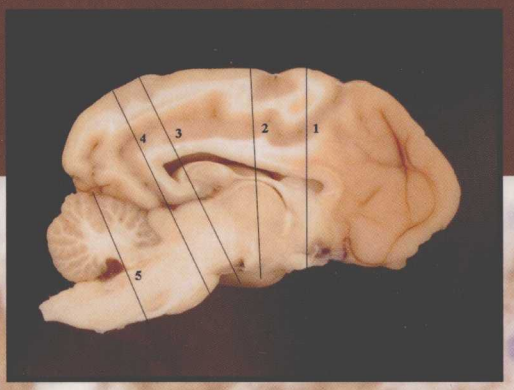
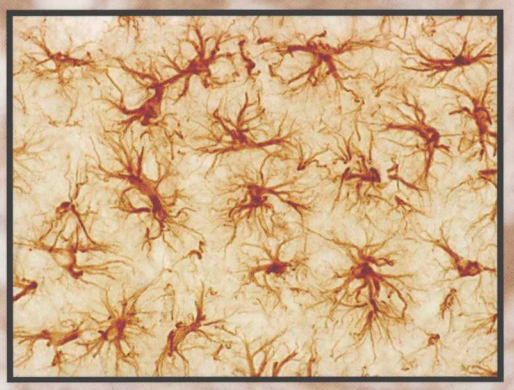
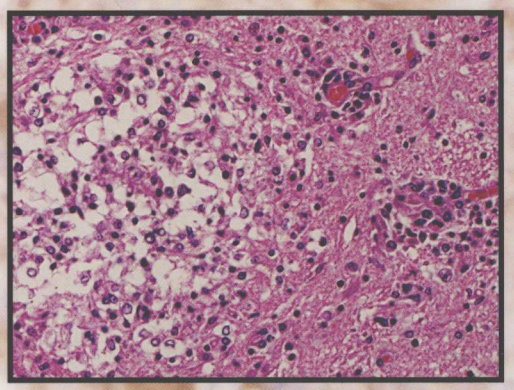
# Fundamental Neuropathology for Pathologists and Toxicologists

## Principles and Techniques





Edited by
**Brad Bolon**
**Mark T. Butt**

WILEY

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# FUNDAMENTAL NEUROPATHOLOGY FOR PATHOLOGISTS AND TOXICOLOGISTS

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# FOREWORD

Although many textbooks include an explanatory preface provided by the senior authors or editors, the practice of including a foreword seems to be on the decline. Thus I was especially pleased to be invited by Drs. Bolon and Butt to pen a few words for their new offspring. It has been said before that a good book needs no justification, whereas a bad book cannot be justified. I have no doubt that this new volume will gain Brad Bolon and Mark Butt many new friends. In a world where the concept of one medicine holds sway, perhaps in toxicological pathology as much as in any medical discipline do physicians, veterinarians, and Ph.D. scientists work side by side. It is no coincidence, then, that Brad and Mark have gathered around them a large and formidable stable of experts from all three professional backgrounds to provide us with a remarkably comprehensive and diverse text that embraces all creatures great and small. Whether in search of knowledge pertaining to neural development, neuroimaging, clinicopathologic correlations, neurobehavioral assays, teratology, species idiosyncrasies, toxicological pathology of the eye, ear, and olfactory systems, regulatory issues, stereology in neurotoxicology, and much, much more—it's all here.

Drs. Bolon and Butt, mid-1980s graduates of veterinary colleges in North America, are seasoned veterinary pathologists who have followed somewhat different career paths but clearly saw the need for a contemporary reference text of toxicological pathology. In recent decades, progressively more trained veterinary pathologists have found employment and made careers in toxicological pathology, especially as it intermeshes with the pharmaceutical industry. This book fills an important need, for it is clear that the nuances of the central and peripheral nervous systems overwhelm many capable anatomical pathologists who will be perfectly comfortable with other tissues and their expressions of disease. In contrast to some organs, the central nervous system (CNS) can be subtle and to many is just a vast wasteland in which the discrimination of normal from lesion and lesion from artifact is a constant dilemma. Indeed, as one colleague put it, the CNS is the only organ that autolyses before death! The first professor of veterinary pathology whom I encountered would examine a case up to the level of the dura mater, at which point the brakes were firmly applied and any evaluation of brain or spinal cord was delegated to "the specialist." *Fundamental Neuropathology for Pathologists and Toxicologist* will help to make all pathologists at home with this organ system.

