MODERN SURGICAL NEUROPATHOLOGY

THE NERVOUS SYSTEM constitutes arguably the most complex organ system in the human body, which contributes to the oversusceptibility of disease in this area. Although brain tumors were once an automatic death sentence, the outlook for recovery has brightened significantly in the past decade. The pathologist plays an indispensable role in surgical diagnosis; he or she must accurately diagnose a potentially wide array of disease entities, determine the spread of disease within millimeters, and assess patient prognosis. This new and modern reference in neuropathology comprehensively covers all the methods used by pathologists to accurately diagnose a wide array of neurologic illnesses. Brain and spinal cord tumors are the predominant focus, but a full spectrum of infectious, inflammatory, and congenital disorders are also covered in detail, in both pediatric and adult populations, with a full range of diagnostic modalities. The book is illustrated with more than 1,200 full-color photomicrographs and accompanied by a CD-ROM of all images in a downloadable format.

Douglas C. Miller, M.D., Ph.D., is Clinical Professor in Pathology and Anatomical Sciences at the University of Missouri School of Medicine, Columbia, Missouri. Previously, Dr. Miller was Professor of Neuropathology and Neurosurgery at New York University Medical Center, where he was also Director of Neuropathology.

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Douglas C. Miller

University of Missouri School of Medicine, Columbia, Missouri

CAMBRIDGE UNIVERSITY PRESS

CAMBRIDGE UNIVERSITY PRESS
Cambridge, New York, Melbourne, Madrid, Cape Town, Singapore, São Paulo, Delhi

Cambridge University Press
32 Avenue of the Americas, New York, NY 10013-2473, USA

www.cambridge.org
Information on this title: www.cambridge.org/9780521869324

First published 2009

Printed in China

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

Library of Congress Cataloging in Publication Data

Miller, Douglas C.
Modern surgical neuropathology / Douglas C. Miller.
p. ; cm.
Includes bibliographical references and index.

ISBN 978-0-521-86932-4 (hardback)

1. Brain – Tumors – Diagnosis. 2. Nervous system – Diseases – Diagnosis. 3. Pathology, Surgical. I. Title.
[DNLM: 1. Nervous System Diseases – surgery. 2. Nervous System Diseases – pathology. 3. Pathology, Surgical – methods. WL 368 M647m 2009
RC280.B7M47 2009
616.99′481–dc22 2008053039

ISBN 978-0-521-86932-4 hardback

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PREFACE

When I was first approached about writing and/or editing a new text on neuropathology, I thought hard about what focus such a book might have and what I could offer that would be different from the several texts that already are available. The last decade has seen an explosion of knowledge of the genetics and proteomics of cancers in general, including central nervous system tumors, and there has been increasing recognition of a wider variety of pathological appearances and clinical–pathological entities among those tumors. The WHO has issued two editions of its classification (Genetics and Pathology) of CNS tumors in this time, but these offer at best brief thumbnail sketches of the pathology of these tumors for those who must make diagnoses for clinical use for patients undergoing operation. Other texts have focused on individual tumor types or broader categories or survey the full field of neuropathology, including detailed genetics for developmental and degenerative diseases studied mostly in autopsies, not in surgically excised tissues. So I concluded that there remained a need for a good working guide for diagnostic pathologists who must deal with surgically excised tissues, including but not limited to neoplasms. I offer this work chiefly to that audience and for that purpose.

Here the reader will find what I intend to be as comprehensive a survey as is possible of the lesions, neoplastic and nonneoplastic, that are encountered, commonly or uncommonly, in biopsies or excisions of pathological processes in the brain, spinal cord, their coverings, and adjacent tissues. I have included discussions and descriptions of essentially all of the specimen types of which I have seen examples in my twenty-eight (as of this writing) years of studying and practicing neuropathology, with the specific exceptions of muscle biopsies and peripheral nerve biopsies. In so doing, I felt that there was a need for more than an atlas; this is not a coffee-table book with numerous pictures but little text. Equally, I thought it necessary nevertheless that the text be accompanied by copious illustrations, not just illustrations of the "best" examples of entities, but, where appropriate, of variants or versions that fit diagnostic categories but lack some of the "textbook" features, which one sometimes finds are, in reality, just not there.

