OTHER SUBJECT COLLECTIONS FROM COLD SPRING HARBOR PERSPECTIVES IN MEDICINE

Type 1 Diabetes
Angiogenesis: Biology and Pathology
HIV: From Biology to Prevention and Treatment
The Biology of Alzheimer Disease

SUBJECT COLLECTIONS FROM COLD SPRING HARBOR PERSPECTIVES IN BIOLOGY

The Synapse
Extracellular Matrix Biology
Protein Homeostasis
Calcium Signaling
The Golgi
Germ Cells
The Mammary Gland as an Experimental Model
The Biology of Lipids: Trafficking, Regulation, and Function
Auxin Signaling: From Synthesis to Systems Biology
The Nucleus
Neuronal Guidance: The Biology of Brain Wiring
Cell Biology of Bacteria
Cell–Cell Junctions
Generation and Interpretation of Morphogen Gradients
Immunoreceptor Signaling
NF-κB: A Network Hub Controlling Immunity, Inflammation, and Cancer
Symmetry Breaking in Biology
The Origins of Life
The p53 Family
Parkinson’s Disease

A subject collection from Cold Spring Harbor Perspectives in Medicine

EDITED BY

Serge Przedborski
Columbia University

Copyright 2012 Cold Spring Harbor Laboratory Press.
Contents

Preface, vii

The History of Parkinson’s Disease: Early Clinical Descriptions and Neurological Therapies, 1
Christopher G. Goetz

Clinical Approach to Parkinson’s Disease: Features, Diagnosis, and Principles of Management, 17
Joa˜o Massano and Kailash P. Bhatia

Parkinson’s Disease and Parkinsonism: Neuropathology, 33
Dennis W. Dickson

Genetics of Parkinson’s Disease, 49
Christine Klein and Ana Westenberger

α-Synuclein in Parkinson’s Disease, 65
Leonidas Stefanis

Leucine-Rich Repeat Kinase 2 for Beginners: Six Key Questions, 89
Lauren R. Kett and William T. Dauer

Parkinsonism Due to Mutations in PINK1, Parkin, and DJ-1 and Oxidative Stress and Mitochondrial Pathways, 99
Mark R. Cookson

Genomics and Bioinformatics of Parkinson’s Disease, 111
Sonja W. Scholz, Tim Mhyre, Habtom Ressom, Salim Shah, and Howard J. Federoff

Parkinson’s Disease: Gene Therapies, 127
Philippe G. Coune, Bernard L. Schneider, and Patrick Aebischer

Functional Neuroanatomy of the Basal Ganglia, 143
José L. Lanciego, Natasha Luquin, and José A. Obeso

Functional Neuroimaging in Parkinson’s Disease, 163
Martin Niethammer, Andrew Feigin, and David Eidelberg

Motor Control Abnormalities in Parkinson’s Disease, 185
Pietro Mazzoni, Britne Shabbott, and Juan Camilo Cortés
Contents

Physiological Phenotype and Vulnerability in Parkinson’s Disease, 203
_D. James Surmeier, Jaime N. Guzman, Javier Sanchez, and Paul T. Schumacker_

Modeling Parkinson’s Disease in Primates: The MPTP Model, 231
_Gregory Porras, Qin Li, and Erwan Bezd_

A Guide to Neurotoxic Animal Models of Parkinson’s Disease, 241
_Kim Tieu_

Animal Models of Parkinson’s Disease: Vertebrate Genetics, 261
_Yunjong Lee, Valina L. Dawson, and Ted M. Dawson_

_Drosophila_ as a Model to Study Mitochondrial Dysfunction in Parkinson’s Disease, 275
_Ming Guo_

Mitochondrial Biology and Parkinson’s Disease, 293
_Celine Perier and Miquel Vila_

The Role of Autophagy in Parkinson’s Disease, 313
_Melinda A. Lynch-Day, Kai Mao, Ke Wang, Mantong Zhao, and Daniel J. Klionsky_

Disruption of Protein Quality Control in Parkinson’s Disease, 327
_Casey Cook, Caroline Stetler, and Leonard Petrucelli_

Programmed Cell Death in Parkinson’s Disease, 345
_Katerina Venderova and David S. Park_

Innate Inflammation in Parkinson’s Disease, 369
_V. Hugh Perry_

Inflammation and Adaptive Immunity in Parkinson’s Disease, 381
_R. Lee Mosely, Jessica A. Hutter-Saunders, David K. Stone, and Howard E. Gendelman_

Index, 399
Preface

Parkinson's Disease (PD) was once a taboo subject as affected individuals made every effort to hide the physical manifestations of their movement disorder. This is no longer true. Rather than hiding their affliction, politicians, artists, and world leaders with PD openly admit to their medical condition and discuss how they cope with the medical, social, and emotional challenges. Yet, the reality is that if today the public awareness of PD runs very high, our understanding of why and how the disease occurs and progresses lags behind. For every stone turned, clinical and basic researchers in the field of PD find many unturned.

If we are to devise effective therapies for this disabling disorder, we must first crack the neurobiology of PD; to do so will require recruiting talented individuals with different skill sets and visions to work in a multidisciplinary manner on the outstanding questions that still plague the field. Clinicians must be encouraged to be exposed to the basic physiology and the molecular and cellular biology of PD and, conversely, basic researchers must be exposed to the finer clinical aspects of PD.

I often hear from colleagues, both clinicians and basic scientists, who would like to join the research effort in PD, “What can I read to educate myself to the disease and the issues surrounding its neurobiology and treatment?” My colleagues in basic science often express frustration in reading clinical textbooks on the subject, because they are too cryptic and detailed for nonclinicians, and, conversely, my clinician friends are often stymied by the technical jargon and concepts that litter the pages of basic science books. I was often left wondering whether I could recommend a single book on PD to both sets of colleagues, but thus far I have been unable to identify one. Such a book would be designed specifically to bridge the clinical and basic science aspects of PD under one cover: It would be more like a textbook describing the forest rather than an overwhelming compendium describing all of the individual trees (and even branches), and it would present fundamental and practical information to the reader, but as a didactic tool with editorializing from each author, aimed at providing take-home messages and pointers.

It was with these ideas in mind that the Cold Spring Harbor Laboratory Press agreed to embark with me on the editing of this mini-textbook on bench-to-bedside understanding of PD. Each expert who agreed to contribute to this book was asked to write a chapter as if they were thinking about what they would say to a new student or faculty member interested in working on PD, irrespective of whether he/she was a basic scientist or a clinician.

Thus, readers will start their journey with the history of PD (Goetz), to set the stage and understand what PD is and how this neurological disorder was initially defined and identified. From there, chapters by Massano and Bhatia and by Dickson provide the clinical and neuropathological bases of this disease. Among other things, they stress the fact that the clinical features of PD are not limited to PD per se, but can be shared by roughly 40 different clinical conditions. Moreover, these chapters also point out that even though PD is essentially known for its motor manifestations and the loss of dopaminergic neurons, a plethora of nonmotor features also exists and nondopaminergic neurons also degenerate, all of which play a critical role in the overall expression of PD and ensuing disability.

As with other prominent adult-onset neurodegenerative conditions such as Alzheimer’s disease and amyotrophic lateral sclerosis, PD presents itself essentially as a sporadic condition, but in a handful of cases, PD can be familial. In these rare instances, the PD-like phenotype is inherited either as a dominant or recessive trait and has been linked to a variety of mutations in seemingly disparate genes. All of these rare genetic forms of PD are under intense scrutiny because of the
expectation that a better understanding of the normal roles of the gene products, and how mutations affect these functions, may provide important hints into the neurobiology of sporadic PD. Several chapters are thus dedicated to the familial forms of PD, first with the introduction to PD genetics from Klein and Westenberger and then with different chapters on selected genes linked to PD including α-synuclein (Stefanis), LRRK2 (Kett and Dauer), and PINK1/Parkin/DJ-1 (Cookson). The genetic chapters culminate in two important discussions: one by Scholz et al. on the unbiased approaches to genetics, which are becoming more popular in an attempt to tease out disease mechanisms, and the other by Coune et al. on gene therapies.

