Progressive Brain Disorders in Childhood

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CAMBRIDGE UNIVERSITY PRESS

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UNIVERSITY PRESS

University Printing House, Cambridge CB2 8BS, United Kingdom

One Liberty Plaza, 20th Floor, New York, NY 10006, USA

477 Williamstown Road, Port Melbourne, VIC 3207, Australia

4843/24, 2nd Floor, Ansari Road, Daryaganj, Delhi – 110002, India

79 Anson Road, #06–04/06, Singapore 079906

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www.cambridge.org
Information on this title: www.cambridge.org/9781107042056
10.1017/9781107323704

First published 2017

Printed in the United Kingdom by Clays, St Ives plc.

A catalogue record for this publication is available from the British Library.

Library of Congress Cataloging-in-Publication Data
Names: Pascual, Juan M., author.
Title: Progressive brain disorders in childhood / Juan Pascual.
Description: Cambridge, United Kingdom ; New York, NY : University Printing House, 2017. | Includes bibliographical references and index.
Identifiers: LCCN 2016047642| ISBN 9781107042056 (hardback : alk. paper) | ISBN 9781107686106 (pbk. : alk. paper)
Subjects: | MESH: Brain Diseases | Child
Classification: LCC RJ496.B7 | NLM WS 340 | DDC 618.928–dc23 LC record available at https://lccn.loc.gov/2016047642

ISBN 978-1-107-04205-6 Hardback

To Albertina and Albertina Manuela

The human understanding from its own peculiar nature willingly supposes a greater order and regularity in things than it finds, and though there are many things in nature which are unique and full of disparities, it invents parallels and correspondences and non-existing connections.
Francis Bacon, The New Organon Or True Directions Concerning The Interpretation Of Nature, Aphorism XLV (2000), p. 42. Cambridge University Press, Cambridge, UK.

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Preface

Neurobiology and the practice of neurology have reached overlap and interdependence. Yet, the bounds of neuroscience are broader, providing neurologists with an ever-growing variety of concepts and techniques. Whereas clinical neurology is an applied science, neuroscience is tasked with the explanation of phenomena that span many orders of magnitude: from cells to nervous systems and their interactions with the environment. This awesome diversity accounts for uneven scientific progress. How neural cells arise, work, and die is progressively better understood such that the next great scientific frontier is posited by the higher order question of what purpose do cells and ensembles of cells serve in the context of the brain and of the organism. In other words, *what* causes them to develop certain properties rather than others and *why* are they ultimately needed? Despite justified enthusiasm in many subfields of neurobiology, it seems that these and many other fundamental uncertainties still remain unmitigated. For example, in spite of the well-known importance of neural activation for perception and movement, why is most of the brain's metabolic activity carried out in disregard of external events? Or why do individual cerebral nuclei not adhere to a simple evolutionary plan to preserve the function of brain structures across all organisms that interact with the environment in similar fashion? Or why do neural stem cells grown under the appropriate conditions self-organize into brain organoids? We simply do not know. An unsettling perspective into these unknowns is that function (and biological purpose) comprises more than we can observe, thus remaining hidden. This too has repercussions in neurology: We set out to alleviate human disease, but still ignore much of what disease does to the complete organism, or even how most of the brain functions in a diseased state. We are thus limited to the observable, the commonly describable as seen with our tools and perspectives. Sometimes, as Wittgenstein noted, the brighter the light that is projected against an object, the longer the shadow that is cast.

This book teaches what can be observed in the course of the formidable interplay between brain disease and the developing individual. In the process, we will learn what can be treated, prevented, or at least anticipated. Physicians are compelled to treat affected individuals, but also to contribute new knowledge, ever mediating the obsolescence of their own scientific context. In the spirit of this principle, and in contrast with other texts, this book makes no attempt to fill explanatory gaps. To the contrary, voids in knowledge have been highlighted and presented as unmet opportunities for investigation. It is hoped that, at the very least, the identification of obscure areas should help researchers working on therapies devise strategies that circumvent obstacles for which investigation must be temporarily postponed. The book makes no emphasis on the historical developments of individual diseases, as I have found them generally uninformative for our purpose, and so I have focused solely on useful facts rather than on the uneven paths that led to them. References have been kept to a minimum. All cases described have been taken from the cited literature or from my clinic records without substantive modification.

This text has several limitations. First, the perceived dichotomy between mind and brain in health and disease is not within its scope, but I hope to remediate this deficiency in a future occasion. Second, it has not been possible to credit all relevant sources of information, which I hope other authors will patiently understand. Next, the book betrays my own deficiencies and areas of insufficient knowledge, but I will gladly try to rectify them if they are pointed out to me. In the interim, I will accept any allegations of conducting my own education in public, as Hegel accused Schelling of doing. Lastly, and unfortunately, the practice of diagnosing and caring for neurodegenerative disorders in young persons lacks excitement

by today's societal standards. I lack the power to change this perception, which is prevalent even among physicians. Indeed, when considering the medical training and resources devoted to this endeavor it does seem that "out of the crooked timber of mankind few straight things are ever made."[1] Nevertheless, I hope that the plight of the many individuals afflicted by these diseases will become at least imaginable after reading the text.

A word on terminology: Common designations, such as "developmental delay" or "mental retardation," are implied or used by force of habit, but with some regret: A "delay" implies subsequent progress along a path, and perhaps eventual arrival, but disturbed development ("developmental delay") usually fails to arrive at the expected destination, or even to follow the normal path, just as it is usually unclear what is "retarded" in the mind of many disabled affected individuals. The term "plasticity" (another favorite) carries a beneficial connotation, but has also been used with caution here, as both adaptive and maladaptive phenomena can result from a "plastic" brain. I have also refrained from referring to "disease modifying" therapies to signify interventions that alter the overall course of a disorder because any treatment that changes any aspect of a disease is a modifier of such a disease. "Seizure disorders" have been referred to by the more economic word epilepsy. Casuistic, classifications, and diagnostic criteria have been restrained to a minimum in keeping with the frontispiece, as they rarely reflect the more complex reality. Common forms of a disease are termed as such or referred by the term canonical rather than "classic," as there is little "classicism" in the study of disorders that have been known for less than a century in most cases. In sum, the usage of words of ordinary language is given priority over clinicians' unnecessary tendency to change the use of terms that are established in common dictionaries.

I wish to thank my family for time lost and not regained in what at times seemed comparable to Sisyphus' task. My production team and editor at Cambridge University Press, Nick Dunton, have been all than an author can ask for and much more. My colleagues have shared clinical demands while I was reading and writing. To them, I owe gratitude and much enlightenment. It is through discussions with them that my own ideas have taken shape. The two generations of affected individuals and families that I have cared for constitute the essence and fabric of this book. Their resilience and loyalty to the selfless cause of scientific understanding for its own sake is a testimony to the heights of the human condition.

[1] Immanuel Kant, *Toward Perpetual Peace and Other Writings on Politics, Peace, and History*, p. 9. Yale University Press, New Haven, USA, 2006.