Dopamine-agonists and L-dopa for the possible appearance of the above mentioned side
effects. It is necessary then to reduce the dosage of Dopamine-agonists first, before changing the dosage of Levodopa. The other side effects related to ergolin agonists are headache, syncope, giddiness and as long-range side effects retroperitoneal and pulmonary fibrosis, cardiac valvular fibrosis which must be taken into account by regular examination of patients who undergo these medication. Under all Dopamine-agonists one must consider the possibility of tiredness during day and particularly sudden tendency to sleep-attacks as in the case of narcolepsy. Because of these side effects it is necessary to tell the patients particularly during the earlier stages of treatment that they should avoid driving. In the event of such rare side effects as hypersexuality and gambling which are possible under Pramipaxole and may be also under Ropinirole the dosage of these drugs must be reduced or the drugs must be stopped and replaced through other agonists or Levodopa. In this connection it is also necessary to consider carefully in the event of a combination of two agonists depending upon the known side effects and the therapeutic profile. Generally it is advantages to have only one Dopamine-agonist where the dosage can be raised to the extent of tolerance.

NMDA-Antagonists

NMDA (N-methyl-D-aspartat)-inhibitor belong to the group of receptor-antagonists which are subtypes of glutamate-receptors. The main drug belonging to NMDA-antagonists is Amantadine, which is an old drug. Another drug Budipin is available in the market only in some countries. This is a drug with several side effects and as such is not available in the market in many countries.
**Amantadine**

Amantadine is known in the pharmacology for nearly 50 years. It was introduced as an antiviral drug and later its efficacy was found in the treatment of Parkinson symptomatic. Consequently it was introduced as an anti-Parkinson drug and has been found to be useful particularly in the treatment of late dyskinesia. The half-life of the drug is from 15-30 hours and the bioavailability is fairly quick as it can be available after oral application in about 2-5 hours. The plasma-protein-binding is around 65% and the excretion is mostly renal. It is a drug which crosses fairly well the blood-brain-barrier. It is available in two forms as Amantadine sulphate and Amantadine hydrochloride. In the pharmacokinetic it is known to inhibit the overactivity of glutamate and acetylcholine. It is a drug which is effective against akinesia, tremor and rigidity. The drug is available mostly in dosages of 100 mg and 200 mg capsules. In the pharmacokinetic it is expected that the therapeutic effect happens probably independent of the Dopamine system. The main indication is the dyskinesia occurring in most of the IPD patients after a clinical course of 5-10 years particularly under the medication of L-dopa. These dyskinesias are probably caused by the imbalance occurring in the striatal NMDA-receptors leading to a high glutamate-sensibility of neurons. This imbalance in the neuronal activity results in the overactivity of neuropeptides which may result in motoric dysfunction in the form of dyskinesia. This hypothesis has been partly proved by animal experiments.33

Amantadine as a NMDA-receptor-antagonist seems to prevent these unphysiological neuronal imbalance and helps to reduce the dyskinesias. It is given in a daily dosage
of 300 mg divided in 2-3 doses. The titration should be made carefully increasing the dosage by 100 mg in intervals of one week. Along with a good antidyskinetic effect Amantadine seems to have some neuroprotective effects as well, to improve cognitive functions. Even though the drug is tolerated in the normal dosage without serious side effects, some patients complain of sleep disturbances, in such cases the drug should not be given late evenings. The contraindications are serious cerebrovascular disturbances, psychosis and epilepsy. If combined with anticholinergic drugs there may be a tendency to psychosis. Amantadine can be given for the treatment of the cardinal symptoms of IPD irrespective of dyskinesia. But in the presence of dyskinesia Amantadine is a drug of choice through which the dosage of Levodopa can be somewhat reduced. Because of these factors Amantadine can be given as a monotherapy also in the beginning of IPD to prevent the early occurrence of dyskinesias. In the selection of Amantadine for clinical efficacy both drugs are suitable namely Amantadine sulphate and Amantadine HCl, even though Amantadine sulphate is used much more commonly than Amantadine HCl.

**Budipine**

Budipine is a drug which belongs to the group of NMDA-antagonists and is mostly used in IPD with tremor-dominance-symptoms. However, the drug is effective also against other cardinal symptoms such as akinesia and rigidity. The drug has side effects similar to the other drugs. However, it is being used comparatively less in the clinical practice because of the restriction involving ECG-controls in patients who receive this drug. In some countries this drug is not available. The principle of use of Budipin is the
basic pathophysiological concept of idiopathic Parkinson disease which should define IPD not only as a Dopamine-deficient-syndrome but also as a multisystem-degeneration involving also different neurotransmitters such as acetylcholine, glutamate, norepinephrin, GABA and serotonin. Accordingly the treatment should be directed not only for the substitution of Dopamine but also with broader indications. It is also effective in other regions of basal ganglia and the brain which are not directly involved with the production of Dopamine. Accordingly the drug has been named as “dirty drug” or “rich compound”. It is effective against the imbalance of the neurotransmitters mentioned above and indirectly for the stimulation of Dopamine-production and prevention of Dopamine-reuptake. However, the drug does not directly stimulate the Dopamine-receptors. Accordingly on the one hand the drug can be considered as a multisided approach related to the neurotransmitters but at the same time as a diffuse therapeutic approach. There have been several studies on the clinical efficacy on this drug both in the monotherapy as well as in combination with other antiparkinson drugs excepting Amantadine which is also an NMDA-antagonist and hence an combination should not be done with this substance. Budipine can be given in a dosage of 30-60 mg per day divided in three doses with slow titration as in the case of other drugs also. Generally the dosage should be kept rather low at 10 mg three times daily. The side effects are mostly cardiovascular and because of which ECG-examinations during the treatment with Budipine are necessary. The contraindications are bradycardia, cardiomyopathy and myocarditis. The patients must be watched during the medication for possible cardiac arrhythmias. Along with that, the side effects such as nausea, dryness of mouth and tiredness are
known. Because of these side effects the drug can be considered as one of second choice in the treatment of IPD.

**MAO (Monoamino-Oxidase)-inhibitors**

The classical MAO-A-inhibitors used in the antidepressive medication are used in the Parkinson medication as MAO-B-inhibitors. The drugs belonging to this group as Parkinson medication are Selegiline and Rasagiline. Selegiline is in the market for many years whereas Rasagiline is rather new and claims to be an improved form of the MAO-B-inhibitors.

**Selegiline**

Selegiline is known as an antiparkinson drug since 1975 almost since the time L-dopa has been used as major drug in the treatment of IPD. Selegiline is a selective irreversible inhibitor of the central monoamino-oxidase-B. It has a long half-life of around 40 hours. The drug was used in the early years more often than it is the case today. The absorption of the drug is quite fast and the drug is metabolised through meta-amphetamine to amphetamine, even though under normal dosage a real amphetamine-effect is not produced. Earlier the drug was called as L-Deprenyl and the drug today is marketed with different trade names. Through the administration of MAO-B-inhibitor the concentration of Dopamine is raised in the synaptic level. To reach a pharmacodynamic effect the MAO-B must be inhibited up to 80%. The recommended dosage is roughly 1 mg per 10 kg of body weight which would be in the range of 5-10 mg per day. The drug can be given as a monotherapy but also in combination with L-dopa or other agonists. Some clinical
studies show good effects against on-off- and freezing-phenomena. However, Selegiline can be considered today as a drug of second choice in IPD. The common side effects are reduced sleep so that the drug should be given preferably not in the late evenings. The other side effects are nausea, giddiness and in combination with L-dopa sometimes even psychotic conditions. In the case of prevailing dyskinesia the drug is not indicated as it may increase this tendency.

**Rasagiline**

Rasagiline is also a MAO-B-inhibitor of irreversible selective nature. Rasagiline is 5 to 10 times stronger as a MAO-B-inhibitor compared to Selegiline. The metabolization occurs mostly in the liver and the metabolite is an amphetamine-derivate similar as in the case of Selegiline. There have been several studies which recommend the drug as a monotherapy in a small dosage of 1-2 mg per day in a single dosage preferably in the mornings. Because of the effect of MAO-B-inhibitor the drug has a psychodynamic effect which improves the mood of the patient. However, the therapeutic effect is seen somewhat later after 3-4 weeks in most of the patients. The general tolerance of the drug is good also in elderly patients. Both drugs Rasagiline and Selegiline should not be combined with serotonin-reuptake-inhibitors (SSRI). In comparison to Selegiline Rasagiline seems to have some additional neuroprotection-effect so that the drug may be helpful in prevention of dementia. However, more studies are needed in this regard for clinical usage. The principle for cognitive improvement is based on the anti-oxidative effect of the substance. However, on the whole the drug seems to play a considerable role as the medication of first
choice in the treatment of IPD. It can be used both as monotherapy as well as in combination with other antiparkinson drugs.

**COMT-inhibitors**

One of the main problems with the L-dopa medication is the availability of the drug in the brain because of the blood-brain-barrier. Consequently only a portion of the L-dopa intake is available in the brain due to peripheral absorption in the gastrointestinal region. This problem was partly solved by the combination of L-dopa with decarboxylase-inhibitors namely Bensarizide and Carbidopa. Already during the earlier phase of L-dopa trials by the pioneer Walter Birkmayer, attempts were made to improve the bioavailability of L-dopa with further combination of COMT-inhibitors. The purpose of COMT-inhibitors is the inhibition of the dissolution of L-dopa to 3-O-Methyl-dopa (3-OMD). This dissolution of 3-OMD happens through the catechol-O-methyl-transferase (COMT). By the application of COMT-inhibitor the peripheral dissolution of L-dopa is reduced. However, the combination of COMT-inhibitor with L-dopa resulted in serious side effects related to liver function disturbances. Two substances were however synthesized with better drug tolerance in the form of a selective reversible inhibitor.

**Tolcapone**

The drug was introduced in Europe after several clinical trials in 1998 as antiParkinson medication. However, during the early phases there were cases of mortality because of acute hepatotoxicity. An improved form of the drug was again introduced which is now allowed for
clinical application in cases where the other COMT-inhibitors namely Entacapone was found ineffective. However, regular hematological and liver function examinations are obligatory for the treatment with Tolcapone. The drug is useful in cases of clinical complications during the course of IPD in form of motoric fluctuations. The medication must be carried out carefully under regular clinical and laboratory supervision of patients. The recommended dosage is 300 – 600 mg per day in divided doses after careful titration.

**Entacapone**

Entacapone is a peripheral effective COMT-inhibitor which improves the plasma-concentration of L-dopa which consequently helps better crossover through the blood-brain-barrier. Consequently there is a better bioavailability of the drug without much imbalance in the serum-availability of L-dopa. With the addition of Entacapone almost up to 100 mg of Levodopa can be saved per day which helps the prevention of early onset of dyskinesia. The addition of Entacapone even in a smaller dosage of 50 mg seems to improve the bioavailability of L-dopa to a considerable extent so that the dosage of Entacapone can be increased with additional benefits. The recommended dosage of Entacapone is 200 mg per day along with Levodopa. The half-life of the drug is short about 3.5 hours, the metabolization is mostly hepatic and the excretion is renal up to 10%. The combination of Entacapone with L-dopa improves the half-life of both drugs which is an advantage for patients particularly during the later stages of Parkinson disease. The pharmacokinetic of Entacapone seems to be similar to that of L-dopa so that a combination is helpful in many cases of complex clinical course.
However, the COMT-inhibitors are helpful only with the basic medication of Levodopa. Even though Entacapone has lesser side effects than Tolcapone the patients sometimes are worried about the yellow color of the urine. The other side effects are nausea and diarrhea of which the latter can be a problem during the treatment with Entacapone. Some patients refuse to take the drug after experiencing serious problems with the diarrhea. Entacapone is not useful in patients who have already started getting dyskinesia as the drug can eventually increase the tendency to dyskinesias. Or in such cases, the dosage of Levodopa has to be somewhat reduced. The introduction of Entacapone as well as withdrawal should be done carefully and in slow phases. The drug should not be given along with MAO-A-inhibitors and with noradrenaline-reuptake-inhibitors because of the side-reactions. On the whole from the two COMT-inhibitors available, the use of Entacapone is easier than that of Tolcapone in the clinical practice.

**Combination of Levodopa, Carbidopa and COMT-inhibitors**

As mentioned, a COMT-inhibitor is effective only with the basic medication of L-dopa also because of the relative short half-life of both drugs. A combination drug containing L-dopa, Carbidopa and Entacapone is available in the market with the trade-name of Stalevo. The advantage of such a combination is for better compliance of patients particularly in later stages of Parkinson disease, where they have to take several drugs per day. Even the combination of three drugs can cause severe side effects such as nausea and diarrhea. The dosage must be therefore titrated carefully beginning with smaller dosage. Some patients refuse to continue the drug because of the side
effects even under smaller dosage; if tolerated the drug can be helpful in patients without dyskinesia. The main advantages are the reduction of the daily number of tablets to be taken.

**The Question of Neurotoxicity with Levodopa**

Even though L-dopa is the basic drug for the treatment of idiopathic Parkinson disease, there are some problems in the long range treatment with this drug. Many clinical neurologists are of the opinion, that the beginning of L-dopa medication should be prolonged as late as possible particularly in patients who get the disease in an early age-group. This is because of the long-range side effects associated with the drug namely the possibility of earlier occurrence of dyskinesias under L-dopa medication. Moreover there is the risk of further long-range side effects such as severe mood-changes and even psychotic disturbances under the chronic medication of L-dopa, which factor however has not been properly established. It is clinically assumed that patients who have started with a medication of Dopamine-receptor-agonists have considerably delayed occurrence of dyskinesia during the course of disease even if they have to take a medication of L-dopa in the later years. Similar is the situation concerning drugs belonging to the group of NMDA-receptor-agonists or MAO-B-inhibitors. All these factors give us an idea that there may be some neurotoxic factors associated with the medication of L-dopa particularly during a prolonged clinical course of IPD. It has been considered that another neurotransmitter glutamate can have a toxic effect on the neurons if consumed for longer time as in the case of food served with the addition of glutamate. This matter has been under consideration by the Food and Drug administration.
of the United States of America also regarding the food generally served in the Chinese restaurants. In case of L-dopa, the substance given as drug is metabolized in the organism and deposited in the form of Dopamine in the region of basal ganglia particularly substantia nigra. These rather unphysiological process of high deposition of Dopamine converted from L-dopa may create an oxidative stress. Oxidative stress can again be one of the reasons for cellular loss in the region of substantia Nigra pars compacta and striatum.