Aside from the actual mechanisms responsible for or contributing to the loss of specific types of neurons in PD, the degenerative process alters the chemical neuroanatomy of the basal ganglia, which underpins the expression of many of the motor abnormalities shown by PD patients. To discuss this important topic, Lanciego et al., Neithammer et al., and Mazzoni et al. start at the level of the patients and explore the neurochemical circuitry using functional neuroanatomy, brain imaging, and electrophysiology to provide a macroscopic view of the disease. A subsequent chapter by Surmeier et al. then discusses a more fine-grained approach to PD microscopical functional imaging techniques to further define the basal ganglia circuitry that is the target of the neurodegenerative process. A key question addressed by this type of research is why some neurons are more susceptible than others to the degenerative process in PD.

Most PD researchers interested in probing the neurobiology of this disorder rely heavily on the use of experimental models. Thus, with the series of chapters authored by Porras et al., Tieu, Lee et al., and Guo, the topic of PD modeling is covered from primate to invertebrate models and from genetic to toxic models.

The final chapters (Perier and Vila, Lynch-Day et al., Cook et al., Venderova and Park, Perry, and Mosely et al.) are dedicated to emerging and seemingly important pathogenic mechanisms in PD; among the selected topics are the roles that mitochondria, autophagy, protein quality control, programmed cell death, and neuroinflammation play in the disease process.

This is the outline of the book. Yet, before starting, I would like to add one more thing: Fasten your seatbelt, sit back, relax, and enjoy the ride in this bench-to-bedside journey. I hope that you will take as much pleasure in reading the volume as my distinguished colleagues and I have had in preparing it.

Finally, I express my gratitude to the authors who took time to contribute to this book and, at Cold Spring Harbor Laboratory Press, to Barbara Acosta and Richard Sever for their invaluable assistance and guidance during the preparation and production of the book.

Serge Przedborski
Columbia University
The History of Parkinson’s Disease: Early Clinical Descriptions and Neurological Therapies

Christopher G. Goetz

Department of Neurological Sciences and Department of Pharmacology, Rush University Medical Center, Chicago, Illinois 60612

Correspondence: cgoetz@rush.edu

Although components of possible Parkinson’s disease can be found in very early documents, the first clear medical description was written in 1817 by James Parkinson. In the mid-1800s, Jean-Martin Charcot was particularly influential in refining and expanding this early description and in disseminating information internationally about Parkinson’s disease. He separated Parkinson’s disease from multiple sclerosis and other disorders characterized by tremor, and he recognized cases that later would likely be classified among the Parkinsonism-plus syndromes. Early treatments of Parkinson’s disease were based on empirical observation, and anticholinergic drugs were used as early as the nineteenth century. The discovery of dopaminergic deficits in Parkinson’s disease and the synthetic pathway of dopamine led to the first human trials of levodopa. Further historically important anatomical, biochemical, and physiological studies identified additional pharmacological and neurosurgical targets for Parkinson’s disease and allow modern clinicians to offer an array of therapies aimed at improving function in this still incurable disease.

Important historical anchors for the study of Parkinson’s disease concern the early descriptions of the disorder, its separation from other neurological conditions, and the evolution of therapy from empirical observations to rational treatment designs based on the growing knowledge of anatomy, biochemistry, and physiology of the basal ganglia. Whereas the rest of this collection will focus on the contemporary and future directions of these issues, this article provides the background history of Parkinson’s disease, highlighting persons and discoveries primarily from the nineteenth and early twentieth centuries.

EARLY CLINICAL DESCRIPTIONS

Defining Parkinson’s Disease

Parkinson’s disease was first medically described as a neurological syndrome by James Parkinson in 1817, though fragments of Parkinsonism can be found in earlier descriptions (Parkinson 1817). As examples, Sylvius de la Boë wrote of rest tremor, and Sauvages described festination (Sylvius de la Boë 1680; Sauvages 1768; Tyler 1992). Much earlier, traditional Indian texts from approximately 1000 BC and ancient Chinese sources also provide descriptions that suggest Parkinson’s disease (Manyam 1990;
In succinct and pithy English, Parkinson captured the clinical picture:

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.

Parkinson reported on six case sketches, three of the patients observed in the streets of London and one only seen from a distance (Fig. 1). Jean-Martin Charcot, in his teaching at the Salpêtrière over 50 years later, was more thorough in his descriptions and distinguished bradykinesia as a separate cardinal feature of the illness (Charcot 1872):

Long before rigidity actually develops, patients have significant difficulty performing ordinary activities: this problem relates to another cause. In some of the various patients I showed you, you can easily recognize how difficult it is for them to do things even though rigidity or tremor is not the limiting feature. Instead, even a cursory exam demonstrates that their problem relates more to slowness in execution of movement rather than to real weakness. In spite of tremor, a patient is still able to do most things, but he performs them with remarkable slowness. Between the thought and the action there is a considerable time lapse. One would think neural activity can only be effected after remarkable effort.

Charcot and his students described the clinical spectrum of this disease, noting two prototypes, the tremorous and the rigid/akinetic form. They described in full detail the arthritic changes, dysautonomia, and pain that can accompany Parkinson’s disease. Charcot was also the first to suggest the use of the term “Parkinson’s disease” rejecting the earlier designation of paralysis agitans or shaking palsy, because he recognized that Parkinson’s disease patients are not markedly weak and do not necessarily have tremor (Charcot 1872).

William Gowers, working in London, contributed an important study of Parkinson’s disease demographics in his “Manual of Diseases of the Nervous System,” describing his personal experience with 80 patients in the 1880s. He correctly identified the slight male predominance of the disorder and studied the joint deformities typical of the disease. Known for his descriptive prose, Gowers offered one of the most memorable similes regarding Parkinsonian tremor (Gowers 1888):

The movement of the fingers at the metacarpophalangeal joints is similar to that by which Orientals beat their small drums.

Further clinical descriptions and studies of the pathologic changes related to Parkinson’s disease were predominantly reported by the French neurologic school. Richer and Meige (1895) provided clinical and morphologic details of the progressive stages of Parkinsonian disability, and the former provided drawings and statues that remain among the most important pictorial documents related to Parkinson’s disease. Babinski commented on the strange motor fluctuations intrinsic to the disease itself (Babinski 1921). Brissaud first proposed damage to the substantia nigra as the anatomical seat of Parkinson’s disease, and Trétiakov and Foix and Nicolesco pursued further pathologic studies of the midbrain in relationship to the disease during the 1920s (Trétiakov 1921; Brissaud 1925; Foix and Nicolesco 1925).

The most complete pathologic analysis of Parkinson’s disease and the clear delineation of the brain stem lesions was performed in 1953 by Greenfield and Bosanquet (Greenfield and Bosanquet 1953). The morbidity and clinical progression of Parkinson’s disease was studied in the important article by Hoehn and Yahr in which their internationally recognized staging system was first introduced. This time-honored staging system is anchored in the distinction between unilateral (Stage I) disease and bilateral disease (Stages II–V) and the development of postural reflex impairment (Stage III) as a key turning point in the disease’s clinical significance (Hoehn and Yahr 1967).

Separating Parkinson’s Disease from Other Disorders

Prior to Charcot, the classification system, or nosology, of neurological disease was primitive, and disorders were largely grouped by primary symptoms, for instance, tremors or weakness.
Figure 1. Essay on the Shaking Palsy. James Parkinson's short monograph is the first clear medical document dealing with Parkinson's disease (Parkinson 1817).
Charcot’s first important contribution to the study of Parkinson’s disease was his differentiation of this disorder from other tremorous disorders, specifically multiple sclerosis (Charcot 1872). Examining large numbers of patients within the vast Salpêtrière Hospital in Paris, he developed a protocol to observe tremor at rest and then during action. He noted that the patients with action tremor had accompanying features of weakness, spasticity, and visual disturbance. In contrast, those with rest tremor differed in having rigidity, slowed movements, a typical hunched posture, and very soft speech. His early tremor studies were highly publicized and helped to establish Parkinson’s disease as a distinct neurological entity that could be confidently diagnosed (Fig. 2).