Drs. Bolon and Butt bring to this new volume a broad perspective, honed by many years engaged in industrial pathology in which they have focused on neuropathology and the potential for chemicals to perturb the nervous system, including experimental investigations and studies in several species, including genetically modified laboratory animals. Guided by the premise "first do no harm," Brad, Mark, and their colleagues have devoted their careers to the proposal that in vivo and in vitro studies of potential new therapeutic compounds can best identify the safest and (what will prove to be) the most efficacious next generation of medicines while often throwing light on disease mechanisms and pathways along the way. Although in recent decades there have been notable successes in human health, there remains a massive need for pharmaceutical products with which to intercede in cardiovascular disease, neoplastic disorders

(now potentially with compounds tailored to individual tumors), and the burgeoning area of dementing diseases as life expectancy in some areas of the world stretches beyond 80 years of age. I am delighted to see the birth of this new textbook, which is certain to secure a home on the shelves of many professionals, including neurologists, toxicologists, pathologists, laboratory investigators, and scientists in our regulatory agencies.

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# PREFACE

The goal of this work was to provide, as much as possible, an essentially complete reference on the design and interpretation of studies involving toxicological neuropathology. It is a book not only for pathologists, but also for toxicologists and other scientists involved in the investigation of neurotoxicity. A series of journal articles to achieve this goal was just too fragmented an approach. A textbook was needed, and here it is.

Although there are numerous descriptions and illustrations of tissue changes, this book is not an atlas of lesions. There are other complete references, in print and online, with a plethora of images and diagnostic terms. Although the chapters contain many literature references, this book relates primarily the knowledge of many veterans of the neuropathology discipline with the hope that others can learn from our experience and mistakes. (Note: We did not specifically mention all of our mistakes.)

As with most projects that are either different or of a greater magnitude than someone is used to, the collection, assembly, and editing of this book took longer than predicted. However, the end result achieved both our vision and our goal.

Many years ago, while serving as chairman for a pathology working group for the National Toxicology Program, I (M.T.B.) pulled out my copy of *Pathology of the Fischer Rat* (Boorman GA, Eustis SL, Elwell MR, Montgomery CA, MacKenzie WF, eds., Academic Press, Inc., San Diego, CA, 1990). Several of the contributing authors were in the group. Each was pleased to see that the binding of my book had long ago broken down because of the number of times I had grabbed it off the shelf for a consult. It is our hope that this book will receive just as much use long before the second edition makes its way into print.


## ACKNOWLEDGMENTS

We would like to acknowledge Jake Butt and James Reickel, whose lengthy (and frequently late-night) formatting sessions provided so much assistance toward the finished product. We also thank our co-workers, who had to manage their schedules around our need to write, edit, format, and compile all the material that formed this volume.

We thank Amanda Amanullah and Jonathan T. Rose (Wiley) for their patience and support in serving as the publisher's editors of this volume, and Colin Moore (Longmont, Colorado; www.colinmoore.us) for preparing the graphic art in Chapter 4. Although not mentioned by name, we thank the many others who helped with editing, formatting, and illustrations.

Finally, and most important, we gratefully and humbly acknowledge the many contributors who took time from their already too full schedules to provide chapters of this book.


MARK T. BUTT
BRAD BOLON

**Color versions of selected figures can be found online at**
***ftp://ftp.wiley.com/public/sci_tech_med/fundamental_neuropathology***

# INTRODUCTION

The 90-day study is over, the pathology data have been collected, and there is a problem: a microscopic change in the brain. The incidence is slightly higher in the treated groups than in the controls, or perhaps it is not present in the control groups at all. Still, the lesion does not seem like much of an issue. There were no in-life changes to suggest a problem. Brain weights were within normal limits. Even the cerebrospinal fluid was normal. No instances of seizures or abnormal ambulation were noted during cage-side observations. But was enough information gathered to make an accurate assessment? Does the lesion, which seems inconsequential to the animals, represent something that will affect the more complex lives of humans in a different and profound way? Is it possible that earlier time points need to be looked at to truly characterize the test article as "safe"? Could additional stains or the collection of morphometric data help? Did this study validate previous studies, and if not, are the differences real or due simply to variable interpretation or dissimilar terms—which, in actuality, mean the same thing? If clinical trials are able to begin, is there any way of tracking, assessing, or following this potential change in patients? These questions are what this book is about.