It is a known phenomena that many drugs along with their therapeutic effect can have toxic side effects to the human organism in the shorter or longer intake of such drugs. Such toxicity may be also dosage-dependant as a higher dosage than the physiologically needed quantity, may be toxic in case of most of the drugs. Other than that there are known short-term acute toxic reactions even in the form of allergic reactions. The concept of neurotoxicity is however complicated and on the whole less defined. The possibility of neurotoxicity related to idiopathic Parkinson disease has been mentioned in the earlier chapters particularly regarding MPTP which leads to a selective dopaminergic neurodegeneration. When we refer to the neurotoxicity regarding the long-range side effect of L-dopa we have to consider the following factors:

- Late dyskinesia
- Cognitive changes
- Psychotic disturbances

These clinical neurotoxic side effects are associated probably with neuronal toxicity as a result of oxidative stress leading to further loss of neurons in the region of basal ganglia. The reason may be a nonphysiological overproduction of Dopamine through the intake of L-dopa
which on the one hand has a therapeutic effect but on the other a neurotoxic side effect. Similar could be the situation in several other substitutive therapies, where the advantages and disadvantages of the medication are closely interconnected. In case of IPD the appearance of late dyskinesias under the medication of Levodopa may be a possible explanation of neurotoxicity. However, dyskinesias may occur in a patient of IPD even without the long-term intake of Levodopa, which factor seems to be not sufficiently studied. For the increased dyskinesia under Levodopa is the possible explanation that with the reduction of L-dopa dosage the dyskinesias somewhat reduces during the clinical course of IPD. Similarly the occurrence of cognitive disturbances, increased mood-changes and psychosis during the long-term therapy of L-dopa has been considered to be of a pharmacotoxic nature. Several animal experimental studies speak also for such an assumption.
Chapter 9

Practical Aspects of Drug-therapy in IPD
There is no proper standardization in the treatment of idiopathic Parkinson disease. Even experienced clinical neurologists have different opinions regarding the beginning and the type of drug treatment. Generally after the beginning of symptoms, it takes some time, until a patient goes to the house physician and consequently to the neurologist. In case of mild symptoms, it can take some more time until the diagnosis of an IPD is made. Even after the diagnosis is more or less confirmed, it may need further time until the physician and the patient come to an agreement regarding the beginning of drug treatment. The necessity of starting a drug treatment may depend on several medical and social factors. If the patient is comparatively young and professionally active, one has to decide whether the symptoms are interfering with his or her profession such as in the case of mechanics, electricians or watchmakers who may need an intact finemotoric. A farmer or a physician who is not working with fine instruments may be less affected by the appearance of for example unilateral tremor. A surgeon may have problems with finemotoric for operations. In any case the patient must be taken into confidence before starting a drug therapy and the various aspects of advantages and disadvantages through the medication must be made clear to the patient as far as possible. The most disturbing feature for patients are their symptoms related to akinesia, which must be considered by the selection of a drug. Individual considerations about the type of Parkinson disease, age, dominant symptoms and the prognosis are necessary before selecting a proper drug.

In general it is now being agreed by neurologists everywhere that in patients who get the disease during younger years in the age-group of 50–60 years, it is proper
to start a treatment with Dopamine-receptor-agonists and not with L-dopa. However the dominant symptoms must be taken into consideration, whether the patient is tremor dominant or has a dominance of akinesia and rigidity. For patients with tremor dominance the Dopamine-agonists Pramipaxole and Ropinirole are drugs of choice for beginning the drug treatment. Even in such cases not only the therapeutic effect but the possible side effect during the titration must be taken into account. In the clinical practice it is seen that with careful titration both drugs namely Pramipaxole and Ropinirole are fairly well tolerated. Side effects of the drugs must be carefully monitored for better compliance of the patients. A Dopamine-agonist can be started in a patient who got the symptoms at the age of 50 or even at the age of 70 if the treatment is started fairly early after the diagnosis of IPD. In other cases also in this age group of patients who have a dominance of akinesia and rigidity, it may be useful to start with NMDA-antagonists or MAO-B-inhibitors. It is better to wait with the medication of Levodopa in most of the cases if the clinical condition permits such a waiting. The dosage of Pramipaxole can be started with 0.125 mg in the evenings and can be increased at intervals of 5 – 7 days with further tablets up to initially a total dosage of 1 mg three times daily. Several patients in the younger age group with tremor dominant IPD respond well to such a treatment, whereby not only their tremor improves but the other symptoms also. Generally after a period of 1–2 years the patients complain of the increase of akinesia and sometimes rigidity. These are then critical situations and may need the addition of L-dopa. However, if the clinical condition permits, the dosage of Pramipaxole may be increased up to a maximum of 5 – 6 mg per day in divided
dosages. If there is no improvement of the symptoms related to akinesia and rigidity or if there are side effects then it is time to add L-dopa to the medication, at the same time slowly reducing the dosage of Pramipaxole again to the level of around 3 mg per day in divided doses. The addition of Levodopa should be maintained at a lower dosage preferably between 200 and 300 mg per day also in divided dosages of 3–4 times per day.

If Ropinirole is preferred as a Dopamine-receptor-antagonist in patients also of the tremor dominant type, the dosage must be similarly carefully titrated beginning with 0.25 mg Ropinirole in the evenings and increasing the dosage in intervals of 5 – 7 days up to daily dosage of 3 – 4 mg per day also in divided doses. If there is a good response depending on the situation the dosage of Ropinirole can be increased up to 4 – 6 mg per day and monitored for the therapeutic effects and side effects. Wherever necessary the Ropinirole can be given also in the retard form of 2 mg or 4 mg tablets however for the phase of titration the smaller dosages are advantages. One can continue with the treatment of Ropinirole only as long as possible depending on the clinical condition. If symptoms of akinesia and rigidity increase, then the drug may be intensified with the addition of NMDA-antagonists, MAO-B-inhibitors or L-dopa. The selection of additional drugs after the introduction of Dopamine-agonist must be considered according to the clinical symptoms and the personality structure of the patient. Combination of drugs namely Dopamine-agonists, NMDA-antagonists, MAO-B-inhibitors and L-dopa must be selected according to individual clinical requirements keeping also in view of the long-term prognosis and the professional and social situation of the patient. This requires a lot of careful planning and discussion with the patient.
In case of patients who are above the age of 70 while getting the first symptoms of IPD, the drug treatment can be commenced directly with Levodopa however in a smaller dosage. Also in such cases the dominance of symptoms must be taken into account. If the patient begins with tremor dominance even if he is above 70 years it would be useful to start with a Dopamine-agonist. On the other hand if the patient has akinesia and rigidity as major symptoms one could start with small dosage of L-dopa and titrate it to a daily dosage to begin with around 300–450 mg L-dopa monotherapy. The second drug if needed must be then selected also carefully. It could be a NMDA-antagonist, MAO-B-inhibitor, a COMT-inhibitor or a Dopamine-agonist. When the second drug is selected, consideration should be made about the longterm side effects. The disturbing feature for patients above the age of 70 years are akinesia and rigidity. Tremor even though socially disturbing is less problematic in the day-to-day management. The generally accepted highest dosage of L-dopa per day is around 1000 mg in divided dosages which however must be avoided to the extent of possible for the risk of earlier occurrence of dyskinesia. On the other hand practically all patients need L-dopa sometime or the other during the course of their illness probably during the major period of their lifetime after beginning of the symptoms associated with IPD. It is necessary therefore to make clear to the patients that they need Levodopa but the dosage must be kept under control.

Case History of Patients

Case History 1
Woman, 63 years, mother of the patient had in old age a Parkinson syndrome probably of the type of idiopathic
Parkinson disease and she died at the age of 83 years. Father had a cerebral insult and died at the age of 85 years on a cardiac infarct. The patient was healthy and had no problems until the age of 50 years. At this age she began to feel a kind of nervousness and problems with management of her stress in daily life which she had otherwise managed well. Because of this she began to experience mild to moderate mood changes with which she however coped up without any medical help. At the age of 51 years she began to feel a tremor of the right hand and the right arm particularly the lower arm. On getting up in the mornings she felt a kind of tremor in all her extremities however more in the right side than in the left. After a few months she started getting a feeling of stiffness of her muscles. Recollecting her earlier mild symptoms she later thought that she got the motoric symptoms also around the age of 50 years. Even though she was an active person, in this phase of life she began to feel that her gait was no longer as dynamic as it was the case earlier. On the advice of her house physician the patient went for a consultation in the neurological hospital. In the outpatient department of the neurological hospital she was examined several times. During the clinical examination the neurologists observed a mild hypomimic expression of the face, slight olfactory disturbances and a mild dysarthria. There was a tremor of the right hand and also of the right leg. The muscle tone on the right arm and leg was slightly raised. There was a mild postural instability. Because of the history and the clinical findings the neurological hospital diagnosed a Parkinson syndrome most probably an idiopathic Parkinson disease. The patient received a medication with a Dopamine-agonist Pergolide which was in 1997 a comparatively new drug for IPD. She received this medication along with Domperidon during the titration.
Over the weeks the dosage of Pergolide was slowly increased up to 1 mg per day. The symptoms of the patient particularly the tremor reduced and there was some improvement also in akinesia. Under this drug treatment the performance of the patient in Webster scale was better. After one year there was again some increase of symptoms in the form of gait disturbances and tremor. Consequently during further treatment in the outpatient department in the neurological hospital the drug was slowly changed to Levodopa with an addition of COMT-inhibitor. She received a daily dosage of Levodopa with Bensarizide of around 200 mg per day as well as Tolcapone 300 mg per day in three divided doses. During this combination of Levodopa and Tolcapone the patient reacted with repeated diarrhea so that the drug had to be changed again in the dosage and later with a replacement of Ropinirole in place of Tolcapone. Under a combination of Levodopa around 300 mg per day and Ropinirole 3 mg per day the patient managed her day-to-day life fairly well. However, there was a slow progression of her clinical symptoms.

The patient came in my neurological consultation with the above mentioned combination of drugs around two years after the beginning of her Parkinson disease. She was then 53 years of age and showed clear symptoms of an idiopathic Parkinson syndrome with somewhat tremor dominant symptomatic. The patient came for consultations in intervals of 2–3 months. In the drug treatment not much was changed in the beginning other than slight changes in the dosage of Levodopa and Ropinirole. The akinesia improved somewhat during the treatment but the tremor of the right hand was disturbing for the patient in her daily activities. The Dopamine-receptor-agonist Ropinirole was slowly changed over to Pramipaxole and the dosage was increased up to 2.5 mg per day keeping the dosage of
Levodopa around 300 mg per day. Under this drug combination the patient managed fairly well in her household and part time job. After about two years of treatment I did not see the patient anymore.

Almost nine years later the patient was again referred to me by her house physician for the further treatment of Parkinson disease. There was a remarkable degenerative change in the clinical condition of the patient particularly in view of severe dyskinesia. During these nine years the patient had several treatments sometimes also with hospitalization. The combination drugs particularly Levodopa, Carbidopa and COMT-inhibitor was not tolerated by her because of severe gastrointestinal problems particularly with diarrhea. On referral the patient had the following medication:

- Levodopa plus Bensarizide combination 1000 mg per day in six divided doses
- Pramipaxole 3 mg per day also in divided doses

On clinical examination the patient showed very exaggerated dyskinesias involving head, neck and all extremities. She could not sit even for a moment without the hyperkinetic movements of her limbs. Her speech was only partly understandable. The movements of the arms showed the nature of chorea-athetosis pattern. She complained of such uncontrollable continuous hyperkinetic movements throughout the day and partly also in sleep whenever she woke up. Under an intensive schedule of treatment her drugs were slowly changed as follows: The dosage of Levodopa plus Bensarizide was reduced at 62.5 mg in intervals of one week. At the same time she received also in these intervals an addition of Amantadine sulphate 100 mg. After a month of therapeutic regime she received a daily dosage of Levodopa/Bensarizide 600 mg, Ropinirole 2 mg and Amantadine 200 mg.
Her symptoms of dyskinesia reduced to a good extent so that the patient found improvement in the quality of her life. During further consultations attempts were made to reduce the dosage of Levodopa further with increase of Amantadine dosage. Under a medication of Levodopa 400 mg per day, Pramipaxole 2 mg per day and Amantadine 300 mg per day around two months after beginning of the treatment the dyskinesia was reduced by over 50%, but the patient developed strong symptoms of akinesia and rigidity so that she was moving like a “wooden statue”. This clinical condition was much more disturbing for the patient because of, as she said “paralyzing” of her entire muscles. In the next attempt the dosage of Levodopa/Bensarizide was slightly increased up to 450 mg per day with unchanged dosage of Pramipaxole and Amantadine. Under this combination the dyskinesias are mostly under control and the akinesia and rigidity have considerably reduced, the tremor is practically insignificant. The clinical condition of the patient under this combination of Levodopa/Bensarizide 450 mg, Pramipaxole 2 mg, Amantadine 300 mg all in divided dosages of 4 – 5 times per day, has remained fairly stable and acceptable for the patient.

Case History 2

Man, 76 years, was professionally active in the field of medicine, has a family with wife and children. No case of Parkinson disease is known in the family. His father died at the age of 73 on cerebral insult and the mother died at the age of 80 without medical problems. Around the age of 63-64 during the active professional life the patient felt slight tremor of the left hand and later also of left leg. These symptoms made him sensitive but he did not go for a medical consultation for another two years. At the age of 66
he went to a neurologist when an idiopathic Parkinson disease was diagnosed. The patient was placed on Amantadine, which it appears did not help him. Later the drug was changed to Levodopa and Comtan. In spite of the medication his symptoms increased in the form of tremor and akinesia. In addition to the above mentioned drugs the patient started trying different kinds of alternative or complimentary methods of treatment with herbal preparations, spiritual healing, acupuncture, all of which did not help him. There was progression in the symptoms particularly with reduced movements, due to akinesia and rigidity.

He came in my consultation in 1999 with following drugs: Levodopa/Benserazide retard form with a daily dosage of 375 mg, Pergolide 2 mg per day and Entacapone 400 mg per day, all in divided dosage. On the first examination the patient had definite symptoms of idiopathic Parkinson disease. He had postural instability and gait disturbances, mild tremor of the left hand and arm as well as tremor of the left leg, muscle tone of the left arm and leg was increased. There was clasp-knife phenomena of the left arm and hand. On the whole the clinical condition was dominated by akinesia and rigidity and less by tremor. The cranio-cerebral MRI showed mild changes of cortical atrophy, without further findings.