Once the archetype of Parkinson’s disease was established, Charcot and his students identified variants with features that were atypical of classical Parkinson’s disease. These were termed Parkinson’s disease without tremor, Parkinson’s disease with extended posture, and Parkinson’s disease with hemiplegia. These cases are of historical interest, because they are likely examples of disorders that would later be grouped under the term, Parkinsonism-plus syndromes, including progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy. As one example, Charcot presented a patient named Bache`re on several occasions. On June 12, 1888, Charcot emphasized that Bache`re did not have marked tremor, and in contrast to the usual arm flexion of typical Parkinson’s disease, he had a stiff and extended posture.

Look how he stands. I present him in profile so you can see the inclination of the head and trunk, well described by Parkinson. All this is typical. What is atypical, however, is that Bache`re’s...
forearms and legs are extended, making the extremities like rigid bars, whereas in the ordinary case, the same body parts are partly flexed. One can say then that in the typical case of Parkinson’s disease, flexion is the predominant feature, whereas here, extension predominates and accounts for this unusual presentation. The difference is even more evident when the patients walk (Fig. 3) (Goetz 1987; Charcot 1888a).

In addition to extended posture, this patient had particular facial bradykinesia and contracted forehead muscles. Charcot commented that the patient had the perpetual look of

Figure 3. Atypical Parkinsonism. (A) Drawing from Charcot’s original lesson, given on June 12, 1888, in which he contrasted a typical Parkinson’s disease showing a flexed posture (left) with a Parkinsonian variant that included the absence of tremor and extended posture (right). Charcot regularly taught his students by comparing and contrasting cases of patients from the Salpêtrière inpatient and outpatient services. (B) Four drawings by Charcot from his lesson on atypical Parkinson’s disease, dated June 12, 1888, showing the distinctive facial features of his patient, Bacheère, showing forehead muscles and superior orbicularis in simultaneous contraction, activation of the palpebral portion of the orbicularis and combined activation of the frontalis superior portion of the orbicularis and platysma, giving a frightened expression in contrast to the placid, blank stare of typical Parkinson’s disease patients. This case is a compelling case of likely progressive supranuclear palsy (Goetz, 1987; Charcot 1888a).
surprise, because the eyes remained widely opened and the forehead continually wrinkled (Fig. 3) (Goetz 1987; Charcot 1888a). In a modern setting, Jankovic has detailed similar facial morphology in Parkinsonism-plus patients, specifically those with progressive supranuclear palsy (Jankovic 1984). No specific supranuclear eye movement abnormalities were described. Another Salpêtrière patient with “Parkinson’s disease in extension” was described by Dutil in 1889 and eye movement abnormalities are mentioned, although a supranuclear lesion is not documented clinically (Dutil 1889; Goetz 1996). This case also had highly asymmetric rigidity of the extremities, a feature more reminiscent of corticobasal degeneration than progressive supranuclear palsy. In this case, the extended neck posture was graphically emphasized:

The face is masked, the forehead wrinkled, the eyebrows raised, the eyes immobile... This facies, associated with the extended posture of the head and trunk, gives the patient a singularly majestic air (Dutil 1889; Goetz 1996).

With clinical features reminiscent of both progressive supranuclear palsy and corticobasal degeneration, this patient was mentioned in several articles from the Salpêtrière school, although no autopsy was apparently performed. Collectively, these cases show that even the earliest diagnosticians recognized classic Parkinson’s disease and cases that needed to be distinguished from it. Today, these Parkinsonism-plus diagnoses are known to have additional distinctive features, including poor response to dopaminergic therapies and different pathological lesions than seen in Parkinson’s disease.

This condition has largely disappeared in the twenty-first century, because the survivors have died and no recurrence of an epidemic of this magnitude has recurred. Other important forms of atypical Parkinsonism to be distinguished from Parkinson’s disease include a juvenile form of Parkinson’s disease, originally described by Willige in 1911 (Willige 1911), with a more full description and its association with atrophy of the globus pallidus provided by Ramsey Hunt and van Bogaert (Ramsey Hunt 1917; van Bogaert 1930).

In the years after these pioneering papers, the concepts of neural circuits evolved with key nuclei of importance to the clinical presentation of Parkinsonism being the substantia nigra, the globus pallidus, and the caudate nucleus and putamen (striatum). Involvement of the striatum resulting in Parkinsonism was documented in a variety of neurological disorders. Striatal-nigral degeneration was described by Adams, van Bogaert, and Vander Eecken, and, though originally classified as a single disease, it has since been merged into the larger diagnosis of multiple system atrophy (Adams et al. 1964). Parkinsonian states related to striatal pathology were later identified in the form of Huntington’s disease, in which a Parkinsonian presentation is referred to as the Westphal variant (Westphal 1883) and in cases of striatal calcification, either on a hereditary basis (Bruyn et al. 1964) or as an acquired metabolic disorder often related to hypoparathyroidism (Muenter and Whisnant 1968).

The historical discussion of Parkinsonian disorders that are frequently confused with Parkinson’s disease includes drug-induced and toxin-induced cases as well. The introduction of the antipsychotic agents, originally termed neuroleptics, led to dramatic improvements in schizophrenic and other psychotic behaviors, but induced Parkinsonism largely indistinguishable from Parkinson’s disease itself (Steck 1954). Later understanding that these drugs block dopamine receptors in the striatum explained this clinical presentation and led to the development of antipsychotic drugs with lower proclivity to block striatal receptors and less propensity to induce Parkinsonism. The
landmark observation on a cluster of young patients who presented with severe Parkinsonism that appeared to be typical Parkinson's disease except for the young onset and severity of signs led to the discovery that the causative agent was a self-administered narcotic derivative, MPTP, that selectively damages the substantia nigra (Langston et al. 1983). This product has provided a means to induce Parkinsonism in experimental animals and remains the "gold standard" model to study Parkinson's disease in preclinical studies of new treatments for Parkinson's disease.

THE EVOLUTION OF TREATMENTS

The history of Parkinson's disease is tightly linked to therapeutic interventions, ranging from serendipitous observations to controlled clinical trials of specifically designed agents.

Parkinson devoted a chapter of his monograph to "considerations respecting the means of cure" (Parkinson 1817). In humility and perhaps with a vision toward current concepts of neuroprotection, he hoped for the identification of a treatment by which "the progress of the disease may be stopped" (Parkinson 1817). To this end, he advocated very early therapeutic intervention when signs were largely confined to the arms without balance and gait impairments. Reflecting therapeutic approaches of the early nineteenth century, Parkinson recommended venesection, specifically advocating bloodletting from the neck, followed by vesications to induce blistering and inflammation of the skin. Small pieces of cork were purposefully inserted into the blisters to cause a “sufficient quantity” of purulent discharge (Parkinson 1817). All these efforts were designed to divert blood and inflammatory pressure away from the brain and spinal cord, and in this way, decompress the medulla that Parkinson considered the seat of neurological dysfunction.

Pharmacological Advances: Charcot and Gowers

Being the two most celebrated clinical neurologists of the nineteenth century, Jean-Martin Charcot and William Gowers serve as important icons for the study of standard and emerging treatments for Parkinson's disease. Charcot's intern, Ordenstein, wrote his medical thesis on the treatment of Parkinsonian tremor with belladonna alkaloids, the first well-established treatment of Parkinson's disease (Ordenstein 1972). These agents are centrally active anticholinergic drugs that later would be understood to affect the cholinergic/dopaminergic balance in the striatum and thereby improve Parkinsonism. The credit of the observation of anticholinergic efficacy surely belongs to Charcot himself who managed his Salpêtrière School with strict centralized supervision and oversaw every aspect of the neurological program. As with other young and aspiring students like Gilles de la Tourette and Pierre Marie, Ordenstein profited from publishing the observation with his name as sole author, but contemporaries would not have been deluded into thinking of it as coming from anyone besides Professor Charcot. Of the many centrally active anticholinergic agents of the era, Charcot's preferred product for Parkinson's disease was hyoscymine. This plant-based agent was prepared as pills, usually powder rolled into bits of white bread, or as a syrup. As shown in a prescription located in the Philadelphia College of Physicians, Charcot's anticholinergic treatment was sometimes combined with rye-based ergot products that in fact are the pharmacological basis of some modern dopamine agonists, drugs that directly stimulate striatal dopamine receptors and thereby simulate the activity of dopamine itself (Fig. 4). Although Tyler has aptly documented that Charcot was not the first interventionist to advocate hyoscymine (Tyler 1992), Charcot's name became linked to the drug because of the widespread international publication of his lectures and classroom demonstrations.