This book provides the working pathologist (or neuropathologist) – those who are in training, new to practice, or lack experience dealing specifically with lesions of the CNS – with my version of how to make diagnoses. I hope that my colleagues with years of experience in neuropathology will also find it at least occasionally useful and perhaps thought-provoking. I think this text fills a need and a niche that has to date been unfilled.

It is important to note that is a single-author text. I decided early on in consultation with the publisher that this text, to be useful, must express points of view as well as objective data. So, for what it is worth, the opinions expressed herein are wholly mine. I have tried to expose controversies, uncertainties, and dilemmas in diagnostic neuropathology and to let the reader make up his or her own mind, but of course I offer the photographic and textual arguments that lie behind the points of view I express herein. I have been formulating these opinions throughout my lengthy career, and pride as well as fact compel me to point out that I have spent most of my career at academic centers known for their high volume of neurosurgical procedures and hence of neuropathological specimens, including the Massachusetts General Hospital, where I trained with E. P. Richardson, Jr., and Tessa Hedley-Whyte, and then the twenty-plus years I spent at NYU Medical Center, where first Joseph Ransohoff and then Patrick Kelly chaired one of the nation's, indeed the world's, great neurosurgery services, especially for the surgical treatment of CNS tumors. During those years, I have adopted a philosophy toward diagnostic procedures that I like to think of as an early version of "evidence-based" medicine. I do not make a diagnosis based on opinion or experience alone; I try to make one based first on accumulated data, whether that means utilizing a battery of immunohistochemical or other "special" stains or referring to statistically valid prognostic data from as many clinical case series as is possible, rather than on how I "feel" about, for example, how a tumor looks. I know that some of my approaches therefore differ significantly from those of some of my peers in the field, and I hope that through this text readers will find a new way to think about how to make diagnoses in surgical

neuropathology. If a reader disagrees with my point of view, so long as I have provoked some thought and an examination of the evidence, then that too is good; this is, like all science, an evolving process that is not now and will never be ready to be engraved on tablets for all time. In that sense, which is the legal system's sense, this is not an "authoritative" text, for I do not believe in science by authority. However, I feel that this text is the best approach to the best possible diagnoses as we understand the evidence and can examine the nature of various diseases as of this time. If this text helps its readers to benefit the patients whom we all serve, then its ultimate goal has been achieved.

DOUGLAS C. MILLER M.D., Ph.D.
Columbia, Missouri

ACKNOWLEDGMENTS

Although I am sole author of this text and take full responsibility for the opinions; approaches; and any errors of fact, omission of important details, or failure to cite a crucial reference or indeed to mention any particular diagnostic entity, it must be clear that no one can produce such a work without being indebted to a host of others.

First, I must thank my original mentors in neuropathology who started me down the path that has now led to (I will not say culminated in) the writing of this text. At the University of Miami School of Medicine, Joseph Parker and David Wolfe first exposed me to diagnostic neuropathology, and I learned many things from them (including the term "primitive neuroectodermal tumor," voiced by Joe in a Kentucky drawl that graced that diagnosis with pregnant meaning). Also in Miami, my graduate school mentors, especially Karl Magleby and Gerhard Dahl in the Department of Physiology and Biophysics, taught me above all to read the scientific and medical literature with a critical eye, to not just believe the latest paper published. This, I think, is often difficult to learn in medical school, where so much of what is taught is handed down as if from "authority," and I am very grateful that I gained this skill early in my career.