The drug treatment was somewhat difficult because of the tendency of the patient to change the medication depending upon his own judgement. He also changed his neurologist from time to time but came again in my consultation. In the beginning the patient had certainly difficulty to accept the diagnosis of IPD but over the years he seems to have made a compromise with himself accepting the disease condition. Drugs were sometimes changed not necessarily because of the increase of
symptoms or the progression of the disease but because the patient was not satisfied with the results of the drug treatment. Practically most of the available anti-Parkinson drugs belonging to different groups were tried keeping Levodopa / Bensarizide combination as the basis however in a smaller dosage. He had over the years such drugs as Cabergoline, Bromocriptine, Entacapone, Pergolide, Ropinirole and Pramipaxole in different dosages. In addition he underwent an expensive treatment with some unconventional acupuncture implantation of the earlobes, also without results. During the almost 10 years of treatment, sometimes I did not see the patient for one year. About seven years after the diagnosis of IPD and commencement of drug treatment the patient came to me after an interval of almost one year with pronounced symptoms of dyskinesia. Even though, he was otherwise an active patient, taking care of regular walking and other healthy methods, he and his family found the dyskinesia most disabling. On this consultation the patient had a combination of Levodopa / Bensarizide 600 mg per day and Pramipaxole 4 mg per day. The medication was slowly changed with reduction of Levodopa and Pramipaxole doses and the addition of Amantadine. Under a changed medication of Levodopa 375 – 450 mg per day, Pramipaxole 2.5 mg per day and Amantadine 200 mg per day, the dyskinesia reduced to about 50%, with the addition of further 100 mg of Amantadine there was further reduction of dyskinesia; however the patient was not completely free of the hyperkinetic disturbances. There is however a considerable improvement in the quality of life, the patient and the family seems to be satisfied with this condition.

Summarizing, one can see that both the patients had complication of dyskinesias. Both patients had a history
of clinical idiopathic Parkinson disease for a period of over 10 years. In case of the first woman patient the condition was most probably provoked by the higher dosages of Levodopa and the duration of the disease, whereas in case of the second patient the actual factors which lead to the occurrence of dyskinesia cannot be properly established. In case of the first patient the early onset of the disease, the duration of the disease and the dosage of Levodopa seem to be significant factors. In case of the second patient duration of the disease and rather inconsequent drug treatment may be responsible for dyskinesia. In both cases Amantadine was a help to reduce these severe hyperkinetic symptoms. In the first case however the basic dosage of Levodopa could be reduced only to a certain extent and not further because of the increase of akinesia and rigidity. This makes us again clear that L-dopa is the most effective drug for IPD until today but it is also probably a neurotoxic substance, and should be carefully monitored regarding the dosage.

Strategy of Drug-treatment

In the strategy of drug-treatment of idiopathic Parkinson disease, the following factors have to be considered:
- Age at the onset of the disease
- Dominance of cardinal symptoms
- Psychosocial aspects of the patient
- Actual professional situation of the patient
- Long-term drug strategy

Several authors consider the age of onset only under two subdivisions namely below the age of 70 years and above the age of 70 years. The age of 70 years for the onset of IPD can however be considered as rather late onset of the disease. It would be useful in the clinical neurological
practice to reassess the patients below the age of 60 years as early onset and the patients around the age of 70 years as late onset of IPD. Accordingly some practical hints are given here for the selection of drugs in these two age-groups.

**Onset around the Age of 60 Years or Below**

**With tremor dominant symptoms**

*Drugs of first choice*
- Dopamine-receptor-agonists of the non-ergolin group
  Pramipaxole or Ropinirole as monotherapy

*Drugs of second choice*
- Dopamine-receptor-agonists with addition of Selegiline or Rasagiline in combination or as monotherapy

*Drugs of third choice*
- Addition of Biperiden or Beta-blocker

**Akinesia and rigidity dominant type**

*Drugs of first choice*
- Dopamine-receptor-agonists in monotherapy, preferably non-ergolin
- Amantadine in monotherapy
- Rasagiline or Selegiline in monotherapy

*Drugs of second choice*
- L-dopa in monotherapy
- L-dopa in combination with Dopamine-receptor-agonists
- L-dopa in combination with Amantadine
- L-dopa in combination with Rasagiline or Selegiline
Onset of IPD around 70 Years or Later

Tremor-dominant type

**Drugs of first choice**
- L-dopa in monotherapy
- L-dopa with Dopamine-receptor-agonists or Rasagiline or Selegiline in combination

**Akinesia-, Rigidity-dominant type:**

**Drugs of first choice**
- L-dopa in monotherapy

**Drugs of second choice**
- L-dopa in combination with Dopamine-receptor-agonists or with further combination of Amantadine and/or Rasagiline or Selegiline

In both groups of patients who begin with the onset of IPD below the age-group of 70 or above this age, the use of ergolin agonists has to be rather preserved for later treatment during the clinical complications because of the side effects of cardiac valvular disease associated with ergolin Dopamine-receptor-agonists. Similar is the case also involving other antiparkinson drugs such as COMT-inhibitors, Rotigotin and other drugs available in the market. The indication for surgical treatment of IPD will be referred in the next chapter.

**Drug-treatment of the Late Clinical Phase of IPD**

The late clinical phase of IPD is characterized by the appearance of different complications involving mostly the motoric system but also other non-motoric disturbances such as mood-changes, cognitive disturbances, depression
and dementia. The drug-treatment in the later phases of IPD must be even more individually structured depending upon the symptoms. In the presence of late dyskinesias which is generally a very disturbing phenomena, the drug of choice remains Amantadine whereby the dosage of L-dopa has to be slowly reduced taking into consideration the changing clinical picture of the patient. The other drugs which are useful in this phase are COMT-inhibitors in addition to L-dopa, Pergolide in combination with L-dopa, Rotigotin also in combination with L-dopa and Apomorphine as subcutaneous or pump or Duodopa-Pump. Depending on further complications and necessity the patients may be referred to deep-brain-stimulation.

Some of the late complications associated with IPD are as follows:

**Motoric disturbances**
- Fluctuations of symptoms
- Dyskinesias and dystonia
- Orthostatic hypotonia
- Postural instability with drops
- The phenomena of freezing
- Muscular pains

**Neurovegetative disturbances**
- Cardiovascular problems
- Gastrointestinal problems
- Urological and sexual disturbances
- Sudden daytime sleep attacks

**Psychiatric disturbances**
- Depression
- Anxiety
- Cognitive disturbances
- Hallucinations
- Dementia

Sleep disorders
- REM sleep disorders
- RLS-syndrome
- Horror-dreams
- Nocturnal hallucinations

The clinical course of various complications and the reasons for these during the late phase of IPD is not properly understood. It may be due to the disease specific etiology as IPD is a progressive disease not only of the motoric system but also associated with other non-motoric symptoms. However, the long-range medication particularly with L-dopa may play a certain role particularly in some specific complications such as the clinical fluctuations and dyskinesias. Under the fluctuation one has to consider the end of akinesia as a kind of wearing-off phenomena. This may be characterized by nocturnal akinesia and early morning akinesia which may be due to the fall of serum-level of the drugs. On the other hand there may be paroxysmal on-off phenomena which may be also due to the delayed on-phenomena during the drug intake. The dyskinesias may be partly associated with peak-dose-dyskinesia or on-dose-dystonia / -dyskinesia. In addition to these phenomena there may be akinetic crisis associated with the late course of IPD.

The fluctuations seen in the later phases may be explained partly through the following hypothesis. During the early phase of IPD the depletion of Dopamine is relative so that a certain amount of Dopamine production is available in the human organism. Moreover the nigral presynapsis show a certain capacity of storing the
Dopamine. Probably because of this reason the L-dopa administered even in smaller doses around three times per day are sufficient to restore the stability in the nigrostriatal neurons. During the course of treatment however the production of Dopamine is continuously reduced so that the storage possibility in the presynaptic nigral neurons is correspondingly reduced. Accordingly the substitution of Dopamine through L-dopa in smaller dosage and in longer intervals is not sufficient to maintain the neuronal stability. The clinical condition is then characterized by the appearance of nocturnal and early morning akinesia. During the further course the akinesia may occur also during the day even during the regular intake of medication in form of the end-of-dose akinesia. These motoric symptoms may also be accompanied by non-motoric symptoms during the end-of-dose akinesia with such phenomena as anxiety, sweating, tiredness and irritability sometimes also hallucinations. The strategy of treatment in such cases of end-of-dose akinesia is the distribution of L-dopa in smaller doses during shorter intervals of 4 – 6 times per day. However, the single doses given during such distribution should be effective enough to maintain the serum level so that the dosage must be minimal in the range of 50 – 100 mg L-dopa. It is almost necessary during this later phase of treatment that the patient receives a combination of medication consisting of L-dopa as basis drug combined with Dopamine-receptor-agonists or drugs belonging to the other group of Parkinson medication. The retard form of L-dopa is sometimes useful in the late phase of IPD but the dosage has to be properly estimated. It is however easier to give the non-retard forms of L-dopa divided into frequent dosages according to the clinical condition of the patient.
The on-off-phase during day

The situation regarding the occurrence of on-off-phase is even less understood. Probably the effect or the absorption of L-dopa is insufficient during such chronic symptoms but it may also be associated with the progressive neurodegeneration. Sometimes the addition of Domperidon along the medication of L-dopa is useful for better absorption of the drug but in other difficult cases the treatment has to be substituted through the application of Apomorphine sc injections or pump or the administration of L-dopa through a Duodopa-Pump. It is however necessary to consider in all cases of L-dopa medication that the drug is given either 30 minutes before a major meal or 90 minutes after the meal for better absorption.

The late complications associated with dyskinesia or dystonia are on the one hand due to the progressive neurodegeneration but on the other hand the long-range dosage of L-dopa medication probably because of a neurotoxic effect through this drug. Even though the appearance of dyskinesias and dystonias is not explained with complete clarity, these conditions seem to be associated with the early onset of IPD and the intake of L-dopa medication over a period of 10 – 15 years. The dyskinesias are subdivided into peak-dose dyskinesia, off-period dyskinesia and biphasic dyskinesia. The peak-dose dyskinesia appears after the intake of L-dopa medication as a result of increased plasma-concentration. On the other hand the patients complain also of off-dose dyskinesia by reduced serum level of L-dopa. During the on-dose dyskinesia the patient shows movement disorders similar to chorea-athetosis kind of movements. The movements are generally without increased pain but disabling for the patient and the dependents. The principle of treatment is
to reduce and correct the dosage of L-dopa and to substitute the medication in the first line with Amantadine and later depending upon necessity with other anti-Parkinson drugs, particularly COMT-inhibitors and Dopamine-receptor agonists. In addition in such cases a treatment with Clozapine is to be tried, which sometimes can show dramatic improvement. However, under the medication of Clozapine regular hematological controls are necessary. Somewhat easier for the addition is Quetiapine, which however may be somewhat less effective than Clozapine. In refractory cases a neurosurgical treatment with a deep-brain-stimulation can be recommended.

The Duodopa-pump is a rather complicated procedure which needs initially a hospitalization accompanied by a surgical procedure making a hole in the abdomen through which a stomach shunt is introduced. The drug consists of L-dopa and carbidopa in the form of a gel, the dosage must be individually estimated and the patient trained for proper application through the drug system made available. The treatment of late complications of IPD with such methods as Duodopa-Pump, Apomorphine SC injection and –pump as well as deep-brain-stimulation should be considered as the last source of treatment and as essential for the maintenance of quality of life.

The akinesia crisis is a dangerous and almost life threatening condition in the late course of IPD which generally results by partial or complete withdrawal of L-dopa. The beginning of such an akinesia crisis has been mentioned in the earlier pages during the first case history of a woman patient who developed these symptoms during the reduction of L-dopa. The patients develop an acute condition characterized by sudden occurrence of severe akinesia which may lead to partial and/or complete
loss of movements. The further complications may be
difficulty of swallowing and other systemic complications.
The treatment should be initiated under hospital conditions
with such methods as slow and continuous application of
L-dopa per Duodopa-pump or Apomorphine injections or
—pump so that the level of drugs is again available
continuously in the required dosage. The treatment should
be considered as a lifesaving procedure and carried out
under intensive hospital set-up.

The phenomena of freezing belongs also to the late
complications of idiopathic Parkinson disease which
however is not related to the symptom complex of
dyskinesia and dystonia. The freezing is characterized by
the difficulty to “start” so that the patient is somewhat
blocked in his or her movements. There is a denervation
of agonistic and antagonistic muscles so that the patient
remains blocked on his or her feet and is not able to move
further. This happens mostly in areas and situations which
are however somewhat restricted such as passing through
a door. During the course of milder symptoms the patients
find their own strategy to manage with their inactivity.
These symptoms in the late phase seem to be more
common with patents who are an akinetic-rigidity
dominant type and not with such ones with a tremor
dominant type. The phenomena is suspected to be based
on a noradrenergic problem. Even though a drug treatment
is less successful the use of thymoleptica for example
amitryptylin or venlafaxin can be tried. Patients who are
under the medication of Selegiline seem to show less
tendency to freezing phenomena which however needs
further studies.

The non-motoric complications associated with late
phase of IPD are treated with conservative medication as
in case of such symptoms associated with other diseases
also. For the treatment of depression both trycyclic antidepressents as well as the newline SSRI-antidepressents may be used whereby care should be taken not to use the MAO-inhibitors when the patients are taking antiParkinson drugs belonging to this group. Among the neuroleptics the two frequently used drugs are Clozapine (Leponex) and Quetiapine (Seroquel). These drugs can be used in the late phase of IPD both for the treatment of motoric as well as non-motoric symptoms particularly such one’s associated with hallucinations and dementia. For the treatment of dementia associated with IPD the drug recommended is Rivastigmine, which however must be considered depending on the nature of dementia and the severity associated with such condition. The psychiatric symptoms and dementia and their treatments will be discussed later in a following chapter.
Neurosurgery in IPD
Stereotactic neurosurgery is known in the treatment of Parkinson syndrome since 1950s, even before the invention of L-dopa. However, the treatment was directed mostly against tremor which showed modest improvements. The stereotactic operative methods were rather abandoned after the invention of drug treatment particularly L-dopa. Later lesion surgery was conducted in the regions of thalamus and globus pallidus internus in the form of thalamoctomy and pallidoctomy. These were partly helpful for the control of dyskinesias but somewhat also for the betterment of other symptoms such as tremor and akinesia. However, these surgical operations were an irreversible method and lead often to complications such as dysarthria, paresis and neuropsychological deficits. Because of these reasons the surgical operations were conducted mostly on the non-dominant hemisphere. Over the years however new methods have been found with less invasive techniques such as neurostimulation.

**Deep-brain-stimulation**

Deep-brain-stimulation is an advancement in the surgical treatment of IPD which is more effective and shows lesser complications particularly because of the less invasive surgery. However, even the method of deep-brain-stimulation is considered as a last resource in most of the patients who suffer from therapy refractory late phase complications of IPD. The method deals with the neurostimulation of the subthalamic nucleus, globus pallidus internus and nucleus ventralis intermedius. High frequency electrodes are inserted under observation through magneto resonance imaging and neuropsychological testing in the preferred region of brain
through which a high frequency impulse is sent in the range of 130–180 Hz. Through this procedure a non-destructive neurostimulation is achieved. This however is an expensive method because of the costs related to the implantation and the complicated operational technique.