A unique historical opportunity to examine the early treatment of Parkinson's disease is provided by a series of 18 unpublished letters in the Charcot collection at the Bibliothèque Charcot in Paris (Portfolio MAVIII: Parkinson's disease). These letters cover a period of at least 15 months from January 1863 through March 1864. Although the collection only contains
the patient’s letters and not Charcot’s replies, one can follow the doctor–patient interaction because of Charcot’s technique of closing his letters traditionally with: “I would be most obliged Monsieur, if you would remind me of this prescription the next time you write.” The patient’s letters therefore systematically begin with a summary of the prescribed therapy and follow with the patient’s own observations. In addition to hyoscyamine and ergot-based products, Charcot advocated an overall program of rest and reduced stress. This type of therapy
was generally advocated for many primary neurological disorders (Mitchell 1908). For this patient, he added camphor, silver nitrate, iron compounds, henbane pills, and zinc oxide. The rationale for using these agents was not explained by Charcot, and their pharmacology does not involve the dopamine system. The use of iron may have been based on Romberg’s earlier observation that carbonate of iron in association with warm baths and cold affusions to the head and back induced “a marked diminution of symptoms.” (Romberg 1846). Whether based on his own experience or Romberg’s warning against trying strychnine, Charcot steered away from this therapy for Parkinson’s disease patients. Charcot was highly specific in his instructions, insisting that quinquina, a quinine derivative, must be diluted with syrup made from orange rind and each dose of silver nitrate must be impregnated in 9 g of soft bread to form an ingestible pill. The letters communicate encouragement to the patient, reinforce the need for patience in facing chronic illness, and a willingness to consider new treatment strategies if traditional ones were unsuccessful. However, his enthusiasm to try new interventions never clouded his objective vision of efficacy. In reviewing pharmacologic treatments for Parkinson’s disease in 1872, Charcot stated:

Everything, or almost everything, has been tried against this disease. Among the medicinal substances that have been extolled and which I have myself administered to no avail, I need only enumerate a few (Charcot 1872).

In rejecting most medicines, Charcot advocated vibratory therapy for the management of Parkinson’s disease. Charcot had observed that after long carriage, train, or horseback rides, patients with Parkinson’s disease experienced marked symptom amelioration. He therefore developed a replication device to provide rhythmic movement by an electrically powered “shaking chair” (fauteuil trepidant) (Fig. 5) (Charcot 1892a). His student, Gilles de la Tourette, fashioned a helmet that was more easily transported and vibrated the brain rather than the body (Goetz et al. 1995). Other used therapies included hydrotherapy, spa treatments, and light exercise. Electrical stimulation by faradic, galvanic, or direct spark (franklinization) therapy was used to stimulate weakened muscles. Charcot was, however, adamant that patients with Parkinson’s disease were not particularly weak, having tested them with dynamometers and finding their strength to be normal for most of the duration of illness. It was partly for this reason that he dismissed the terms, paralysis agitans and shaking palsy,
and advocated instead the designation, Parkinson’s disease.

A more unusual and hazardous early treatment of Parkinson’s disease involved the use of a suspension apparatus to stretch the spinal cord (Goetz et al. 1995). Developed in 1883 in Russia, the apparatus gained celebrity when Charcot examined its safety and efficacy in a variety of disorders, including Parkinson’s disease. Using gravity and the patient’s weight to put excessive vertical traction on the spinal cord and nerves, the therapist hoisted the subject in mid-air with a pulley and a harness that slipped under the chin and occiput. In Parkinson’s disease patients, rigidity and some sensory symptoms improved, but tremor was not ameliorated. Edmond de Goncourt described the therapy with allusions to the macabre artwork of Goya, and the serious side effects and stress on patients led Charcot to abandon this strategy shortly after its introduction in France (de Goncourt and de Goncourt 1887–1889).

Charcot’s British contemporary, WR Gowers, followed similar treatment strategies. He stressed the negative effects of mental strain and physical exhaustion, advocating that “life should be quiet and regular, freed, as far as may be, from care and work.” (Gowers 1899). For tremor, he used hyoscyamine and also noted arsenic, morphia, conium (hemlock), and “Indian hemp” (cannabis) as effective agents for temporary tremor abatement. Writing specifically of the power of cannabis and opium in combination, he stated: “I have several times seen a very distinct improvement for a considerable time under their use.” (Gowers 1899). Today, cannabis is known to have some dopaminergic activation properties, but opium affects the motor system in a generalized, sedative manner without direct or primary dopaminergic involvement.

**Levodopa and Dopamine-Based Therapies**

Through the mid-twentieth century, the treatment of Parkinson’s disease remained largely that of the nineteenth century, and though a wide variety of centrally active anticholinergic drugs were developed and used, they all were similar in their efficacy and side effect profiles. In the *Handbook of Clinical Neurology*, the chapter, “Drug treatment of parkinsonism and its assessment” (published in 1968) discusses ten synthetic anticholinergic compounds and a potpourri of agents under the designation “Other drugs which have been recommended, some of them without any justification.” (Onuguluchi 1968). The emphasis of this period remained on supportive physical therapy and the management of hypersalivation, seborrhea, decubiti, and infections. In the context of this relative stagnation, the impact of levodopa was magnified.

As summarized by Hornykiewicz, dopamine was first synthesized in 1910 by G. Barger and J. Ewens (Hornykiewicz 2002). In the same year, H. Dale discovered its weak sympathomimetic qualities. These observations were later remembered when P. Holtz discovered the enzyme, dopa decarboxylase and documented that levodopa was synthesized to dopamine through its action. At this time, dopamine was relegated to a simple intermediate compound for the synthesis of noradrenaline and adrenaline. The consistent identification of substantial amounts of dopamine in various tissues, however, prompted the search for a more primary role. Working in Blaschko’s Cambridge University laboratory, Hornykiewicz studied blood pressure control in experimental animals and clearly confirmed that dopamine had distinct effects independent of other catecholamines. Shortly thereafter, in the late 1950s, two seminal discoveries occurred: dopamine localization within the brain, specifically in the striatum; and the development of the reserpine-model, later to be used as the first model of Parkinsonism that was reversed by levodopa treatment. In concert, these discoveries rapidly advanced hypotheses on the role of dopamine loss in the pathogenesis of Parkinson’s disease itself (Carlsson et al. 1958; Sano et al. 1959), and led Bertler and Rosengred to conclude that “dopamine is concerned with the function of the striatum and thus with the control of movement.” (Bertler and Rosengred 1959). Ehringer and Hornykiewicz turned to human brain and after examining a series of
control specimens, discovered the striatal dopamine depletion in Parkinson’s disease and postencephalitic parkinsonism brains (Ehringer and Hornykiewicz 1960). With the knowledge that levodopa was the natural precursor to dopamine, Hornykiewicz was now prepared to suggest human trials in Parkinson’s disease patients.

Birkmayer received Hornykiewicz’s supply of laboratory levodopa and injected it intravenously for the first time to Parkinsonian patients in 1961. The antiakinetic effects were quickly published:

Bed-ridden patients who were unable to sit up, patients who could not stand up when seated, and patients who when standing could not start walking performed all these activities with ease after L-dopa [levodopa]. They walked around with normal associated movements and they could even run and jump. The voiceless, aphonie speech, blurred by palilalia and unclear articulation, became forceful and clear as in a normal person (Birkmayer and Hornykiewicz 1961).

Subsequent open-label levodopa trials with oral preparations confirmed both short and long-term benefits, and a double-blind placebo controlled trial followed (Barbeau 1969; Cotzias et al. 1969; Yåhr et al. 1969). These reports launched levodopa’s establishment as the premier agent to treat Parkinson’s disease symptoms and signs. Although new formulations and peripherally acting dopa-decarboxylase inhibitors have added new dimensions to the therapy, none of these events rival the first discoveries.