Second, I owe an enormous debt to those who taught me pathology and neuropathology as a resident at the Massachusetts General Hospital. I learned to be thorough, careful, and observant of all details from superb general surgical pathologists, including Robert Scully, Alan Schiller, Eugene Mark, Max Goodman, Ben Pilch, and Austin Vickery. I had the great privilege of learning neuropathology from E. P. Richardson, Jr., and Tessa Hedley-Whyte, who had different approaches to teaching and diagnosis that were valuably complementary and who, with the other MGH pathology faculty, always stressed the importance of clinical (and neuroradiological) correlation with pathological data. Such correlations have been a cornerstone of my diagnostic work (and much research and publication) throughout my career. One other important lesson I learned from EP, as he was always known, was how to not take forever agonizing over a frozen section; either you know what is there or you do not, and poring over the same slides over and over is not likely to benefit you or the patient. This was great advice, given mostly by example, and I freely pass it along in this book.

At MGH, I also had the privilege of learning much neurology through correlative conferences from C. Miller Fisher, Allan Ropper, Elizabeth Dooling, and Fred Hochberg. Fred and I became close friends, collaborators, and coauthors, particularly in work on CNS lymphomas and the early recognition of the substantial increase in the incidence of that tumor in the early 1980s, and so a special thanks goes to him for years of discussions, advice, and counsel. I also collaborated on a number of CNS tumor studies with Robert Martuza, who is now Chief of the Neurosurgery Service there. With Bob, I began working on the pathological features of rodent models of CNS and peripheral nerve tumors, an experience that has always been valuable and that represented "translational" research before the term was popular.

Following three years on the faculty of the Robert Wood Johnson Medical School, I began my twenty-year experience at New York University School of Medicine, enticed there by one of the great neurosurgeons of the twentieth century, Joseph Ransohoff. Joe was also one of the great characters of American medicine of those times, and he was a model of how to be a great chairman; he built a department by a combination of bringing in outsiders and fostering the development of trainees who eventually became well-respected subspecialists in pediatric neurosurgery (Fred Epstein, Jeff Wisoff, and Howard Weiner), vascular neurosurgery (Gene Flamm and Jafar Jafar), epilepsy neurosurgery (Michael Dogali and Werner Doyle), spine surgery (Vallo Benjamin, who did my own lumbar spine operation in 2006, and Paul Cooper), and pituitary surgery. Joe was a great believer in the importance of quality neuropathology to neurosurgery and patient care and was a great mentor, friend, and guide in my early years at NYU. I owe Joe a huge debt, and I honor his memory.

Joe was succeeded by Patrick Kelly, who was and in my view remains the greatest master of stereotactic neurosurgery, whether it be volumetric resection of brain tumors, serial stereotactic biopsies, or stereotactic deep brain stimulation. Pat brought a different style and much skepticism about pathology to NYU, and it took a few years of interaction for us to each fully acknowledge the contribution the other made to their work, but I look at Pat's time at NYU when I was there as an

enormously fruitful one that gave me a great amount of tumor tissue to study and a colleague and friend who came to value my approach and thus my diagnostic opinions. Weekly Tumor Boards with Pat and all the neurooncology team members were the highlight of most weeks, and once again clinical–radiological–pathological correlations were at the heart of what we did. Pat is the epitome of a "no-nonsense" man who tolerates no obscurantism, false pretenses, or sycophantism, which I greatly appreciate.

Fred Epstein was another pioneer in modern neurosurgery, and he not only supported my career early at NYU and brought in great cases from a worldwide referral base; he also began routine safe radical resections of intramedullary spinal cord tumors in both children and adults, providing me as a neuropathologist with a unique experience with (comparatively) large samples of tissue, which I could then fully study with special stains and make more precise diagnoses.

I learned most of my epilepsy pathology from doing it; I gave myself a crash course in the literature then extant when NYU started doing epilepsy surgery in 1989, and because the center grew to be the largest (allegedly) in the country, I eventually saw a large number of cases (probably more than 100 per year for at least fifteen years). My thanks to Werner Doyle, the main epilepsy neurosurgeon during that time, for helpful clinical correlations, careful consultations over specimens, and respect for our mutual abilities and results.