Different neurosurgical centers which conduct the procedure report good results in patients of IPD, who are otherwise not treatable with conservative medication. By the neurostimulation of the thalamus region there is a betterment of rest and postural tremor whereas the stimulation of globus pallidus internus and nucleus ventralis intermedius the other cardinal symptoms are also considerably reduced. The dyskinesia caused through progressive IPD as well as L-dopa medication are influenced through the stimulation of globus pallidus internus. Because of the improved technique and less invasive operative methods the side effects are considered to be minimal. The lesions created by this deep implantation are rather minimal and if necessary the method is somewhat reversible. The criteria of patient selection has to be considered as follows:

- A high amplitude therapy refractory tremor which is disturbing in daily life
- Serious akinesia which results in the incapacity of patients to move around or to get up from bed
- Serious movement disorders leading to freezing accompanied by drops
- Late phase dyskinesia or dystonia which are disabling for the patient
- Inability to improve the above mentioned deficits through conservative drug therapy

As in case of all neurosurgical operations the procedure must be discussed in detail with the patient and the
concerned physicians. It is also necessary to consider the possible complications involving the motoric and non-motoric symptoms of the patient. The possible contraindications for surgical operations even with deep-brain-stimulation are as follows:
- The clear clinical presence of dementia
- Psychosis associated with hallucinations
- Brain atrophy particularly of an advanced type
- Long range anticoagulation
- Advanced age of the patient generally above 80 years

Even though there are some advantages in difficult cases of late phase of IPD through the deep-brain-stimulation, there are also some unfavorable findings in the postoperative course particularly in the form of neuropsychological deficits. The next case history is related to a patient who underwent deep-brain-stimulation(Figs 10.1 and 10.2).

Fig. 10.1: Graphic of deep-brain-stimulation
Case History

Woman, 71 years without a history of neurological diseases in the family. She was an active woman, working off and on depending upon her family situation. After the age of around 45 years and her divorce, she was working continuously. She did not have any serious health problems. Around the age of 56 years she began to feel a kind of weakness in the left arm followed by rest-tremor. Later she felt the tremor and weakness also in the left leg. In the beginning she ignored the symptoms but after sometime she started getting regular back pain particularly in the lumbal region. She went for a medical consultation and was referred to a neurological hospital where the diagnosis of idiopathic Parkinson disease was done. For the next two years she avoided taking drug treatment for IPD. Around the age of 58 years there was a progressive symptomatic of her left sided tremor and akinesia so that she was started with a treatment of Selegiline 10 mg per day in divided doses twice daily which she did not tolerate because of severe side reactions such as giddiness and gastrointestinal disturbances with diarrhea. She did not take any treatment for some more time but the symptoms
increased and she was started again on a smaller dosage of L-dopa and Bensarizide about 180-200 mg per day in three divided doses. Along with the motoric symptoms the patient felt right from the beginning mood changes with depression and general tiredness.

Around the age of 58 years, two years after the diagnosis of IPD, she came in my consultation from a long distance, which journey took her 5 hours by train (one way). On examination I found a clear case of IPD with all the cardinal symptoms such as hypomimia, left sided tremor and rigidity as well as akinesia with postural instability. The patient remained on the one hand in further treatment at a neurological hospital in the region of Geneva came to my consultations 3 – 4 times a year. The symptoms of IPD were progressive in spite of the drug treatment. Keeping the L-dopa medication under a dosage of 300 – 400 mg per day, the patient received such drugs as Pramipaxole and COMT-inhibitor in combination, which however did not help the patient much to reduce her symptoms. All along she received also an antidepressive medication for her depressive condition. In spite of the low dosage of L-dopa the patient developed dyskinesia about 6 – 7 years after the diagnosis of Parkinson disease. There was also an increase of akinesia but tremor was more or less under control. Because of the dyskinesias the drug regimen was changed to a combination of L-dopa, Bensarizide and Amantadine up to 300 mg per day. Under this combination the dyskinesia of the patient improved somewhat but she had increased akinesia which created her problems in her daily life. The patient had however a tendency to change her drugs according to her own judgement.

Around 10 years after the diagnosis of IPD and under a medication of L-dopa 450 – 500 mg per day as well as
Amantadine 300 mg per day the patient had still certain amount of dyskinesia, somewhat severe akinesia with postural instability. However, she was still in a condition to make the long train journey to my consultation in intervals of 3-4 months. In spite of her increasing symptoms she even made a group travel to India staying in Kerala for a period of two weeks. The neurological hospital decided however to treat the patient on neurosurgery because of her progressive symptomatic particularly akinesia and the tendency to dyskinesia. She was considered to be a suitable candidate because of her increasing symptoms but also on the basis of her intact cognitive functions, even though there were some cognitive disturbances associated with the depression. A bilateral deep-brain-stimulation was performed with the implantation of electrodes in nucleus subthalamicus. After the neurosurgery the patient seems to improve in her symptoms and the drug dosage was reduced. Three months after the neurosurgery there was reduction of symptoms associated with the akinesia and dyskinesia as well as tremor. After some time the patient heard from somebody about the so called “drug-holiday” and stopped all the medication for a period of nearly one month. She started developing again her earlier symptoms with increase of akinesia and tremor. On the initiation of drug treatment her motoric symptomatic improved again. However, around one year after the surgical treatment the patient developed increased cognitive disturbances with symptoms of dementia. She could not make the travels to me anymore independently and around 18 months after the operation the patient was found not capable of living in her own apartment and had to be shifted permanently to an institution with nursing and medical care. Even
though an increase of cognitive disturbances and dementia are known after deep-brain-stimulation the clinical development with the patient concerned was rather dramatic. It is difficult to decide whether her clinical course has lead to this condition or the deep-brain-stimulation has influenced her negatively in respect of dementia. Both factors seem to play a role however the provocative role of deep-brain-stimulation in this case can not be underestimated.
Chapter 11

Parkinson Syndrome and Dementia
180 **Step by Step Treatment of Parkinson Disease**

Among the non-motoric symptoms of IPD, depression is a common factor associated with the clinical condition. Depression may be present already in the preclinical phase of IPD and may continue throughout the clinical course of the disease. Idiopathic Parkinson disease and other Parkinson syndromes are all neurodegenerative disorders, which may end-up increasing cognitive disturbances and also with dementia. Some of the other Parkinson syndromes such as dementia with Lewy-bodies (DLB) show the development of dementia already in the early stages, in case of IPD the patients may be spared of this disabling condition for years. In some cases of IPD with mild or moderate clinical symptoms, dementia is not seen even after 10 - 15 years of clinical course. However, the longer the disease process of IPD, there may be more tendency for the occurrence of dementia at some stage or other. In other cases of Parkinson syndromes such as multi-system-atrophy the clinical course is different as the life expectancy of the patients is considerably reduced. Similar is the case also in DLB as well as in other kinds of major dementia such as associated with Alzheimer disease. In case of IPD the early occurrence of dementia is not seen. On the other hand many authors consider that dementia at a later phase of Parkinson disease is possible and does occur in milder or severe form. The late phase of IPD is generally associated with also progression of motoric symptoms and reduced effect of known antiParkinson drugs so that the condition of severe motoric disturbances as well as cognitive problems involving dementia may be interconnected. However, dementia associated with idiopathic Parkinson disease is not a frequent occurrence in the clinical practice of IPD. Some studies show that 0.5% of subjects over the age of 65 years have the risk of a
dementia associated with Parkinson disease which makes a total of 3.5% of all dementia cases. Roughly 25 – 30% of IPD patients suffer from dementia at the later phase of clinical course. However, these figures are from different epidemiological studies and cannot be considered as standard data of the worldwide distribution of cases. The risk factors associated with dementia are the longer duration of the disease, akinesia dominant type and psychosis. Late age of IPD as well as early presence of cognitive disturbances have also been considered as risk factors for the occurrence of dementia in IPD patients. These factors are meant for general orientation to the effect that dementia associated with IPD is not the frequent form of dementia and is a problem only in about 25% of the cases during the late phase of the disease.

The frequency of dementia among the general population is generally classified in the following order:
1. Dementia associated with Alzheimer disease
2. Dementia associated with cerebrovascular disease
3. Dementia of the type of Lewy-body dementia
4. Dementia as late phase of IPD

Even though dementia is a clinical condition, the differentiation of the different forms of dementia is available more from the autopsy-studies based on the neuropathological evaluation. Among the dementias associated with Parkinson syndrome, dementia with the Lewy-bodies (DLB) is much more common than dementia associated with IPD. Accordingly the early occurrence of severe cognitive disturbances leading to the development of a dementia must give us hints for the diagnosis of DLB rather than IPD. There is however a considerable overlap in the clinical condition as well as in the pathology involving DLB and dementia associated with Alzheimer disease (AD). At the same time because of the
extrapyramidal symptoms there is also an overlap of symptoms between the clinical picture of DLB as well as dementia of IPD. However, in case of DLB there is a direct connection to the severity of Lewy-body pathology and indirectly related to the severity of Alzheimer type pathology which however are the results of autopsy-studies. In a handbook on idiopathic Parkinson disease and Parkinson syndromes such as this one, we have to make a clear differentiation between the clinical picture and pathology associated with DLB and IPD dementia. Both these conditions are directly related to α-Synuclein (alpha-Synuclein) pathology where presynaptic α-Synuclein aggregates are found. The degeneration leading to dementia is possible only through the synucleinopathies which lead to the neuro-degeneration leading to dementia.

**Dementia with Lewy-bodies (DLB)**

Dementia with Lewy-bodies begins generally in the form of an idiopathic Parkinson disease with similar extrapyramidal symptoms. The difference is seen however in the early occurrence of cognitive disturbances and dementia. Even though clear statistics regarding the epidemiological situation concerning DLB are not available, it is considered to occur in around 1-5% of the people above the age of 80 years. There is a slight dominance of men in comparison to women. The symptoms begin with visual hallucinations and cognitive disturbances and show early a clinical picture of dementia similar to the one seen in Alzheimer type dementia. The difference in Lewy-body dementia is the presence of extrapyramidal symptoms whereas Alzheimer dementia is generally without such symptoms. The further course of progression seem to be faster in case of DLB than in
Alzheimer type. Life expectancy in DLB after the beginning of dementia is considered to be around 40 months. The disease is characterized by presynaptic \( \alpha \)-Synuclein aggregates which cause neuro-degeneration leading to the disorder. In all cases of dementia whether it is of the DLB-type, Alzheimer-type or late IPD-type, the accumulation of \( \alpha \)-Synuclein proteins as aggregates is necessary for neurodegeneration leading to dementia. The alterations in the balance between factors which cause aggregation and clearance as well as synthesis of \( \alpha \)-Synuclein may be centrally involved in the formation of oligomers in the pathology of neurodegeneration. The accumulation of such toxic oligomers occurs initially probably in the synapses, later spreading to axon and neuronal cell body. In addition to the \( \alpha \)-Synuclein aggregates the accumulation of Tau-proteins may play a role in the pathology of neurodegeneration leading to dementia. The altered occurrence of these phenomena in the pathology may be to begin with the aggregation of \( \alpha \)-Synuclein leading to synaptic damage consequently progressing to neurodegeneration and dementia. It has been agreed that a \( \alpha \)-Synuclein aggregation is necessary for neurons to degenerate leading to the development of dementia. Dementia with the Lewy-bodies (DLB) as well as dementia with IPD (PDD) even though different in the dominance of occurrence, once they are clinically full blown they show a similar picture of dementia associated with extrapyramidal symptoms. Both disorders are characterized by \( \alpha \)-Synuclein pathology in the brainstem, neocortex and limbic region and both these conditions may have a concomitant pathology to Alzheimer disease dementia. However, the cognitive deficits and the progression of dementia accompanying each condition is clinically different. DLB and PDD are associated with Parkinson syndrome whereas Alzheimer
disease has no such basis. The severity of visual hallucinations may be considerably pronounced in the case of DLB than in PDD or AD. This may also give us some hints regarding the rapid cognitive deterioration in case of DLB compared to PDD. In the clinical picture of IPD the occurrence of mild cognitive impairment already in the beginning of the diagnosis, may give us some hints regarding the possibility of dementia over the course of years.

Even though the above mentioned three kinds of dementia are clinically different in the severity and duration of illness, all the three forms may show in the postmortem findings the occurrence of Lewy-bodies as well as α-Synuclein pathology. In case of Alzheimer disease Amyloid plaques are seen already during life time through neuro radiological imaging. In the autopsy finding Amyloid plaques were seen also in patients who suffered from DLB and PDD. At the same time it is known through different autopsy studies that even normal individuals may have the presence of certain amount of Lewy-bodies, α-Synuclein aggregates as well as Amyloid plaques even though they never suffered from either dementia or extrapyramidal symptoms. Different basic researchers have put the question accordingly about the significance of such pathological findings related to neurotoxicity and neuro protection involving particularly α-Synuclein aggregates.

**Dementia with Parkinson Disease**

Dementia associated with Parkinson disease can not be considered always as an obligatory phenomena and if it does occur, it is generally seen after a clinical course of 10–15 years. Mild cognitive impairment is on the other
hand a generally accompanying phenomena in IPD which may remain with certain amount of variation over the clinical course of several years. Whereas in case of dementia with the Lewy-bodies the clinical picture is characterized within a period of months to years through the occurrence of dementia, IPD on the other hand is predominantly a motoric disorder of the extrapyramidal system which however is secondarily accompanied by non-motoric symptoms. The risk factors involving a later dementia in IPD are considered to be the following:

- Older age
- Duration of Parkinson disease
- Akinesia, rigidity-type
- Hallucinations and delusions
- Severe mood changes and depression

The occurrence of cognitive impairment early during the course of IPD is considered to be a further risk factor for later development of dementia. The different studies show that there is a possibility of around 25 - 45% people with Parkinson disease developing dementia during the late phase of IPD. Even in this kind of dementia a pathology of the α-Synuclein and Tau-proteins is known. For the prognosis of a later dementia the suggestive factors are the presence of nearly 20% mild cognitive impairment during the early stages of IPD and may be many other unknown factors. α-Synuclein is an abundantly found protein genetically linked to Parkinson disease. Aggregation of α-Synuclein protein is an important factor in the familial and sporadic occurrence of IPD and several other neurodegenerative disorders which are considered to lead to dementia. Other degenerative disorders such as multiple system atrophy and a certain Lewy-body variant of Alzheimer disease are also pathologically linked to the aggregation of α-Synuclein protein. Some studies with
genetic analysis of familial dominance of IPD have identified dominant mutations in α-Synuclein and recessive mutations in parkin gene. In spite of this similarity in the pathological aspect, the clinical picture associated with dementia of IPD and DLB seems to show clear differences involving the cognitive deficits. The entire course of clinical development is different in conditions of IPD and DLB. IPD as has been mentioned earlier is characterized by predominantly motoric symptoms however also with associated non motoric symptoms which can not be underestimated. Lewy-body dementia on the other hand does show extrapyramidal symptoms such as the one's found in IPD but the predominant clinical picture is characterized by the early occurrence of dementia. Neuropsychologists have identified visual dysfunction as an early quantifiable marker of DLB which may be associated with the severity of α-Synuclein pathology. These visuospatial disturbances lead to a fast global cognitive deficit in patients with DLB, which is not the case in dementia associated with IPD.