Given that levodopa is a naturally occurring amino acid, researchers have reexamined older therapies to search for possible discoveries of levodopa-containing compounds in early medicine. Of note, cowage or cowitch plant (Mucuna pruriens) is known under the name of Atmagupta in Sanskrit and contains levodopa (Manyam 1990). One of the remedies used to treat the condition thought to be possible Parkinson’s disease in traditional Indian medicine is called Masabaldi Pacana, which contains beans of Mucuna pruriens. These observations offer interesting, albeit indirect, evidence that patients with Parkinsonism may have experienced the benefit of levodopa early in the history of medicine.

The more modern discoveries of dopamine agonists and enzyme inhibitors that enhance the bioavailability of dopamine (monoamine oxidase inhibitors and catechol-O-methyl transferase inhibitors) date to the contemporary period and are of less importance to this historical review that emphasizes early discoveries. These developments have been based on the logical understanding of the dopamine system, metabolic pathways, and receptor populations. Further discoveries of modulating influences by serotonin, adenosine, GABA, and glutamate systems have opened horizons for further pharmacological developments. The history of amantadine is of interest because of its serendipitous discovery as an anti-Parkinsonian agent. Developed as an antiviral agent, it was used widely in nursing home populations, and Schwab noted its unexpected benefit on tremor, balance, and akinesia in both Parkinson’s disease and postencephalitic parkinsonian patients (Schwab et al. 1969). This agent has mild dopamine effects, likely due to inhibition of striatal synaptic dopamine reuptake so that more dopamine is left within the synapse to activate dopamine receptors. It has effects on the glutaminergic system with likely indirect effects on dopamine function through this mechanism.

Surgery

In the early 1900s, surgery for movement disorders was pioneered by V. Horsley and his engineering colleague, R.H. Clarke (Fig. 6). They developed early stereotaxic equipment to target brain nuclei, though their early surgeries dealt with hyperkinetic disorders rather than Parkinson’s disease (Horsley and Clarke 1908). Bucy and Case and Klemme excised cerebral cortex to treat Parkinsonian tremor, but this type of ablative surgery induced hemiparesis and was abandoned (Bucy and Case 1939; Klemme 1940). Meyers first focused on the basal ganglia as a lesion target for abating Parkinsonian tremor in the 1940s and noted that rigidity improved as well as tremor.
Importantly, spasticity and paresis did not compromise the improvement (Meyers 1940). In 1953, by accident, I. Cooper cut the anterior choroidal artery during surgery on a Parkinsonian patient and was forced to ligate it to prevent a hematoma. The unexpected and remarkable relief of tremor and rigidity on the contralateral side led to more widespread use of this procedure, though mortality was approximately 10% (Cooper 1953). Electrical coagulation procedures involving the globus pallidus, thalamus, and the ansa lenticularis (ansotomy) were performed with early stereotaxic procedures (Spiegel and Wycis 1954). Hassler and Reichert focused more directly on the ventrolateral nucleus of the thalamus, also referred to as the Ventral Oralis Anterior (Voa) nucleus (Hassler 1955; Reichert 1962). All these reports were hampered by the lack of involvement by medical neurologists with resultant concerns of incomplete reporting, lack of long-term follow-up and potential minimalization of morbidity. Further, the role of surgery was eclipsed by the advent of levodopa in the 1960s, so that a long hiatus occurred when surgery was not extensively used in Parkinson’s disease. During this time, however, more advanced surgical techniques were developed, and these innovations would be later applied to Parkinson’s disease patients near the end of the twentieth century. Such treatments date to the contemporary period and include pallidotomy, subthalamic nucleus ablation, deep brain stimulation to thalamus, pallidum and subthalamus, and various transplantation procedures. Most recent are the developments of gene-based therapies that have entered clinical trials.

Placebo Therapy

The relationships between dopamine release and positive motivation, novelty seeking behaviors, and attention have allowed researchers to understand the long-acknowledged placebo impact on Parkinson’s disease. The Charcot letters cited above suggest that Charcot too understood clearly the importance of his presence and command over the patient’s well-being. As anchored as he remained in neuroanatomical concepts through the end of his career, Charcot’s last monograph was titled “Faith Cure” and dealt with the profound improvements that some patients with neurological disease experienced through nontraditional therapies (Charcot 1892b). Placebo-controlled trials have become standard in Parkinson’s disease, even in the surgical arena, mainly because a large percentage of patients on placebo treatment experience objective improvement in Parkinsonism (Goetz et al. 2008).
striatal dopaminergic activity in these settings has been shown by neuroimaging techniques (de la Fuente-Fernandez et al. 2001). The funding of federal grants for the specific study of placebo effects in Parkinson's disease is, in itself, of historical significance (Goetz et al. 2008).

CONCLUDING REMARKS

Historical documents on Parkinson’s disease and descriptions that evoke Parkinsonism from eras prior to the first full medical delineation of the disease provide a continuing source of potential neurological insights. As only one example, summarized in a review of traditional and complementary therapies for Parkinson’s disease (Manyam and Sánchez-Ramos 1999), in 1928, Lewin isolated an alkaloid from the Banisteriopsis caapi vine used in ceremonial medicine among Amazonian tribes. He provided purified banisterine to his colleague, Beringer, who tested it on patients with Parkinson’s disease with reported marked benefit. The data were presented to the Berlin Medical Association along with a film documenting the changes in rigidity, bradykinesia, and gait impairment. Though this agent was not pursued further, the example underscores the potential lessons from careful reading of traditional medicine sources and the prospects for new discoveries based on older observations. Charcot’s advocacy for vibratory therapy has been tested in a modern setting (Kapur et al. 2011), but Gowers’ encouraged use of Cannabis has yet to be systematically evaluated with strong clinical trial methodology. Numerous other therapies have suggestive roles in Parkinson’s disease but have not been rigorously tested, including specific forms of physical exercise, massage therapy, and relaxation techniques. The active participation of the Parkinsonian subject in these treatments complicates a controlled study design, but these interventions scientifically deserve to be tested with the same rigor as new pharmacological or surgical treatments. In the continuing search for therapies to ameliorate current disability and to slow the natural deterioration that is implicit to Parkinson’s disease today, the guiding words of Charcot remain modern and applicable: “If you do not have a proven treatment for certain illnesses, bide your time, do what you can, but do not harm your patients” (Charcot 1888b).

ACKNOWLEDGMENTS

Dr. Goetz acknowledges the Parkinson’s Disease Foundation that supports the Rush University Medical Center Parkinson’s Disease and Movement Disorder Program with an annual grant.