Pat Kelly brought in or trained several excellent tumor neurosurgery specialists to NYU while I was there, and I had close working relationships with each of them that contributed to this work as well. Notably these include John Golfinos and Erik Parker, who carry on Pat's work in stereotactic neurosurgery for radical excision of gliomas. John also became the principal pituitary surgeon when Paul Cooper decided to concentrate on difficult spine cases, and many of the cases I have seen that have gone into this text are his. Joe Ransohoff did many eighth-nerve tumor resections in my early years at NYU, something I had become familiar with at MGH, where Robert Ojemann was renowned for his abilities to preserve facial nerve function in such surgery in the CT era. In the years after Joe retired from NYU, John Golfinos with his otolaryngology colleague Tom Roland took over this work when, during the MRI era, more and more patients began to expect (and were able to have) hearing conservation. My studies of eighth-nerve schwannomas began in the Ransohoff era and continued with John and Tom. This would not have been possible without their help, consultations, and collaborations.

Similarly, Joe Ransohoff and Vallo Benjamin had established as parts of their practices a large volume of patients with meningiomas. Utilizing these patient specimens and their very thorough follow-up records, I was able, with my fellow neuropathologist George Kleinman and the neurosurgeons, to do some of the early work in establishing criteria for the then-new diagnosis of "atypical" meningioma.

Much of my early work at NYU on the genetics of gliomas, and on the immunohistology and pathology of gangliogliomas, was started in collaboration with Maxim Koslow, then as now Chief of Neurosurgery for Bellevue Hospital. Those projects may never have started without Max, and they are important foundations for the glioma and ganglioglioma sections of this text.

As in my residency, my close associations with clinical colleagues during my many years at NYU were important to me and hence to the development of this book. Apart from the neurosurgeons I have mentioned, I must stress the value of the clinical–pathological correlations and follow-up with Drs. Michael Gruber, Jeffrey Allen, and Jonathan Finlay that I enjoyed and that illuminate portions of this book. Jeff was instrumental in having me join the Children's Cancer Group, now part of the Children's Oncology Group, and through those activities, I have seen a larger number of pediatric CNS tumor pathology specimens than I ever could have at a single institution, even one as busy as NYU. Many of those cases have served to illustrate this text. Others at CCSG or COG to whom I owe thanks in this context include Russ Geyer of the University of Washington and Ian Pollock of the University of Pittsburgh. My experience with skin biopsies for genetic and metabolic diseases of the nervous system I owe to Edwin Kolodny, whom I knew when I was a resident in Boston and who later was and remains Chairman of Neurology at NYU.

When I joined NYU's faculty in 1987, the already–long serving Chairman of Pathology was Vittorio Defendi, who remained in that position until 2002. Vittorio was an important support for me and the neuropathology service during all that time. When I started, the neuropathology service included Irwin Feigin, already semi-retired; Humberto Cravioto; John Pearson, largely immersed in administration of Bellevue Hospital Pathology; and Gleb Budzilovich. Gleb was a diagnostically brilliant pathologist and a keen observer, but a reluctant author, and so much of what he did went (and continues to be) unnoticed. Many of the illustrations in this text are inherited from him, and in the seven or so years in which he and I were the two main neuropathologists at NYU, he was the ideal colleague with whom to puzzle over a difficult case.

The larger community of neuropathologists includes many I count as friends and friendly colleagues, but I must mention special thanks to Lucy Rorke of Children's Hospital of Philadelphia. I treasure the hours she and I sat across a double-headed microscope looking at the more than 200 cases of intramedullary spinal cord tumors that Fred Epstein had removed.