Episodic visual hallucinations and further cognitive impairments are generally diagnostic features of dementia both in the case of DLB as well as IPD. In case of IPD these hallucinations are seen during the later stages of the disease whereas in DLB they are early occurrences. It is therefore useful in the clinical practice to explore the patients belonging to both groups about the possibility of visual hallucinations which the patients generally do not mention out of their own initiative. The occurrence of visual hallucinations may be indicative of an ongoing pathological process leading to the development of dementia in both IPD and DLB. Patients with Alzheimer type of dementia generally do not have such visual hallucinations; or in a considerably lesser measure than
patients with Parkinson disease. These hallucinations are connected with the possibility of the impaired dopaminergic activity in the retina and the basal ganglia. During autopsy studies of such patients an abnormal accumulation of Lewy-bodies in the anterior and inferior temporal lobe and the amygdala have been noticed.

The assessment of cognitive profile in patients with IPD plays a lesser role during the clinical management because of the predominantly motoric symptoms. However a majority of patients with IPD may have even during the early years of the disease cognitive problems connected with executive impairment which include working memory and attention shift as well as visual partial dysfunctions. Evaluations of cognitive disturbances during the clinical management of IPD are a good marker for the possible late development of dementia. The practical aspect of such a management is the selection of proper drugs to prevent the early occurrence of further developments leading to dementia. However, this is a difficult procedure because the attention has to be given primarily for the improvement of the motoric symptoms with basic drugs such as Levodopa combined with other anti Parkinson drugs. In the selection of the second group of drugs it is possible to select such drug as Rasagiline or Amantadine in view of possible prevention of dementia.

**Drug Treatment for Cognitive Symptoms and Dementia**

The availability of the drugs for the treatment of dementia related to DLB and IPD is rather limited. In both kinds of dementia the main symptoms are disturbances related to visual partial and cognitive executive functions leading to impairment of memory, concentration and occurrence of
visual hallucinations. Further there may be the episodic occurrence of psychosis, REM sleep disorders and the further range of autonomic functional disturbances. Depression and mood-changes including neurovegetative disturbances may be preceding phenomena which can be managed to a fairly good extent with conservative drugs. Even the early occurrence of visual hallucinations can be managed fairly well with such drugs as Clozapine and Quetiapine. The drug licenced in several countries for the treatment of dementia associated with IPD and DLB is the only cholinesterase inhibitor rivastigmine. This drug is now available both for oral intake as well as for subdermal application through Plaster. The other antidementive compounds licenced for the treatment of dementia of the Alzheimer type seem to be not very useful for the treatment of dementia associated with IPD and DLB, may however be tried in complicated cases. These drugs include donepezil, gallantamine and memantine. Large scale-studies with these drugs for the treatment of dementia related to DLB and IPD are not available. The two neuroleptics already mentioned namely Clozapine and Quetiapine can be tried in combination with rivastigmine in case of dementia of IPD and DLB type. During the treatment of DLB or IPD dementia it is necessary to withdraw Dopamine-agonists from the long range treatment as these drugs seem to enhance the psychotic symptoms. Problematic REM-sleep disorders occurring during the phases of dementia may be treated with Clonazepam or melatonin however as an additional drug.

Disturbances of Autonomic System in IPD

In addition to the motoric disturbances related to the extrapyramidal system which come under the cardinal
symptoms of idiopathic Parkinson disease, there are disturbances of autonomic nervous system which run parallel to the motoric symptoms. The disturbances related to autonomic dysregulation may be present already during the preclinical phase which accompanies the clinical motoric symptoms throughout the disease and then may increase during the chronic phase of IPD. This makes IPD not only a motoric disease restricted to the degeneration in substantia Nigra and striatum but more of a multi system degeneration covering the central and peripheral nervous systems. Braak and co-workers postulated the theory that the disease may begin through an unknown pathogenic influence in the enteric nervous system and proceed through a retrograde axonal transportation through the peripheral nervous system and lead to the basal ganglia which then result in the neuronal degeneration. The same authors have mentioned the occurrence of Lewy-bodies and α-Synuclein aggregates in the cerebral, spinal as well as in intestinal plexus. Even though certain aspects of the basic etiological mechanisms are not properly known one can infer from the clinical symptoms that IPD is a disease more than the generally accepted concept of cardinal symptoms related to the motoric system only. It is therefore of much clinical importance to explore the possibility of autonomic system disturbances as well as other mood related factors in addition to the motoric symptoms during the early diagnosis of IPD. Different studies show that the subjective functional autonomic disturbances may be present in all cases of IPD, however in a variable percentage. The common disturbances are the following:
- Olfactory dysfunction
- Optic disturbances
- Giddiness and syncope
- Cardiovascular dysfunction
- Sleep disturbances
- Orthostatic dysregulation
- Urge incontinence
- Increased perspiration

Practically every unit of the autonomic nervous system is involved in the process of dysfunction in lesser or higher degree in all patients with IPD. The dysfunction related to autonomic nervous system is not directly related to the intensity of motoric symptoms but may be independent of them. Different authors mention the occurrence of autonomic disturbances between 15 and 80%, in general about 50% of patients with IPD complain of disturbances of the autonomic nervous system which may be present in all stages of the disease. Around 50% of the patients, if properly explored mention the presence of symptoms of dullness, visual disturbances, nausea and giddiness. Disturbances of consciousness are rather seldom but may occur during the course of the disease. The most common disturbances associated with the clinical symptoms are orthostatic hypotonia which may lead to cardiovascular dysfunction. The patients with IPD show in the clinical practice generally reduced blood pressure which may be associated with the orthostatic dysregulation. Even though such findings are mentioned often in the literature, the real cause for such orthostatic dysregulations is not known. Along with the general condition of the patient with tendency to autonomic dysfunction, the long-range medication may play a role in the occurrence of cardiovascular functional disturbances. Along with the degeneration of neurons in the region of substantia Nigra and striatum there may be further degeneration of neurons involving hypothalamus, pituitary and sympathetic ganglia. These disturbances may play a role on the
mechanism of hormonal regulation which may be an additional factor. It is therefore useful to advise the patients with cardiovascular and orthostatic dysregulation for the prevention, such simple methods as raising the level of head while sleeping and liberal intake of fluids and if possible a diet rich in natrium. Depending on the clinical course changes in the antiparkinson medication and the addition of Domperidon may be necessary.

The increased sweating may be disturbing for many patients particularly at night. In such cases a treatment with anticholinergic drugs or beta-receptor blockers such as Propranolol may be useful. Gastrointestinal disturbances are common in patients of IPD particularly in the form of constipation. This factor has been recognized even by James Parkinson in some of his patients. The reasons for constipation have been considered to be due to the possibility of degenerative changes in the plexus in the regions of esophagus, intestine and colon by the appearance of Lewy-bodies. During the course of illness several patients develop also swallowing difficulties and hypersalivation. The difficulty of swallowing may result from the akinesia associated with the muscles of chewing. A reduced peristaltic has also been suspected. The patients have an increased tendency to chronic laryngitis, acute and chronic bronchitis as well as for aspiration pneumonia, even though the patients who get such a pneumonia are relatively a small number and not significantly higher than the general population. There are no proper drugs to improve the situation, the patients may be trained however to follow a different discipline in the way of chewing and swallowing. Several patients with IPD complain of gastric disturbances which may be associated with reflux esophagitis. However, the most common symptoms related to gastrointestinal system seem to be the
constipation which may be present already during the preclinical stages and may continue throughout the clinical course. Constipation may be a symptom which occurs independent of the medication, the other gastrointestinal complaints may be at least partly the result of antiparkinson medication. The treatment of most of these complaints is of symptomatic and conservative nature.

The constipation can be a very disturbing feature in patients of idiopathic Parkinson disease. Several reasons for the presence of constipation have been discussed which are disturbed contraction of the voluntary muscles in the region of rectum and anus, local dystonia and reduced defecation reflex. Some authors discuss the possible influence of on-off-phases independent of the anorectal influences. Because of the akinesia the patients slowly lose the power to press during the defecation which is particularly disturbing because many patients with IPD have a tendency to slower transit of feces in the entire colon. It may be sometimes necessary to make further investigations through radiological methods in the event of disturbing chronic constipation. The treatment of such problems is generally through dietetic and conservative methods such as the increase of ballast substances, intake of sufficient fluids and regular movements assisted by physiotherapy. In certain cases drug treatment is necessary which must be decided according to the individual requirements. Useful may be the change of schedule in the antiparkinson drugs particularly with the reduction of anticolinergic or other drugs which the patients found as clearly leading to the increase of constipation. In severe cases a treatment with Botulin toxin as well as operative measures have been recommended.

Both urge incontinence and even spontaneous urine incontinence may be present in some cases of IPD.
particularly in advanced stages. The reasons for such disturbances have also not been clearly understood. A possible cause may be the progressive degeneration in the region of basal ganglia which then has a negative influence on the bladder and urethra. Peripheral neurogenic disturbances have also been suspected as the cause of urine incontinence. Many patients during the course of disease complain of urge incontinence which may partly be the result of the basic illness but also may be caused through antiparkinson drugs. On the other hand a betterment of the bladder function is sometimes found with the medication of Levodopa. The influence of anticholinergic drugs can be both positive as well as negative depending upon the individual condition of patients. In case of male patients one must consider the possibility of disturbances related to prostrate and gynecological examination must be done in case of female patients to explore the possibility of urine incontinence which may be independent of the Parkinson disease. The treatment should be based on the possible exploration of the cause of urine incontinence to the extent possible. Along with physical training, behavioral therapy and suitable drugs may be tried.

**Sexual disturbances** are possible in many cases of IPD. This involves both reduced libido as well as erectile dysfunction. Disturbed libido has been known in many patients of both sexes. In some cases of IPD sexual disturbances involving reduced libido may be a first symptom even during the preclinical phase of IPD both in men and women. The symptoms then resemble as in cases of depression as many patients also have a tendency to depression already during the preclinical phase. Disturbed sexual functions seem to have some connection with the dysregulation of Dopamine which precedes the disease sometimes for years. During the course of illness however
the patients may react with hypersexuality particularly under the medication of Dopamine-receptor agonists such as Pramipexole or Ropinirole but also under a medication of Levodopa. The therapy aspect of sexual disturbance must be considered individually with proper methods of psychotherapy or drug adjustment.

Sleep disturbances are common phenomena associated with the non-motoric symptoms of IPD. There may be generally disturbed sleep or may be severe sleep disturbances during the REM-phases where the patients become hyperactive and react with symptoms similar as in case of frontal lobe epileptic seizures. Further there may be sleep apnea which is a disturbing feature. The exploration of severe sleep disturbances may be necessary in a sleep laboratory for proper treatment. The general sleep disturbances may be treated with antidepressive or similar drugs. The influence of antiparkinson medication and the occurrence of sleep disorders as a response to any single medication must always be considered. The other neuro-vegetative disturbances are night sweating, blood pressure changes, cold extremities, giddiness and such other complaints which must be managed accordingly.

Drug-related Complications

Idiopathic Parkinson disease being a chronic neurological degenerative disorder requires intensive drug therapy, which during the course of the disease may create several problems. The usual practice is to start the drug treatment with a single drug which can be a Dopamine-receptor agonist if the onset of illness is below the age of 70 years and Levodopa if the onset of disease is after 70 years. However, there is no hard and fast rule in commencing the treatment based only on the age. There should be other
considerations as well, such as the general condition of the patient, the type of IPD whether it is a tremor dominant or whether it is akinesia-rigidity type and further considerations regarding the familial, professional and other psychosocial aspects of the patient. If the treatment is started with a Dopamine agonist in patients with earlier onset, it is generally known from the clinical practice that these patients after a period of 2 to 3 years need an addition of Levodopa or another antiparkinson drug. But during the course of illness generally within 5 years after onset of IPD, patients need, the until now known basic drug Levodopa in combination with Benserazide or Carbidopa. Later they may require other drugs of the other groups so that after a clinical course of 5 to 10 years most of the patients are placed on a polytherapy with a combination of two to three drugs for Parkinson disease and may be other drugs because of other problems. Not only the combination of drugs can create interactions but the necessity of drug intake of 4 to 5 times a day makes the patients problems in daily life. Some drugs meant for other conditions are not generally suitable for Parkinson disease patients such as some analgesics or antihypertension drugs as well as drugs belonging to the group of different neuroleptics (other than Clozapin and Quetiapin), as also Dopamine-antagonists other than Domperidon. It is necessary to individually evaluate the use of further drugs depending on the clinical course. Drugs against hypertension may dangerously reduce the blood pressure in patients with IPD who generally have a tendency to lower blood pressure. Similarly the use of different neuroleptics may aggravate extrapyramidal symptoms which would then result in a complicated clinical course. Medication against sleep disorders may reduce the further vigilance of patients who sometimes have a tendency to
day-sleep as well as to sudden sleep attacks similar to narcolepsy. At the same time several drugs may complicate the clinical symptoms with increase of hyperkinesias and dyskinesia or tremor if given for longer periods. Some of the major drugs which may trigger the occurrence of dyskinesias are as follows:

**AntiParkinson drugs**
- L-Dopa
- Dopamine-receptor agonists
- Anticholinergic drugs

**Dopamine-receptor antagonists**
- Butyrophenone
- Phenothiacine
- Tetrabencine

**Antiepileptica**
- Carbamazepine
- Phenytoin

**Other drugs**
- Flunaricine
- Cimetidine
- Tricyclic antidepressive
- Selective serotonin-retake-inhibitors
- Lithium
- Antihistaminics
- Benzodiazepine
- Digoxin

As there is a basic tendency in the nature of illness to produce hyperkinetic and dyskinetic symptoms as well as other extrapyramidal dysfunctions, in the choice of drugs for the Parkinson disease or for other concomitant diseases
much care must be taken prior to the introduction of the drug. The major problem however is by the anti-Parkinson drugs which may create various problems. There seem to be however some individual variations in the occurrence of side reactions after the administration of Parkinson drugs. This is not a special situation only involved with Parkinson patients but an individual reaction related to the drugs in general, which however in case of IPD may create further complications. It is useful to know in detail the possible negative consequences involved in the long range treatment with Levodopa as this is the main drug practically in all the patients. Some of the major complications are as follows:
- Increase of on-off phases
- Dyskinesia
- Dystonia
- Hyperkinesias
- Sleep disorders
- Cognitive and psychiatric problems
- Autonomic nervous system dysfunction

With the present stage of development in the drug treatment of IPD, it is not possible to manage the patients without the medication of Levodopa in the long term. At the same time we know that Levodopa is one of the main drugs which create complications with dyskinesias which may be to a certain extent dosage dependant. Accordingly it is useful to keep the dosage of L-dopa low if the clinical condition permits. However, a response to Levodopa may not be available until a sufficient dosage has been administered for a considerable length of time which is also an important factor. It is therefore useful to begin the treatment with other drugs such as Dopamine-receptor agonists or MAO-inhibitors or Amantadine and then

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combine with Levodopa which in many cases may not need a very high dosage. After the early phases of “honeymoon” with Levodopa, one would notice that the effect generally reduces not only from the point of non-reduction of symptoms but also with the appearance of frequent on-off-fluctuations and freezing. This is an indication for increase in the dosage of L-dopa in the frequency of intake but also from the point of view of sufficient dosage.