REFERENCES


Index

A
AADC. See Aromatic amino acid decarboxylase
AAV. See Adeno-associated virus
Acetylcholine (ACh), functional imaging, 174–175
ACh. See Acetylcholine
Adaptive immune system
   central nervous system, 381–382
   cross-regulation with innate immunity in central nervous system, 382–384
   misfolded proteins in immune activation, 384–385
   Parkinson’s disease dysfunction, 385–388
   prospects for study, 391
   therapeutic targeting, 388–391
Adeno-associated virus (AAV)
   gene therapy vectors, 129
   mouse models of Parkinson’s disease, 265
Aging
   DNA polymerase-γ studies in mutant mice, 218
   macroautophagy in protein quality control effects, 336
   mitochondria aging hypothesis, 211–213, 305–306
Akinesia, motor control, 196–198
α-Methyl-p-tyrosine, animal models of Parkinson’s disease, 24
α-Synuclein (SNCA)
   aggregation potential, 69–70
   autophagy
      autophagy response, 317–318, 337
      chaperone-mediated autophagy degradation, 316
      inhibition by mutant forms, 316–317, 336–337
   mitophagy role, 318
   autosomal dominant Parkinson’s disease clinical features, 24, 54–55
   biomarkers, 77–78
   function, 67–69
   gain-of-function and accumulation, 72–74
   gene dosage in Parkinson’s disease, 66
   knockdown therapy, 135–136
   Lewy body, See Dementia with Lewy bodies; Lewy body
   lipid interactions, 71–72
   loci. See PARK1; PARK4
   misfolded proteins in immune activation, 384–385
   pathogenic effects
      cytoskeleton, 74–75
   endoplasmic reticulum/Golgi apparatus, 76
   lysosome, 75
   mitochondria, 75
   nucleus, 76
   proteasome, 75
   secretion and uptake, 77
   synapse, 74
   posttranslational modifications, 70–71
   protein–protein interactions, 71
   structure, 67–68
   synucleopathy models, 69
   therapeutic targeting, 77–78
   transgenic mouse, 266–267
   ubiquitin proteasome system effects of mutation, 331–332
AMPA receptor, neuronal phenotype of Parkinson’s disease, 204
Amphetamines, animal models of Parkinson’s disease, 248–249
Animal models.
   See α-Methyl-p-tyrosine; Amphetamines; Drosophila; 6-Hydroxydopamine; Isoquinoline; Lipopolysaccharide; 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; Mouse models; Paraquat; Reserpine; Rotenone
Apoptosis. See Programmed cell death
Aromatic amino acid decarboxylase (AADC), gene therapy, 130–131
ATP13A2, mutation
   Parkinson’s disease, 57–58
   ubiquitin proteasome system dysfunction, 337–338
Autophagy
   α-synuclein
      autophagy response, 317–318, 337
      chaperone-mediated autophagy degradation, 316
      inhibition by mutant forms, 316–317, 336–337
   mitophagy role, 318
   cytoplasmic cell death overview, 355
   paranatos, 355–356
   necroptosis, 356
   DJ-1 role, 322
   functions, 315–316
   leucine-rich repeat kinase-2 role, 321–322
   macroautophagy in protein quality control
Autophagy (Continued)
aging effects, 336
impairment in Parkinson’s disease, 336
overview, 334–335
oxidative stress effects, 335–336
mitophagy
parkin-dependent mitophagy, 320
Parkinson’s disease, 319–320
molecular mechanisms, 315
organellar specificity, 314–315
PINK1 function
isoforms, 321
overview, 320–321
protective function, 321
programmed cell death
defects in Parkinson’s disease, 353–354
mitophagy, 354–355
overview, 353–354
prospects for study in Parkinson’s disease,
322, 356–357
types, 313–314, 333–334
Autosomal dominant Parkinson’s disease
clinical features, 24–25
gene mutations, 24–25, 54–55
mouse models, 263
pedigrees, 50, 52–53
Autosomal recessive Parkinson’s disease
clinical features, 25–26
gene mutations, 25–26, 56–57
mouse models, 264
pedigrees, 50, 52–53
B
Basal ganglia
function and motor symptoms, 198–199
functional imaging at rest, 168
functional organization
classic model, 152–154
corticostriatal connections, 155
corticosubthalamic connections, 155–156
domains, 154–155
subcortical connections, 156
gross anatomy, 143–144
nuclei
globus pallidus external segment, 150
substantia nigra pars compacta, 151–152
subthalamic nucleus, 150–151
pathophysiology
dyskinesia, 157
parkinsonism, 156–157
striatum
compartments, 146–147
output nuclei
globus pallidus internal segment, 149
substantia nigra pars reticulata, 149–150
projections
afferents, 147–149
efferents, 149
neurons and interneurons, 144–145
Bcl-2 proteins, apoptosis mediation, 349–350
β-Glucocerebrosidase (GBA)
α-synuclein accumulation effects, 75
mutation and Parkinson’s disease risk, 58–59
bioinformatics
biomarker discovery, 118–120
overview, 115–116
Braak staging, Parkinson’s disease, 41
Bradykinesia
motor control, 192–196
Parkinson’s disease, 18
speed selection abnormalities, 186
C
Calcium flux
L-type calcium channels
dopaminergic neuron susceptibility role in Parkinson’s disease, 214–216
therapeutic targeting, 221–223
metabolic burden on neurons, 205–207
mitochondria in homeostasis, 207–208, 294,
301–303
neuronal pacemaking and ionic homeostasis challenge, 208–209
neuron vulnerability in Parkinson’s disease
dopaminergic neurons, 213–220
nondopaminergic neurons, 220
Caspase, activation in apoptosis, 348, 350
CBD. See Corticobasal degeneration
CDK5. See Cyclin-dependent kinase-5
Charcot, Jean-Martin, 2, 4–5, 7–10, 12, 17
Chronic traumatic encephalopathy (CTE),
overview, 43
Clarke, Robert Henry, 11–12
Clinical presentation, Parkinson’s disease
autosomal dominant Parkinson’s disease, 24–25
autosomal recessive Parkinson’s disease, 25–26
exclusion criteria, 38
historical perspective, 1–7
motor symptoms
animal models
assessment, 253–254
MPTP monkey model, 233–234
bradykinesia, 18
overview, 186–188
postural and gait impairment, 19
rest tremor, 18–19
rigidity, 19
nonmotor symptoms, 19–20
Corticobasal degeneration (CBD), overview, 43
CTE. See Chronic traumatic encephalopathy
Cyclin-dependent kinase-5 (CDK5), dysfunction in Parkinson's disease, 351–352

D
Dardarin. See Leucine-rich repeat kinase-2
Default mode network (DMN), functional imaging, 171–173
Dementia with Lewy bodies (DLB) differential diagnosis, 23
parkinsonism etiology, 25
Diagnosis, Parkinson's disease clinical examination, 21
criteria, 22
differential diagnosis
dementia with Lewy bodies, 23
drug-induced parkinsonism, 22–23
essential tremor, 23
fragile X-tremor ataxia syndrome, 24
multiple system atrophy, 23, 37–39
progressive supranuclear palsy, 23–24, 37–39
vascular parkinsonism, 22
historical perspective, 1–7
imaging, 21–22
incorrect diagnosis features, 21
medical history, 20
DIP. See Drug-induced parkinsonism
DJ-1
apoptosis protection, 347–348
autophagy role, 322
autosomal recessive Parkinson's disease clinical features, 26, 57, 100
Drosophila studies of PINK1/Parkin pathway modulation, 285
evolution, 100–101
function, 104–106
genetic testing, 59
knockout mouse, 268–269
locus. See PARK7
mutation studies of parkinsonism development, 101–102
prospects for study, 106
DLB. See Dementia with Lewy bodies
DMN. See Default mode network
DNA polymerase-γ (POLG)
aging studies in mutant mice, 218
mutation effects, 298
L-Dopa. See Levodopa
Dopamine
history of Parkinson's disease treatment, 10–11
striatum dopamine quantification in animal models of Parkinson's disease, 252
Drosophila
advantages as Parkinson's disease model system, 277–278
gene identification in Parkinson's disease, 276–277
genetic and compound screening, 279
knockdown studies, 279
mutagenesis and loss-of-function studies, 278
overexpression studies, 278–279
prospects for Parkinson's disease studies, 285–286
PTEN-induced putative kinase-1/Parkin pathway studies
links with other PARK loci, 284–285
mitochondrial fission promotion and fusion inhibition, 281–282
mitochondrial integrity, 279–281
mitochondrial transport, 283–284
mitophagy promotion, 282–283
site-specific transgenesis, 279
Drug-induced parkinsonism (DIP)
differential diagnosis, 22–23
drug types, 25
Dyskinesia. See specific dyskinesias

E
Endoplasmic reticulum (ER)
α-synuclein mutant effects, 76
apoptosis response, 351
protein quality control. See Autophagy; Ubiquitin proteasome system
Epidemiology, Parkinson's disease, 17–18
ER. See Endoplasmic reticulum
Essential tremor (ET), differential diagnosis, 23
ET. See Essential tremor

F
FDDNP, protein aggregation imaging, 175–176
FDOPA. See Positron emission tomography
fMRI. See Functional magnetic resonance imaging
Fragile X-tremor ataxia syndrome (FXTAS), differential diagnosis, 24
Functional magnetic resonance imaging (fMRI) default mode network, 171–173
principles, 165
FXTAS. See Fragile X-tremor ataxia syndrome

