Parkinson's Disease

A subject collection from *Cold Spring Harbor Perspectives in Medicine*

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COLD SPRING HARBOR LABORATORY PRESS
Cold Spring Harbor, New York • www.cshlpress.org

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Articles online at www.perspectivesinmedicine.org

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Publisher John Inglis

Front cover artwork: Putamen in the brain. Computer artwork of a person's head showing the brain inside. The highlighted area (center) shows the putamen, which is located at the base of the forebrain (telencephalon). The main function of the putamen is to regulate movements and influence learning. It does this through the regulation of the neurotransmitter dopamine. As such it plays a role in degenerative neurological disorders, such as Parkinson's disease, which are thought to be linked to a decrease in the production or effect of dopamine. Photo from Roger Harris/Photo Researchers, Inc.

Library of Congress Cataloging-in-Publication Data

Parkinson's disease / edited by Serge Przedborski.
p.; cm.
"A subject collection from Cold Spring Harbor perspectives in medicine".
Includes bibliographical references and index.
ISBN 978-1-936113-32-3 (hardcover : alk. paper)
I. Przedborski, Serge. II. Cold Spring Harbor perspectives in medicine.
[DNLM: 1. Parkinson Disease--genetics--Collected Works. 2. Parkinson Disease--physiopathology--Collected Works. 3. Disease Models, Animal--Collected Works. WL 359]

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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.

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