**Suboptimal Peak-response to L-dopa**

An optimal response to L-dopa is characterized by the effectiveness of the dosage intake and the reduction of clinical symptoms associated with akinesia and tremor. If the dosage is too small or the frequency of dosage intake is delayed there may be suboptimal response to L-dopa in the form of on-off-fluctuation or freezing. The dosage of L-dopa should then be increased and the frequency of drug intake should also be improved. However, in the increase of dosage one must see that not a very small dosage of L-dopa is added or also not very high dosage. Generally an increase of 125 to 250 mg of L-dopa can be given per dosage, taking care that the daily dosage does not exceed 750 mg to the extent possible. If no betterment is seen with this dosage, then it is time to add a second drug to L-dopa, with Dopamine-receptor agonists or such drugs as Selegiline/Rasagiline or with COMT-inhibitors. The ideal combination will be depending upon the clinical condition to keep the dosage of L-dopa in the range of 500 to 600 mg/day in divided doses of 125 mg four times combined with Dopamine-agonists or drugs belonging to other groups of NMDA-antagonists or MAO-inhibitors. In the event of
unexpected wearing-off phenomena, it may be useful to increase the frequency of dosage of L-dopa combined with COMT-inhibitors or Dopamine-receptor agonists. If in some cases even after an adequate dosage of L-dopa the patients do not show a response to this drug, then it could give us a hint that the diagnosis of IPD may not be correct. If this happens particularly during the early phase of the disease when the patient is not much known to the physician, one must seriously think about the differential diagnosis involving multisystem atrophy or other extrapyramidal disorder. The failure to drug response at the later stages of IPD may be possible but even then a response to an adequate single dosage of L-dopa should almost always be possible.

A proper evaluation of the drug response particularly in regard to Levodopa and the subsequent symptoms involving on-off phenomena and freezing is sometimes possible only with the help of history taking through the patients and the dependants. This is particularly necessary in case of the peak-dose-hyperkinesia and –dyskinesia as a response to Levodopa medication. One must try to find out at what dosage and under which frequency the dyskinesias occur in the way of peak-dose symptoms. It is then easier to set the single dosage of drugs better, to prevent such dyskinesias. From the clinical practice it is generally known that among all the symptoms associated with IPD dyskinesias are the most disturbing phenomena particularly in the sphere of social activities. It is therefore necessary to make regular monitoring of patients during the medication particularly with L-dopa until a more or less standardized dosage has been reached. One must try to assess over and again about the time interval of drug intake particularly related to L-dopa also in relation to the
intake of major meals. It must be made clear to the patients and dependants that L-dopa should be taken generally half an hour before a major meal or 1½ hours after that for the purpose of better absorption.

Dystonia associated with Dyskinesia are also disturbing phenomena for the patients particularly because they cause pain in the feet. Many patients learn to take the drug immediately on getting up from bed, in some cases however this is not fast enough to help them to reduce the painful dystonia in the feet. In such cases subcutaneous applications of Apomorphine is useful which is faster acting. Some patients are helped through late intake of L-dopa before going to bed. The general principle however in case of painful dystonia is to reduce the dosage of Levodopa but combine it with Dopamine-receptor agonists or with Rasagiline.

Freezing is a difficult phenomena in the clinical course of IPD which is also not very responsive to medication. The patient may feel the freezing as a partial or complete reduction of movement either under peak-dose L-dopa or during the off phases. It is generally difficult to improve this condition immediately even with the help of subcutaneous Apomorphine but it can be tried or by changing the combination of drugs during the course of medication. The alternative here is also a combination with Dopamine-receptor agonists which can be given even in higher dosage with a corresponding reduction of L-dopa. The addition of Rasagiline to the basic medication of L-dopa is also a further alternative.

Dopamine Dysregulation Syndrome

Dopamine dysregulation syndrome is characterized by the occurrence of severe drug related side effects. This clinical
phenomena is seen mostly among male patients who receive Dopamine agonists particularly of the type of Pramipaxole and Ropinirole. However, the female patients may also be affected from this kind of side effects related to the above mentioned drugs. A tendency to hypersexuality among patients receiving Pramipaxole and Ropinirole has already been mentioned. However, in this comparatively rare condition there is an uncontrolled hypersexuality occurring in male patients who then seem to lose control over their emotional and social inhibitions and tend to indulge in sexual activity with frequent change of partners. The spouses of the patients sometimes are so exhausted that they seek separation or divorce from their husbands as they are also not in a position to understand the changed mentality. Such increased tendency to sexuality is known even among elderly patients who otherwise tend to have erectile dysfunction. There seems to be a pathological increase of libido in these patients. Such overreaction of sexuality is known even among the female patients however considerably less than among male patients. In addition to the hypersexuality the patients tend parallel or alternatively to gambling, where they sometimes loose lots of money leading to a ruin of familial and social situation. This is however a reversible phenomena and the patients seem to get better once the responsible Dopamine-receptor agonists are removed from the medication. It is therefore necessary to ask the patients from time to time about their sexual behavior particularly when they are taking the above mentioned Dopamine agonists, as otherwise the patients out of the own initiative rarely mention about the change in their sexual habits. Both the drugs particularly Pramipaxole but also Ropinirole are very commonly used Dopamine-receptor agonists and are also very useful in the treatment of Parkinson disease as
monotherapy or in combination with Levodopa. Whether such behavior is dosage dependant has not been clearly established. On the whole this is a comparatively rare phenomena but if it does occur, may have disastrous consequences for the patients and their dependents. It is a compulsive behavior both in respect of hypersexuality and gambling.

**Drug Related Psychiatric Complications**

Psychiatric symptoms related to depression, hallucinations, psychosis and dementia are possible during the clinical course of idiopathic Parkinson disease. Apart from depression the other complications generally do not occur during the early phases of IPD. However, certain combination of Parkinson drugs may provoke pharmacogenic psychosis with symptoms such as hallucination, delusion and other psychotic conditions. Such a situation can occur even in the earlier phases of IPD if they are drug related. In such an event it is necessary to see the combination of drugs and change such drugs which may be responsible for the occurrence of psychosis. It will be necessary to change the anticholinergic and MAO-inhibitors or reduce them wherever possible. Even drugs such as Amantadine should be reduced and one should also consider the possibility of psychosis occurring through the medication of other Dopamine agonists or L-dopa. In the second step the use of neuroleptic drugs may be indicated however one should take care not to use drugs such as Haloperidol or similar drugs because of the risk of increasing extrapyramidal symptoms. The two suitable drugs in similar situation are Clozapin and Quetiapin with close monitoring particularly in case of Clozapin. However, great care must be taken in changing
the basic drugs such as L-dopa and Dopamine-receptor agonists because of the risk of initiating severe withdrawal symptoms. Even in the treatment of depressive symptoms one has to be careful in selecting a drug as several antidepressive drugs may cause interaction with antiParkinson drugs. For example, the combination of a SSRI-antidepressive such as Fluoxitin with antiParkinson drugs of the group of MAO-B-inhibitors like Selegiline or Rasagiline is rather contraindicated because of the side reactions. Otherwise it may be useful to select an antidepressive drug from the group of SSRI-inhibitors in the first line and if unsuitable to select a tricyclic antidepressive drug. Even Entacapone may create complications in combination with tricyclic antidepressive drugs. Patients with Parkinson disease require long range medication with a combination of drugs and as such any other drug meant for other complaints should be carefully examined before introducing it in the medication particularly if required for longer periods.
Other Forms of Treatment for Parkinson Disease
The drug treatment with L-dopa and Dopamine-agonists as well as other drugs has been established in the treatment of idiopathic Parkinson disease. In spite of the several side effects through these drugs an early commencement of drug treatment is indicated in most of the patients with IPD. Even though the drug treatment cannot contain the basic problem of neuronal degeneration, it can greatly substitute the deficit of Dopamine and improve the quality of life for patients. The problem arises in the late phases of Parkinson disease with the occurrence of hyperkinetic symptoms and non-motoric complications. Even these conditions can be controlled to a certain extent with the modification of the drugs or through the neurosurgical methods of deep-brain-stimulation of subthalamic nucleus or globus pallidus. The various motoric complications associated with chronic IPD and the frequent administration of antiParkinson drugs are a serious problem for the patients and the physicians during the later phases of IPD. As Parkinson disease is a major neurological problem occurring worldwide, several research groups and pharmaceutical concerns are planning the improvement of the existing drugs and the introduction of new drugs. Among the improvement of the present drugs the following galenic and biosynthetic forms are planned:
- Apomorphine in the form of long acting plaster
- L-dopa for inhalation
- Pramipaxole plaster
- Rotigotin nasal spray
- New drugs with neuroprotective effect

There are research activities related to the dopaminergic neuronal replacement through transplantation from mesencephalon tissues of the human fetus through the cultivation of dopaminergic neurons in the striatum.
are also plans for transplantation of embryonic stem cells for cultivation of nerve cells in the striatum. There are research activities involved in the application of gene therapy in the form of Dopamine synthesis genes transferred to cells in the striatum as well as in nucleus subthalamicus. These are however future activities and may not be in a position to replace the present treatment for the next several years.

**Herbal Supplement of Drugs**

Herbal drugs containing standardised dosage of L-dopa are already being used. One of the commonly used drugs is Mucuna Pruriens taken over from the ancient Indian medicine Ayurveda which has been used in this system of medicine for hundreds of years for diseases of the nervous system as well as an Aphrodiasec. Mucuna Pruriens available from the beans of a tropical legume Mucuna Pruriens (Kapikachu) has been made available in the form of powder and tablets. One gram of this substance contains roughly 30 mg of L-dopa. In a scientific double blind study it has been shown that the drug given in a dosage of 30 gram per day had equal effects compared to a similar dosage of synthesised L-dopa. Even in the clinical practice the use of this drug during the early phases of Parkinson disease seems to be effective. The problem arises because of the large dosage of 30 gram necessary for daily intake. One possibility is to combine this drug in the early stages with Dopamine agonists. However, after a period of -2 years the dosage of Mucuna Pruriens which can be generally given up to about 6-9 gram per day must be supplemented through pharmaceutical preparations of L-dopa. However, an indiscriminate use of these herbal preparations in the treatment of Parkinson disease is
contra-productive because of the possible side effects and the inability to decide the total dosage of L-dopa per day. Reports have been published about the effectiveness of similar preparations from beans available in the Mediterranean region. In the application of any drug herbal or synthetic in the treatment of IPD, it is important to know the effectiveness and the side effects of the drug concerned so that an intervention should be possible at any time of the clinical course.

Many patients have a tendency to try different kinds of treatment which is understandable from the point of view of their daily problems and the necessity to take a long range medication with combination of drugs. There are patients who spend lots of money for unconservative methods of treatments such as with strange forms of acupuncture associated with titanic ear-implantation, exaggerated methods of spiritual healing, which all seem to be costexpensive. It is useful to hold discussion with the patients from time to time mentioning the possibilities and contraproductivity of such unconservative treatment methods. However, the patients have a right and should be encouraged to adopt all possible non-medical healthy habits to improve their general wellbeing. Some of the physical methods are advisable and may help all patients with IPD. These include the following:

- Physiotherapy
- Gymnastic training
- Yoga and Meditation
- Other methods such as Qi Gong
- Regular walking
- Proper diet

Physiotherapy is useful for patients with IPD during all phases of the disease. It is however necessary to have
the proper physiotherapy for Parkinson patients which should be planned according to individual requirements. Doing such physiotherapy as done for patients after cerebral insults or spasticity is not a proper method for Parkinson patients. It should be understood that the patients with IPD have not lost their movements because of an upper motor neuronal disorder but because of the akinesia and rigidity, that they have day-to-day problems with the muscular movements. It is characterized by the reduction of movement in general and reduced movement in the muscles and joints. Further there is a reduced vitality characterized by the depressive mood changes so that they must be trained to improve these conditions. There is generally also a postural instability which can be improved through the physiotherapy as well as through the physical training at home. Many patients have back pain and muscular pain which can also be helped through physiotherapy. Similar is the situation related to gymnastic training which the patients can practice to whatever extent possible. One sees in the clinical practice that patients who have regular training either at home or in the special centers have better mobility and control of their postural instability than those who do not practice. Yoga exercises including breathing technique are also useful for patients with IPD. Through Yoga, meditation or other methods such as Qi Gong the patients can help themselves to ward off their depressive mood changes. Other daily activities such as regular walking should be encouraged for all patients at all phases of Parkinson disease to the extent possible. One must however warn the patients from overdoing because of the tendency to drops during such over exercise particularly by long distance walking. Even though there is no special diet meant for patients with IPD it is useful to
tell them over and again that the intake of L-dopa must be properly controlled so that the drug is taken around ½ hours before food or 1½ hours after food to help better absorption from the gastrointestinal tract. At the same time proper diet containing roughage and vitamins is useful to reduce the tendency to constipation. The intake of fluids should also be emphasized from time to time particularly also during the later phases of IPD as the patients reduce drinking of fluids because of swallowing difficulties. The use of alcoholic drinks may not be prohibited but the consumption should be as low as possible.
Chapter 13

The Environment of the Patient
The idiopathic Parkinson disease is a neurological condition which begins slowly over a period of years with mild symptoms. As already mentioned before the diagnosis is made it takes sometimes several years as many patients because of their mild symptoms do not go to the physician in the earlier stages. Several of the symptoms which may be present during the preclinical phase of the disease are such ones which any middle aged or elderly person can get.