G
GAD. See Glutamic acid decarboxylase
Gaucher's disease, parkinsonism risks, 337–338
GBA. See β-Glucocerebrosidase
GCH-1. See GTP cyclohydrolase-1
GDNF. See Glial-derived neurotrophic factor
Gene therapy
enzyme replacement
aromatic amino acid decarboxylase, 130–131
glutamic acid decarboxylase, 132–133
GTP cyclohydrolase-1, 130, 132
tyrosine hydroxylase, 130, 132
Index

Gene therapy (Continued)
glial-derived neurotrophic factor, 134–135
principles, 127–128
viral vectors
adeno-associated virus, 129
lentivirus, 128
Genetics, Parkinson’s disease
classification by loci, 50–51
genetic testing, 59
identification of new genes and risk
factors, 53–54
linkage analysis, 53–54
loci. See specific loci
monogenetic Parkinson’s disease, 54–58
pedigrees, 50, 52–53
risk gene mutations in Parkinson’s
disease, 58–59
Genomics, Parkinson’s disease
aberrant network activity identification, 116–118
bioinformatics
biomarker discovery, 118–120
overview, 115–116
historical perspective, 113–114
Mendelian versus complex disease, 112–113
therapeutic application, 120–122
Glial-derived neurotrophic factor (GDNF)
α-synuclein knockdown therapy, 135–136
direct injection studies, 133–134
functional overview, 133
gene therapy, 134–135
parkin, 136–137
prospects, 137–138
Globus pallidus
external segment, 150
internal segment, 149
Glutamic acid decarboxylase (GAD), gene therapy,
132–133
Gowers, William, 2, 7, 10
GTP cyclohydrolase-1 (GCH-1),
gen gene therapy, 130, 132

H
Historical perspective, Parkinson’s disease
clinical descriptions, 1–3
differential diagnosis, 2, 4–7
genomics, 113–114
treatment, 7–13
Horsley, Victor, 12
HtrA2. See Omi/HtrA2
6-Hydroxydopamine (6-OHDA)
animal models of Parkinson’s disease, 244
brain physiology, 243–244
structure, 242
toxicity mechanisms, 246
Hypokinesia, motor control, 192–195

Inflammation
adaptive immune response. See Adaptive immune
system
innate immune response. See Innate immune system
Innate immune system
cross-regulation with adaptive immunity in central
nervous system, 382–384
inflammation in Parkinson’s disease
animal Parkinson’s disease model studies
lipopolysaccharide, 376
overview, 374
toxin models, 374–375
transgenic mouse studies, 375–376
epidemiological studies, 374
microglia
activation in Parkinson’s disease, 372–374
activators, 376
characteristics and functions in brain,
370–372
prospects for study, 377
systemic inflammation impact on innate
immune cells, 372
T cell activation, 374
misfolded proteins in immune activation, 384–385
Isoquinoline, animal models of Parkinson’s disease,
249–250

J
Jellinger staging, multiple system atrophy, 42

K
Knockout mouse. See Mouse models

L
Lentivirus, gene therapy vectors, 128
Leucine-rich repeat kinase-2 (LRRK2)
autophagy role, 321–322
autosomal dominant Parkinson’s disease clinical
features, 25, 55–56, 91–92
discovery, 89–90
functions
cytoskeleton, 93–94
membrane trafficking, 92–93
Parkinson’s disease protein pathway
overlap, 95
genetic testing, 59
locus. See PARK8
mutation
frequency, 90–91
functional effects, 94
sites, 92
protein–protein interactions, 92
structure, 92
transgenic mouse, 267
Levodopa, history of Parkinson's disease

treatment, 10–11
Levodopa-induced dyskinesia (LID)
functional imaging, 168–170
MPTP monkey model, 235
Lewy body. See also α-Synuclein; Dementia with
Lewy bodies
characteristics, 39–40
detection in animal models of Parkinson's
disease, 252–253
immunohistochemistry
multiple system atrophy, 35–36
Parkinson's disease, 35–36, 67
multiple system atrophy glial cytoplasmic
inclusions, 40, 66
Lipopolysaccharide (LPS)
animal models of Parkinson's disease, 250
innate inflammation studies in Parkinson's
disease models, 376
LPS. See Lipopolysaccharide
LRRK2. See Leucine-rich repeat kinase-2
L-type calcium channel. See Calcium flux