In the last twenty-one years, I have had a considerable number of trainees, in neuropathology and pathology. Many have become colleagues as well as friends and were of assistance to me in assembling information or illustrations for parts of this text. I must single out Drs. Suash Sharma (now at Medical College of Georgia) and Mary Fowkes (now at Mt. Sinai School of Medicine) in particular for their help in this regard. My two most recent (and last) NYU Neuropathology Fellows, Drs. Ingeborg Fischer and Clare Cunliffe, have also provided some photomicrographs and slides to fill a few holes in this text, and their specific contributions are acknowledged as well in the figure legends, as are those of Drs. Sharma and Fowkes. Dr. Fischer also read the first few chapters in draft form and offered helpful suggestions.

Tessa Hedley-Whyte reviewed the draft outline for this text and made helpful suggestions, and then she thoroughly read through the first chapter; I think there were more red font lines in the Word file she returned to me than there were black ones from the original draft, and although I cannot say I took every suggestion, I was glad to have each one, as indeed I have valued

Tessa's mentorship and friendship for all the years I have known her.

In addition to the contributions to this book from Drs. Fowkes, Sharma, Fischer, and Cunliffe, cases as glass slides to be photographed, or in an instance or two actual photomicrographs in digital form, were also provided by Dr. Hedley-Whyte, Dr. Chandrakant Rao of SUNY Downstate Medical Center, and Dr. BK DeMasters of the University of Colorado Health Sciences Center. Additionally, I must thank Dr. MaryAnn Clayton, Chief Medical Examiner of Bergen County in New Jersey, and Dr. Ron Suarez, Chief Medical Examiner of Morris County in New Jersey, for the loan of some slides from their offices' files, which I had seen as their consultant and which had features I needed to illustrate here. I have used photomicrographs from slides (and one electron micrograph) for a few rarities from my collection of cases from the Diagnostic Slide Session of the American Association of Neuropathologists. The DSS is always the highlight of the AANP annual meetings but beyond that the distribution of the cases allows one, as I have, to retain materials for teaching and, as here, publication with proper credit given, and I am happy to acknowledge that without the DSS, I would not have been able to illustrate these entities.

For well over half of my years at NYU and through to the time I left, Mrs. Janis Demas worked as my secretary. Janis was invaluable; her contributions to my practice of surgical neuropathology and thus indirectly to this text are too numerous to detail. One of the major advantages of working at NYU for the years I was there was that we had a separate neurohistology laboratory, which processed all of the neurosurgical specimens (as well as all the autopsy tissue) and which produced high-quality sections and stains, by far the best of all the several NYU histology laboratories. This was, of course, a major aid in making diagnoses. For this, I must thank the histotechnologists who did such good work: Laura Anderson, the laboratory supervisor; Melinda Jocson; Nathalie Henry (now Jean); and Gaulette Zamor, who became our immunohistochemistry expert and who was then appropriated to that role for all of Bellevue Hospital Pathology. For several years, I had outside support for a research histotechnologist, Sonny Bhalla (now Dr. Bhalla), who also did superb work including immunohistochemistry. My long-time administrative assistant, Ms. Leslie Brandeis, was also important to my ability to practice and in particular was instrumental in the arrangements that allowed me to start up the epilepsy pathology part of our service, which was originally based on specimens done at the Hospital for Joint Diseases, where NYU first built the epilepsy surgery center.

Writing, editing, illustrating, and referencing a text such as this take many things, among them a great deal of time. I must thank Cambridge University Press and particularly Marc Strauss, the publishing director of their scientific, technical, and medical division in North America, not only for approaching me with the notion of doing this text in the first place but more importantly for his support and patience as this, like most such tasks, has seen several deadlines pass prior to its actual completion. My chairman here at the University of Missouri School of Medicine, Dr. Douglas Anthony, also a neuropathologist, has tolerated the time I have spent on this work, which has not interfered with clinical neuropathology but has been my major "academic" focus for most of my first year here.

Finally, and most importantly, the time it takes to write this book had to come from somewhere, and in my case, I have stolen many, many hours from family on vacations, evenings, and weekends; for their forbearance and support, I owe them more than I can repay, especially my wife, Sherry, to whom this book is dedicated.

DOUGLAS C. MILLER M.D., Ph.D.
Columbia, Missouri