- Back pain
- Constipation
- Depressive mood changes
- Sleep disturbances
- Night sweating

It is only when the patient begins to have a tremor that the patients and their close relatives notice the changes. However, about 40-50% of the patients particularly during the early stages have no tremor at all. The symptoms which represent akinesia and rigidity may be mild and show mild movement disorders. The diagnosis is particularly delayed and difficult in case of people getting the IPD below the age of 50 years. The frequent symptoms felt by the patient and noticed by the close environment are the general slowing of movement during walking and talking, difficulty in writing, one sided symptoms of reduced movement of the arm and the leg. There may be postural instability. The facial expression gets changed with reduced mimic. Even though IPD is predominantly a motor system disorder it is almost always accompanied by other non-motor symptoms particularly neurovegetative disturbances and depression. Excessive tiredness and reduced capacity for work are associated symptoms. As mentioned most of these conditions may be present in
different stages of elderly people, which make the early diagnosis of IPD difficult. Attempts must be done on the one hand for the evaluation of motoric disturbances particularly with unilateral occurrence of akinesia, rigidity and tremor but at the same time there should be assessment of the accompanying non-motoric symptoms. A complete neurological examination is obligatory for the diagnostic evaluation but other tests such as a minimental and handwriting test may be useful. In cases where a diagnosis is difficult one could try Levodopa test or Apomorphine test for further assessment. By further difficulty in the differential diagnosis other neuroradiological methods such as MRI or PET may be necessary. The history taking should be done wherever possible not only from the patients but also with the help of other family members.

The physician concerned must be convinced about the diagnosis of IPD before it is carefully pronounced to the patient. It is a blow of destiny for the patients and the dependants concerned and all the care and tactic must be used in discussing this aspect. Some of the important points to remember in such discussions are to make the situation as clear as possible. The seriousness of the illness can be however mentioned in such a way that the patient needs medical management particularly the intake of regular drugs. At the same time it is useful to tell the patient that the quality of life can be improved with the early beginning of medication and IPD generally does not reduce life expectancy. It is not a good idea to describe to the patient and the dependants in the early stages particularly when the patients are of younger age about the later complications leading to cognitive deficits or dementia. The patients must be encouraged to maintain their profession if they are in a working age and certain
adjustments may be advised. In any case one must consider
the emotional aspects of the patients and the dependants
during the discussion regarding diagnosis and prognosis.
Even though every attempt should be made to encourage
the patient in spite of the progressive neurological disease,
false hopes of getting better should be avoided. The
discussion should be fairly open concerning various
aspects of personal health and family as well as social life.

The diagnosis of Parkinson disease, in whatever way
it is mentioned to the patients and their dependents,
changes the life for patients and their environment. Some
patients before they come to the neurologists have some
information through the family physician about the
possibility of such disease in which case they are somewhat
less shocked than the others who get the diagnosis without
any earlier warning. It can result in a situation leading to
shock, anxiety, panic and depression not only in case of
the patient but also in the spouse. On the other hand the
patient who had some doubts about the possible diagnosis
of IPD before they came to a neurologist may feel to begin
with, somewhat relaxed because of the pronouncement of
diagnosis but at the same time even they may feel the
emotional instability as mentioned above. Depending upon
the situation counseling of the patient through the
neurologist, family physician or psychologist may be
necessary. However, it is important that the physicians or
the psychologists concerned are well informed about the
various aspects of IPD. It is useful in the clinical practice
not to discuss about the prognosis or of the later phase of
IPD during the early stages when the patient has one’s
own problem of accepting this difficult diagnosis. Even
the clinical course is somewhat variable in different
patients, as such it may be rather advisable to wait for a
period of one or two years until the discussion of further problems involved in the later phase of IPD are done. Already during the early years the patients feel their difficulty, try to collect information through internet or such media and generally are in a better position to accept the difficulties involved in the later years of living with Parkinson disease. As IPD is a common neurological disorder, there are in most of the larger places, Parkinson societies consisting of patients and sometimes assisted by specialists. An exchange of information through other patients may be useful, should however be left to the decision of the patients. Depending upon the personality of the patient and the spouse discussion may be held regarding the sexuality. Majority of the patients seem to have reduced libido earlier or after the onset of IPD which may be associated with the pathophysiology of Dopamine regulation. As mentioned in the earlier pages some patients may react later due to the drug influence particularly by Dopamine-receptor antagonists of the type of Pramipaxole and Ropinirole to hypersexuality. All these aspects need careful and long range discussions with the patients and the family. There seems to be a somewhat higher tendency to suicidality with IPD patients because of the chronic depression associated with IPD. The complementary therapies such as physical activity, physiotherapy, Yoga, meditation may be useful particularly for such patients however parallel to the drug therapy. Some patients have a tendency to stop all medication during the course of the illness in the form of “drug holiday” which is a dangerous situation as it may lead to akinesia crisis. Even this aspect should be discussed with the patients if the physician notices a tendency to such drug withdrawal. Of utmost
importance is the discussion regarding the side effects of antiParkinson drugs particularly during the change of drug schedule. Encouraging the patients to follow other hobbies such as moderate sports, music, art and other cultural activities are always beneficial.
Chapter 14

Case Histories of Patients
Case History 1

Man, aged 75 years, came for neurological treatment in 2004. An elder brother of the patient got Parkinson disease around the age of 60 years which showed a progressive clinical course. Another elder brother got multiple sclerosis in midlife which was also progressive. The patient started getting tiredness, concentration difficulties and depression around the age of 60 years which he tried to ignore. At the age of 64 years he started getting speech difficulties, neck pain and back pain, loss of body weight and tremor of the left hand accompanied by weakness of the left hand and leg. The patient was advised to go to a neurologist who diagnosed at the age of 66 years an idiopathic Parkinson disease and placed the patient on a medication of L-dopa and Ropinirole. The preparation of Cabergoline was not tolerated by the patient.

Four years after the diagnosis of idiopathic Parkinson disease the patient was found in a reduced general condition. There was hypomimic facial expression, postural instability with slow gait and bending of the patient forwards, low speech, general psychomotor slowing, difficulty of writing properly. He had a tremor of both hands left more than right and increased muscle tone of left arm with tendency to clasp-like phenomena. The drug dosage was changed with increase of Levodopa and Ropinirole to a daily dosage of Levodopa up to 750 mg and Ropinirole 8 mg per day. The tremor reduced somewhat but akinesia particularly the difficulties of walking and speaking was not better. The patient started getting symptoms of dyskinesia so that the dosage of L-dopa had to be reduced again to 600 mg per day. Addition of other drugs such as COMT-inhibitors was not tolerated by the patient in spite of parallel intake of
Domperidon. There was progression of the motoric and non-motoric symptoms particularly depression, sleeplessness and concentration problems. Around eight years after the diagnosis of IPD the patient showed definite progression of symptoms leading to dementia. Two years after the beginning of treatment at my practice the patient developed in addition to his IPD a prostrate carcinoma for which he had to be treated with radiotherapy. Eventually the patient stopped consultations at my practice and restricted himself to his place which was 300 km away. Irrespective of the later illness with prostrate carcinoma the patient showed rather fast progression of motoric and non-motoric symptoms associated with IPD and the beginning of dementia. In the history there was a preclinical phase of around 5 years with symptoms of tiredness, sleeplessness and depression. On the whole this patient was a difficult case for treatment because of rapid progression of symptoms and difficulty in the tolerance of antiparkinson drugs. After the onset of dyskinesia and symptoms of dementia it was planed to treat the patient with such drugs as Rasagiline, Amantadine and Clozapin. This patient had in the history a strong genetic tendency with elder brother suffering from idiopathic Parkinson disease. The clinical course was characterized by fast progressive symptoms with extrapyramidal and cognitive disturbances. It is suspected that the patient had the clinical symptoms probably for a longer period without diagnosis and treatment.

Case History 2

Woman, aged 52 years, was referred for a neurological diagnosis because of reduced muscle function in the left hand which she began to notice around the age of 48 years.
She has no family history of IPD. The patient tried to improve her condition by doing fitness training which however did not seem to help her. She complained of back pain, reduced dynamic and tiredness, a tendency to positional syncope, lack of power in the left leg and left hand followed by mood changes. Until the age of 52 years that means almost 4-5 years after the beginning of her symptoms, she did not go for a medical consultation. She tried to improve her condition by taking vitamins, ginseng and also by spiritual methods.

On examination there was slightly reduced mimic with a mask-like face, rest tremor of the left hand, increased muscle tone of the left arm and leg. The gait was slow but there was no definite postural instability. Rigidity of the muscles was not present. However, there were definite signs of akinesia and unilateral tremor of the left hand. There was a dysdiacokinesia of the left hand as well as difficulty in writing a proper script. On the basis of these symptoms an idiopathic Parkinson disease was strongly suspected, the patient was however not prepared to accept the diagnosis. As the symptoms increased over the next few months she came again for a consultation when the treatment was started with a Dopamine agonist Cabergoline as the patient wished to take the minimal number of tablets. An MRI of brain showed normal findings. The dosage of 1 mg per day was tolerated by the patient which however did not help her much. The drug was changed later to Pramipaxole up to 3 mg per day. The tremor of the left hand seemed to improve but there was an increase of akinesia and also rigidity of the left arm. The drug had to be supplemented with the addition of Levodopa in a slowly increasing dosage up to 350 mg per day, in the beginning assisted by Domperidon. There was
an all round betterment of the symptoms both in view of akinesia as well as tremor. The patient however made her own changes of the drug dosages so that the clinical condition showed instability particularly in respect of akinesia and rigidity. From the non-motoric symptoms she had mood changes and sleep disturbances which she tried to treat with spiritual healing methods.

On the whole 5 years after the diagnosis and initiation of treatment the patient is managing fairly well with her akinesia-rigidity predominant symptoms under a combination of Levodopa and Pramipaxole in a low dosage of 350 mg Levodopa and 3 mg Pramipaxole per day. Even this medication is considered by the patient as a higher dosage which she tends to change out of her own initiative from time to time with the consequences of instability in the clinical course of IPD. In this case the clinical manifestation of the IPD occurred fairly early around the age of 45 years but the progression of the disease is rather slow even with a low medication.

Case History 3

Man, aged 73 years, has no family history of IPD or other Parkinson syndromes. Around the age of 68 he began to feel a tremor of the left hand and the left leg as well as weakness on walking and in general. He was otherwise a very active person and the tremor and weakness disturbed him so that he went for a neurological consultation fairly early after the beginning of these symptoms. A neurologist diagnosed an idiopathic Parkinson disease and started him with a combination of Levodopa and COMT-inhibitor in a low dosage. The patient was a very disciplined person and took the medication regularly but found an increase
of symptoms particularly on walking. On examination 2 years after the diagnosis was made and the drugs were introduced, the patient showed rest-tremor of 4-6/sec as well as other symptoms such as reduced mimic, posture bent to the front, slow walking and hypophonia. He lost weight of several kilos over a period of 2 years and according to his own opinion started aging fairly fast. The patient showed a tremor-dominant type but with the presence of other symptoms of akinesia, rigidity as well as postural instability. He took regular long walks every day and tried to keep himself active. In spite of this the symptoms particularly tremor and akinesia increased so that the drug was changed to a combination of Levodopa plus Carbidopa and COMT-inhibitor (Stalevo). In addition he received Ropinirole retard 4 mg per day. Under this combination the patient was maintaining comparative stability in his health, however with the usual restrictions associated with IPD. He is a disciplined person and shows excellent patient compliance. From the point of non-motoric symptoms he has a depressive tendency and sleeplessness but no signs of other cognitive disturbances 6 years after the diagnosis of IPD.

**Case History 4**

Man, aged 70 years, came for consultation at the age of 66 years. His mother died at the age of 86 years on Alzheimer disease. Around the age of 60 years the patient suddenly began to get tremor of the right hand which happened after he lost his daughter on cancer. To begin with he thought the tremor was because of the shock he got out of this family tragedy and tried to ignore it. Later he realized difficulty also on walking particularly with weakness of
right leg. His house physician diagnosed a Parkinson syndrome and prescribed him Ropinirole which he did not tolerate properly. His symptoms of tremor and weakness of the right side increased slowly. However, he continued with the same drug and supplement of Mucuna powder for the next some years when both tremor and akinesia increased considerably. Maximum problem the patient had was with writing. However, he kept himself active with regular walking and playing tennis.

On examination I found an intensive rest-tremor of the frequency of 4-6/sec of the right hand, reduced facial mimic, difficulty in walking particularly on the right side. There was a rigidity of the right arm and increase of muscle tone right arm and right leg. There was a dysdiadocokinesia of the right hand and very small script. The patient showed a tendency to depression and frustration. The drug was changed from Ropinirole to Pramipaxole to a daily dosage of 3 – 4 mg which however did only a small help. After one year of treatment particularly on the wish of the patient only with Pramipaxole and Mucuna Pruriens the drug was slowly changed to a combination of Levodopa with Bensarizide and Pramipaxole. Under a clinical observation of nearly 4 years the clinical improvement is rather modest. There is an increase of all the cardinal symptoms such as tremor, akinesia, rigidity and postural instability. However, from the aspect of non-motoric functions there are not much negative changes other than the depressive mood changes. The patient is not in a position to play tennis, however he is trying to keep up to his daily regular walking. This is a patient where all the cardinal symptoms are present particularly tremor and akinesia which however could be treated better with further combination of drugs.
patient wants to avoid higher dosage of drugs and accordingly efforts will be made to combine the drug schedule of Levodopa with COMT-inhibitor and Pramipaxole. The progression of motoric symptoms seem to be in this case faster whereas non-motoric disturbances play a marginal role.

**Case History 5**

Woman, aged 58 years, came for a consultation from the neighboring country Germany. A professionally active woman began to feel at the age of 54 years a slowness of muscle dynamic while walking. After a few months she started feeling a weakness of the right hand and right leg as well as back pain. There was a kind of nervousness and mood changes which was noticed by her husband. She ignored these symptoms and continued to work further and carry on the household functions as well. As the symptoms increased she went to a neurologist who diagnosed an IPD. She was stared on a medication of Ropinirole in a small dosage. The patient had difficulty to accept the diagnosis as she did not have tremor and also in taking the medication. As the problem increased which created her difficulty in her professional activity she went again to the neurologist who increased the dosage of Ropinirole up to 12 mg per day. She received along with Ropinirole Domperidon for better gastrointestinal tolerance.