M
Macrophage. See Microglia
Magnetic resonance imaging (MRI), Parkinson's disease
diagnosis, 22
Methamphetamine, animal models of Parkinson's
disease, 248–249
N-Methyl-D-aspartate receptor (NMDAR), neuronal
phenotype of Parkinson's disease,
204–205
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
(MPTP)
mitochondria effects, 296
monkey models of Parkinson's disease
anatomo-pathology, 232–233, 245
behavioral assessment, 235
cognitive impairment, 234
dyskinesia, 235
Lewy body lack, 233
limitations, 235–236
motor symptoms, 233–234
sleep disturbances, 234–235
species, 232
mouse models of Parkinson's disease, 236–237
species response in modeling Parkinson's disease,
231, 245
structure, 242
toxicity mechanisms, 245
ubiquitin proteasome system effects, 332
Microglia
activation in Parkinson's disease, 372–374, 387
activators in Parkinson's disease, 376
characteristics and functions in brain, 370–372
Mitochondria
aging hypothesis, 211–213, 305–306
α-synuclein function, 75, 318–319
calcium homeostasis role, 207–208, 294,
301–303
compartments, 293–294
Drosophila studies of PINK1/Parkin pathway
links with other PARK loci, 284–285
mitochondrial fission promotion and fusion
inhibition, 281–282
mitochondrial integrity, 279–281
mitochondrial transport, 283–284
mitophagy promotion, 282–283
dynamics
fusion/fission, 298–300
motility and regional distribution, 300–301
turnover, 301
mitophagy. See Autophagy
neuronal function, 209–210
oxidative phosphorylation system
complex I blockade consequences, 296
overview, 295
oxidative stress, 210–211
Parkinson's disease dysfunction overview, 306–307,
318–319
Parkin targets, 320
programmed cell death
fragmentation, 352–353
pathways, 303–305, 349
Monkey models. See 1-Methyl-4-phenyl-1,2,3,6-
tetrahydropyridine
Motor control
akinesia, 196–198
animal model assessment, 253–254
bradykinesia, 192–196
hypokinesia, 192–195
levels of description, 189–190
motor symptom to motor control, 190–191
overview, 188
rigidity, 190–192
Mouse models, Parkinson's disease
autosomal dominant Parkinson's disease, 263
autosomal recessive Parkinson's disease, 264
characterization, 266
knockout mouse models
DJ-1, 268–269
overview, 264–265
parkin, 267–268
PTEN-induced putative kinase-1, 268
MPTP, 236–237
overview, 262
prospects, 269–271
transgenic mouse models
Mouse models, Parkinson’s disease (Continued)
α-synuclein, 266–267
constructs, 262
innate inflammation studies, 375–376
leucine-rich repeat kinase-2, 267
test-off conditional models, 262, 264
virus-induced models, 265–266
MPTP. See 1-Methyl-4-phenyl-1,2,3,6-
tetrahydropyridine
MRI. See Magnetic resonance imaging
MSA. See Multiple system atrophy
Multiple system atrophy (MSA)
brain morphology, 34, 39
clinical features, 38
differential diagnosis, 23, 37–39
bieloy body immunohistochemistry, 35–36
Jellinger staging, 42
Lewy body immunohistochemistry, 35–36
pathology comparison with Parkinson’s disease and
progressive supranuclear palsy, 40–41
substantia nigra degeneration, 34–35
N
Necroptosis, dysfunction in Parkinson’s disease, 356
Neuronal phenotype, Parkinson’s disease
calcium channel, L-type targeting, 221–223
mitochondrial burden
spiking, 205–208
synaptic transmission, 209
mitochondria
aging hypothesis, 211–213
oxidative stress, 210–211
overview, 204–205
pacemaking and ionic homeostasis challenge,
208–209
reconciliation with other pathogenesis models,
220–221
vulnerable neurons
dopaminergic neurons, 213–220
non-dopaminergic neurons, 220
Niemann-Pick disease, parkinsonism risks, 337–338
NMDAR. See N-Methyl-D-aspartate receptor
6-OHDA. See 6-Hydroxydopamine
O
Omi/HtrA2
Drosophila studies of PINK1/Parkin pathway
function, 284
Oxidative stress
α-synuclein role, 75–76
macroautophagy effects, 335–336
mitochondria
MPTP effects, 296
role, 210–211
P
p53, expression in Parkinson’s disease, 352
p62, parkin-dependent mitophagy, 320
Paranatos, dysfunction in Parkinson’s
disease, 355–356
Paraquat
animal models of Parkinson’s disease, 246–247
structure, 242
PARK, autosomal dominant Parkinson’s disease clinical
features, 24
PARK1. See also α-Synuclein
autosomal-dominant Parkinson’s disease clinical
features, 24
PARK2. See also Parkin
autosomal recessive Parkinson’s disease clinical
features, 25, 56–57
mutation and Parkinson’s disease
susceptibility, 53
PARK4. See also α-Synuclein
autosomal-dominant Parkinson’s disease clinical
features, 24
PARK5. See also Ubiquitin carboxy-terminal
hydrolase-1
autosomal-dominant Parkinson’s disease clinical
features, 24–25
PARK6. See also PTEN-induced putative kinase-1
autosomal recessive Parkinson’s disease clinical
features, 26, 57
mutation and Parkinson’s disease
susceptibility, 53
PARK7. See also DJ-1
autosomal recessive Parkinson’s disease clinical
features, 26, 57
PARK8. See also Leucine-rich repeat kinase-2
autosomal dominant Parkinson’s disease clinical
features, 25, 55–56, 91–92
PARK9. See ATP13A2
PARK13. See Omi/HtrA2
Parkin
apoptosis protection, 348
autosomal recessive Parkinson’s disease clinical
features, 25, 56–57, 100
Drosophila studies of PINK1/Parkin pathway
links with other PARK loci, 284–285
mitochondrial fission promotion and fusion
inhibition, 281–282
mitochondrial integrity, 279–281
mitochondrial transport, 283–284
mitophagy promotion, 282–283
evolution, 101
function, 102–104
gene therapy, 136–137
genetic testing, 59
knockout mouse, 267–268
locus. See PARK2
mitochondrial targets, 320
mitophagy role, 320, 354
mutation studies of parkinsonism development, 101–102
prospects for study, 106
ubiquitin proteasome system effects of mutation, 331–332
Parkinson, James, 1–3, 17
Parkinson-dementia complex (PDC), overview, 43–44
Parkinson’s disease-related cognitive pattern (PDCP), functional imaging, 171–172
Parkinson’s disease-related pattern (PDRP), positron emission tomography, 166–168
Parkinson’s disease tremor-related pattern (PDTP), positron emission tomography, 168
PCD. See Programmed cell death
PDC. See Parkinson-dementia complex
PDCP. See Parkinson’s disease-related cognitive pattern
PDRP. See Parkinson’s disease-related pattern
PDTP. See Parkinson’s disease tremor-related pattern
PET. See Positron emission tomography
PIB. See Pittsburgh Compound B
PINK1. See PTEN-induced putative kinase-1
Pittsburgh Compound B (PIB), protein aggregation imaging, 175–176
Placebo therapy, historical perspective, 12–13
POLG. See DNA polymerase-γ
Positron emission tomography (PET)
default mode network, 171
functional imaging
dopaminergic dysfunction and motor symptoms, 165–166
metabolic networks, 166–168
levodopa-induced dyskinesia, 169–170
neurotransmitter imaging, 173–175
Parkinson’s disease diagnosis, 21
principles, 164–165
protein aggregation imaging, 175–176
resting metabolism studies, 171–172
Programmed cell death (PCD)
apoptosis
animal models of Parkinson’s disease, 347–348
assays, 346–347
Bcl-2 proteins, 349–350
caspase activation, 348, 350
cyclin-dependent kinase-5 dysfunction, 351–352
endoplasmic reticulum response, 351
p53 expression, 352
pathways, 348–349
autophagy
defects in Parkinson’s disease, 353–354
mitophagy, 354–355
overview, 353–354
mitochondria
fragmentation, 352–353
pathways, 303–305, 349
overview, 345–346
Progressive supranuclear palsy (PSP)
brain morphology, 34, 39
clinical features, 38–39
differential diagnosis, 23–24, 37–39
pathology comparison with Parkinson’s disease and multiple system atrophy, 40–41
staging, 42–43
substantia nigra degeneration, 34–35
tau
immunohistochemistry, 35, 37
pathology, 40
Proteasome. See Ubiquitin proteasome system
Protein quality control. See Autophagy; Ubiquitin proteasome system
PSP. See Progressive supranuclear palsy
PTEN-induced putative kinase-1 (PINK1)
apoptosis protection, 348
autophagy function
isoforms, 321
overview, 320–21, 354
protective function, 321
autosomal recessive Parkinson’s disease clinical features, 26, 57, 100
Drosophila studies of PINK1/Parkin pathway
links with other PARK loci, 284–285
mitochondrial fission promotion and fusion inhibition, 281–282
mitochondrial integrity, 279–281
mitochondrial transport, 283–284
mitophagy promotion, 282–283
evolution, 101
function, 102–104
genetic testing, 59
knockout mouse, 268
locus. See PARK6
mutation studies of parkinsonism development, 101–102
prospects for study, 106
R
Reserpine, animal models of Parkinson’s disease, 248
Rest tremor, Parkinson’s disease, 18–19
Rigidity
motor control, 190–192
Parkinson’s disease, 19
Rotenone, animal models of Parkinson’s disease, 247
S
Single-photon emission computed tomography (SPECT)
Parkinson’s disease diagnosis, 21
principles, 164–165
protein aggregation imaging, 175–176
Index

Sleep disorders, Parkinson’s disease
  MPTP monkey model, 234–235
  overview, 20
SNc. See Substantia nigra pars compacta
SNCA. See α-Synuclein
SPECT. See Single-photon emission computed tomography
STN. See Subthalamic nucleus
Striatum
  basal ganglia projections
    afferents, 147–149
    corticostriatal connections, 155
    efferents, 149
    neurons and interneurons, 144–145
  output nuclei
    globus pallidus internal segment, 149
    substantia nigra pars reticulata, 149–150
  compartments, 146–147
  dopamine quantification in animal models of Parkinson’s disease, 252
  dopaminergic terminal quantification in animal models of Parkinson’s disease, 252
Substantia nigra, degeneration in parkinsonian disorders, 34–35
Substantia nigra pars compacta (SNc)
  dopaminergic neuron quantification in animal models of Parkinson’s disease, 251–252
  neuron vulnerability in Parkinson’s disease, 214–220
Substantia nigra pars reticulata, 149–152
Subthalamic nucleus (STN)
  corticosubthalamic connections, 155–156
  overview, 150–151
Surgical therapy, historical perspective, 11–12

T
  Tau, progressive supranuclear palsy
    immunohistochemistry, 35, 37
    pathology, 40
T cell
  activation in Parkinson’s disease, 374, 378–388
  central nervous system, 382
  cross-regulation with innate immunity in central nervous system, 383–384
  regulatory T cell therapeutic targeting, 388–391
TDP-43-related parkinsonism, overview, 44
TH. See Tyrosine hydroxylase
Tyrosine hydroxylase (TH), gene therapy, 130, 132

U
  Ubiquitin carboxy-terminal hydrolase-1 (UCHL1)
    locus. See PARK5
    Parkinson’s disease susceptibility gene, 58
Ubiquitin proteasome system (UPS)
  ATP13A2 mutation and dysfunction, 337–338
  MPTP effects, 332
  overview, 329–331
  parkin mutation effects, 331–332
  protein misfolding versus clearance in Parkinson’s disease, 328–329
  α-synuclein mutation effects, 331–332
UCHL1. See Ubiquitin carboxy-terminal hydrolase-1

V
  Vascular parkinsonism, differential diagnosis, 22
  Ventral tegmental area (VTA), dopaminergic neuron susceptibility in Parkinson’s disease, 214, 216
Vibratory therapy, historical perspective, 9
VTA. See Ventral tegmental area