On examination 4 years after the first symptoms and around 2 years after the diagnosis and intake of medication there was clearly masked facial expression with reduced mimic. The gait was small stepped and with bending forwards. The akinesia with a right sided dominance was
very clear. There was also mild tremor of the right hand but also of the left hand. Muscle tone of the right hand and right leg was raised with clear cogwheel phenomena of right arm. From the clinical point of view the patient had a akinesia-rigidity dominant type with the presence of other symptoms such as postural instability and slight tremor also. The clinical progression of the motoric symptoms was clear but there was also progression of cognitive impairment which could be evaluated by minimental test. This patient needs a combination of drugs at this stage with the addition of Levodopa and in a combination of either Amantadine or Rasagiline depending upon the further clinical course. Only the present single drug Ropinirole is certainly not sufficient for the treatment of the cardinal symptoms. However, this patient needs lot of counseling to reach an understanding which needs patience also from point of view of the treating physician.

Case History 6

Man, aged 73 years, came for a consultation at the age of 71 years. The patient is a reputed physician and was active in his profession for over 30 years. At the age of around 63–64 he began to feel mood changes with depression for which he could find no reason. His wife noticed that along with the mood changes there was a general psychomotor slowing and some difficulty in writing. In his professional activities where he was involved with fine surgical work, the patient found some difficulties with the fine motoric. In the family history his mother had at the age of 84 years a Parkinson syndrome. The patient himself had for some years arterial hypertension which was under medication
and was no longer problematic. Because of the family history and the symptoms the patient went for a neurological consultation where a Parkinson disease was strongly suspected.

In the medical report there was reduced mimic, akinesia of the right arm and leg, rigidity of the right arm, slowing of gait and difficulty in writing as well as certain amount of hypophonia. There was practically no tremor. The craniocerebral MRI did not show any pathological changes. After two consultations the patient was diagnosed of having idiopathic Parkinson disease and was started initially with Dopamine receptor agonists such as Pramipaxole, Ropinirole and Cabergoline. Non of these drugs helped the patient and he had difficulty related to tolerance with such side effects as gastrointestinal disturbances and tiredness.

About five years after the diagnosis and attempts with some combinations of antiParkinson drugs the patient came in my consultation. At this phase of his illness, he had clearly akinesia-rigidity dominant type of IPD associated with such nonmotoric symptoms as constipation, sleeplessness and depression. The patient came in my consultation for a second opinion about his disease and the combination of drugs which he was taking. He was on a combination of Levodopa, Carbidopa and Comtan with a total dosage of around 500 mg of Levodopa, in addition he was taking Rasagiline 1 mg and Rotigotin Plaster 4 mg per day. Under this combination the clinical condition showed however some progression both in view of motoric and nonmotoric symptoms but the patient was doing fairly well in his day-to-day activities. There were no symptoms of dyskinesia or dementia. Regarding the mood changes the patient had his own strategy of

226  **STEP BY STEP TREATMENT OF PARKINSON DISEASE**
managing with occasional drugs and other complementary methods. He was advised to keep the dosage of Levodopa as far as possible under 700 mg per day.

Case History 7

Woman, aged 68, came for a neurological consultation. She mentioned of having hypertension for the last few years which was compensated with medication. Around the age of 67 she felt that her right arm was not swinging sufficiently during walk. Sometimes she felt like losing the power of right hand while doing her household work. Somewhat later she also felt that there was slight tremor of the right hand which was disturbing her and was also noticed by her environment. At the same time she felt a reduced strength on walking particularly on the right side. Sometimes she felt that her speech was reduced in the dynamic, because of all these she went for a neurological consultation. The neurologist made a suspected diagnosis of idiopathic Parkinson disease and advised the patient not to have any medication for the next six months or so.

The patient felt a little increase of the symptoms mentioned above and came for a second opinion particularly in view of the medication. She was not feeling well with the suspected diagnosis and at the same time of not doing anything to compensate her symptoms. On examination there was no hypomimia, but akinesia and increased muscle tone of the right extremities above and below were present. The script was small, the gait was with small steps and slow. The cranio-cerebral MRI showed no pathological changes. Because of the clinical findings a idiopathic Parkinson disease with akinesia, rigidity type of the right side could be diagnosed. The
patient was slowly placed on a Dopamine receptor agonist Pramipaxole on a total dosage to begin with 1.5 mg per day. On this medication the patient feels reduction of akinesia and slight improvement of speech and writing. The Dopamine agonist was given even without tremor as the symptoms of IPD are still mild. Depending on the further clinical course one has to think of a further combination. In any case in spite of the rather late beginning of the condition it is better to wait as long as possible before initiating a treatment with Levodopa.

**Summary of Case Histories**

In dealing with cases of IPD it is important to note that there are a lot of individual variations in spite of the cardinal motoric symptoms and associated non-motoric disturbances. Most of the patients have all the cardinal symptoms however some patients have in the beginning no tremor. Similar is the situation in regard to motoric and non-motoric functions. Even though neurovegetative disturbances such as disturbed olfactory functions, sleep disturbances, constipation as well as depression are often present, not all patients show these disturbances always. There are patients who seem to manage fairly well 10 years or longer with IPD without serious cognitive impairment or dementia, but there are others who develop the symptoms already after 5 years of clinical course. Similar is the situation concerning the progression of motoric functions. Patients with milder symptoms manage well even after 10 years without the development of dyskinesias; the others may develop them earlier. One must however consider the possibility of dyskinesia in all patient with IPD over a period of 10 years and accordingly
keep the dosage of Levodopa as low as possible. However, a treatment without Levodopa after a clinical course of several years is at the present stage of drug development seems to be not possible. The question of dealing with the non-motoric symptoms must be individually managed with regular discussions with the patient. Many patients think that their depressive mood changes are a part of their personality and they do not like to treat it with drugs. In such cases a careful counseling also with the spouses of patients is useful. A perfectionistic tendency in combining the medication for any of the symptoms must be avoided. At the same time when the physician is convinced about the necessity of a complicated treatment he or she should not be hesitant to mention this to the patient concerned as otherwise it is not in keeping with the ethics from the point of view of clinical neurology. One must also not hesitate to mention one’s professional view in respect of the new developments in treatment such as deep brain stimulation, cell transplantation and other developments. This is only possible when the physician concerned keeps oneself abreast of the newest developments in the field of Parkinson disease.

**Antiparkinsonia Drugs Available in India**

- Levodopa
- Carbidopa
- Amantadine
- Benserazide
- Biperiden
- Bromocriptine
- Entacapone
- Tolcapone
• Orphenadrine
• Pergolide
• Piribedil
• Pramipexole
• Procyclidine
• Promethazine
• Ropinirole
• Selegiline
• Trihexyphenidyl
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## Index

### A
- Abnormal gait and posture 23, 53
- Acetylcholine 64
- Akinesia 19, 20, 52, 91, 161, 162, 167
- Alien-limb-syndrome 17
- Alpha-dihydroergocriptine 124, 127
- Alzheimer disease 47, 65, 79, 181
- Amantadine 229
- Amphetamine 64
- Anticholinergic drugs 110, 196
- Antiepileptica 196
- AntiParkinson drugs 109, 196, 229
- Apomorphine 64, 125
- test 122, 123
- Arteriosclerotic parkinsonism 18
- Athetosis 13, 14, 41
- Autonomic nervous system dysfunction 197

### B
- Back pain 212
- Basal ganglia 62
- Bayonet finger 42
- Benserazide 229
- Benzodiazepine 196
- Biperiden 229
- Blood brain barrier 64
- Bradykinesia 91
- hands 55
- Brainstem 62

### Breathing
- difficulties 58
- disturbance 19
- Bromocriptine 124, 126, 229
- Budipine 138
- Butyrophenone 64, 196

### C
- Cabergoline 124, 126
- Carbamazepine 196
- Carbidopa 144, 229
- Carbon dioxide intoxication 18
- Cardiovascular dysfunction 190
- Catecholamine 64
- Catecholomethyltransferase (COMT) 64
- Cell aging 84
- Cerebellar diseases 34
- Cerebrovascular disease 181
- Chorea 13, 14, 40 gravidarum 40
- Huntington 34
- Cimetidine 196
- Clinical aspects of IPD 77
- side effects of dopamine-agonists 135
- symptoms of IPD 58
- Cognitive and psychiatric problems 197
- Combination of levodopa 144
- COMT-inhibitors 142, 144
Constipation 192, 212
Corpus striatum 12
Cortex 13
Cortico-basal degeneration 16
Counseling of patient 214
Creutzfeldt-Jakob disease 47

D
Deep-brain-stimulation 172
Degenerative diseases 18
Dementia 20
Dementia with
Lewy-bodies 17, 182, 183
Parkinson disease 184
Depression 24
Depressive mood changes 212
Diagnosis of idiopathic Parkinson disease 92
Difficulty of swallowing 191
Digoxin 196
Dihydroxyphenylalanine 64
Discussion of findings 89
Disturbances of autonomic system in IPD 188
Disturbed automatic motoric functions 19
Dopamine 64
antagonistic drugs 43
agonists 22
dysregulation syndrome 200
receptor 64
agonists 196
antagonists 196
Dopaminergic agonists 64
Dosage of levodopa 117
Drug related
complications 194
dyskinesia 20
psychiatric complications 202
Drug treatment
cognitive symptoms and
dementia 187
late clinical phase of IPD 162
Duodopa-pump 121, 167
Dysarthria 172
Dyskinesia 197, 200
Dystonia 13, 14, 42, 197
Dystonic movement disorders 19

E
Edison’s disease 41
Encephalitis lethargica 41
Endogenous and exogenous toxic factors 87
Entacapone 143, 229
Epilepsy 3
Ergoline 133
dopamine agonists 124
Essential tremor 14, 36
Extrapyramidal disorders 34
system 13

F
Facies 57
Flunaricine 196
Freezing 200
Functional entity 12

G
Gait 56
Gastrointestinal disturbances 58
Genetic factors 87
Gilles De La Tourette’s syndrome 45
Globus pallidus 12
Glutamate 64
Gymnastic training 208
INDEX

H
Hallervorden-Spatz disease 42, 79
Hemiballism 34, 41
Hemiballismus 13, 14
Herbal supplement of drugs 207
Honergoline agonists 133
Huntington’s
disease 42, 43, 79
Hemiballismus 13, 14
Honergoline agonists 133
Huntington’s
disease 42, 43, 79
Hyperkinesia 91, 197
Hypersalivation 58
Hypokinesia 91

I
Idiopathic Parkinson
disease 25, 84
syndrome 19
Increased sweating 191
Indications for levodopa 118
Juvenile Parkinson syndrome 81

L
L-dopa test 122, 123
Levodopa 40, 111, 145, 229
treatment 7
Lewy-bodies 62, 69
Lewy-body dementia 25, 47, 79, 181
Lisuride 124, 128
Lithium 40, 196

M
Manganin intoxication 18
Midbrain 13, 62
Milestones in
Parkinson syndrome 102
treatment of IPD 103
Monoamino-oxidase inhibitors 140
Motoric
disturbances 163
weakness 19
Multisystem atrophies 13, 14, 34
Muscular pain 59
Myoclonus 44

N
Neuropathological aspects 88
Neuroprotection through
dopamine-agonists 134
Neuro-psychological
deficits 174
tests 60
Neurovegetative
disturbances 163
symptoms 58
Night sweating 212
NMDA-antagonists 136
Nonergoline dopamine-agonists 124
Non-motoric complications 168
Normal
posture 55
pressure hydrocephalus 46
Nuclear caudatus 12, 62
Nucleus
lentiformis 12
ruber 12
subthalamicus 62

O
Olfactory dysfunction 189
Olivopontocerebellar atrophy 15
Optic disturbances 189
Oral contraceptives 40
Orphenadrine 230
Orthostatic dysregulation 190
hypotonia 58
Oxidative stress 84, 86

P
Pale-bodies 70
Pallidum 62
Paralysis agitans 6
Parkinson
dementia complex 18
disease 14, 17, 30, 50, 62
societies 215
symptoms 79
syndrome 2, 9, 13, 30
Pathophysiology of IPD 68
Percutaneous endoscopic
gastrostomy (PEG) 121
Pergolide 124, 128, 230
Personal independence 57
Phenomena of freezing 168
Phenothiacine 64, 196
Phenylalanine 64
Phenytoin 40, 196
Pimozid 64
Piribedil 230
Positron emission tomography 34
Postencephalitic parkinsonism 18
Postural instability 19
Pramipaxole 129
Pramipaxole plaster 206
Procyclidine 230
Programmed cell death 86
Progressive supranuclear
paralysis 16
Promethazine 230
Pseudonyms chorea 40
Psychiatric
disturbances 163
exploration 53
Psychic symptoms 20, 58

Q
Question of neurotoxicity 145

R
Rasagiline 141
Rest tremor 36
Restless legs syndrome 45
Rigidity 21, 52, 55, 91
dominant type 161, 162
Ropinirole 131, 230
Rotigotin nasal spray 206

S
Seborrhea 57, 58
Selective serotonin-retake-inhibitors 196
Selegiline 140, 230
Sexual disturbances 58, 193
Shaking palsy 6, 24
Single photon emission computer
tomography 34
Sleep
disorders 58, 164, 197
disturbances 194, 212
Speech 57
disturbance 19
problems 59
Steel-Richardson-Olszewsky
syndrome 16
Strategy of drug-treatment 160
Striatonigral degeneration 15
Suboptimal peak-response to
L-dopa 198
Substantia nigra 12, 62
pars compacta 62, 67
Superoxide dismutase 72
Swinging of upper extremities 56
Systemic lupus erythematoses 41
<table>
<thead>
<tr>
<th>Index</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T</strong></td>
<td><strong>U</strong></td>
</tr>
<tr>
<td>Tetrabencine 196</td>
<td>Urge incontinence 190, 192</td>
</tr>
<tr>
<td>Thalamus 13</td>
<td>Urinary incontinence 58</td>
</tr>
<tr>
<td>Thyreotoxicosis 41</td>
<td><strong>V</strong></td>
</tr>
<tr>
<td>Thyroxin 64</td>
<td>Vestibular disorders 59</td>
</tr>
<tr>
<td>Tics 44</td>
<td>Visual difficulties 59</td>
</tr>
<tr>
<td>Tolcapone 142, 229</td>
<td><strong>W</strong></td>
</tr>
<tr>
<td>Torsio dystonia 42</td>
<td>Webster rating scale 55</td>
</tr>
<tr>
<td>Torticolis spasticus 42</td>
<td>Wilson’s disease 42, 45, 79</td>
</tr>
<tr>
<td>Tremor 21, 51, 56, 91</td>
<td>Writing problems 59</td>
</tr>
<tr>
<td>dominant symptoms 161</td>
<td></td>
</tr>
<tr>
<td>type 162</td>
<td></td>
</tr>
<tr>
<td>Tricyclic antidepressive 196</td>
<td></td>
</tr>
<tr>
<td>Trihexyphenidyl 230</td>
<td></td>
</tr>
</tbody>
</table>