Diseases of the nervous system have a major impact on individuals and society. For many, perhaps for most, of these diseases we are not much closer to an effective treatment or cure than we were 10 years ago. Research moves slowly, but we need to make sure that it moves progressively and as quickly as possible. Lives are literally in the balance. We now know that Huntington's disease is a trinucleotide repeat disorder. Based on the number of repeats, we can even predict the probable progression of the disease. But we have very little to offer in terms of treatment. Using whatever tools necessary, we need to change that.

There is one nervous system. It consists of the brain and the spinal cord and the motor nerves. It is also comprised of sensory and autonomic ganglia, intraepidermal nerve fibers, and neurons that act more like endocrine glands than like traditional bipolar cell bodies. The brain is attached to the eye, to the ears, and to the pelvic ganglia, which all interact. The brain is a group of physically, chemically, and metabolically diverse groups of neurons that may look similar and may be located in generally the same place (inside the skull), but the differences end there. These groups of cells require examination. You cannot think of the brain as a liver or a kidney: one section of a brain (or even three sections) does not allow for adequate examination of the brain. The nervous system is a complex system that requires more than a lifetime to understand. This complexity is one of the central themes of this book.

This volume has been assembled to provide neuropathologists and neurotoxicologists, as well as toxicological pathologists and general toxicologists with an interest in the field, with a single resource that provides the introductory and advanced information needed to develop proficiency in the design, analysis, and interpretation of toxicologic neuropathology experiments.

Part 1 provides information on fundamental neurobiology. Since an understanding of the anatomy of the nervous system is paramount to assessment, Chapters 2 to 4 focus on neuroanatomy. Neuroanatomy is daunting, but once the anatomy is known, you can often predict where a lesion may be, based on the presenting clinical signs. That is the thrust of Chapter 5. Because the morphological evaluation of tissues is only one step toward understanding nervous system function, Chapters 6 and 7 focus on behavioral systems and cognitive assessments, and Chapter 8 deals with the effects of aging on brain structure and function. These are areas in which the

neuropathologist and neurotoxicologist require general familiarity as well as specific knowledge on a study-by-study basis. Finally, Chapter 9 provides a framework for understanding the issues relevant to the design of a neurotoxicity study that will capture important morphological endpoints.

Part 2 deals primarily with methodology: how, when, and why. Chapters on practical methods of neurohistology, specialized (rapidly becoming commonplace) markers for neurotoxicity, processing and evaluation of peripheral nerves and muscle, and cerebrospinal fluid are all included, as is an essential chapter on stereology. You won't find everything you need in Part 2 (that's why second editions were invented), but it's a very good start.

Part 3 continues with more methodology, providing chapters on evaluation of the adult nervous system, the developing nervous system, the peripheral nervous system, and the ophthalmic otic and olfactory systems. The techniques described in Part 3 provide an excellent foundation for an evaluation of the nervous system.

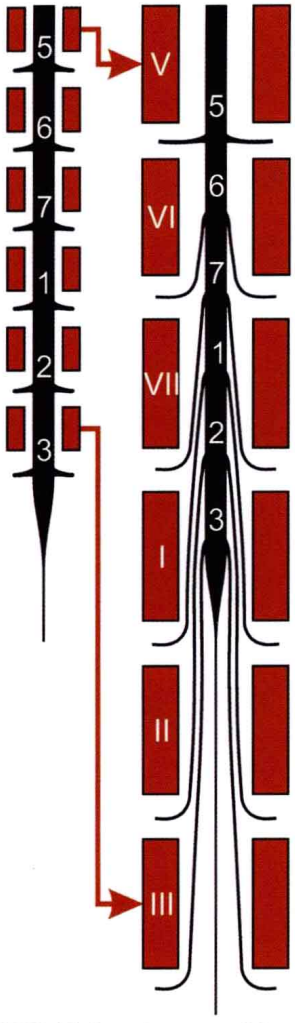
Part 4 includes those chapters considered important to a thorough understanding of the issues facing neuropathologists and, by extension, study directors and investigators involved in running neurotoxicity studies. Direct delivery is an increasingly common means of getting various test articles, especially proteins, antibodies, lipophobic drugs, and stem cells to the central and peripheral components of the nervous system. Of those methods, spinal delivery is one of the most common, so a chapter on that delivery system and the drug safety implications is included. Other direct delivery methods, including intracerebroventricular catheters, direct parenchymal infusions, deep brain stimulation devices, and stem cell implants, were not included, due to space limitations. But through the context of intrathecal delivery, Chapter 27 does include many of the issues, real and potential, that are encountered when delivering drugs directly to the central nervous system.

The regulatory aspects of toxicologic neuropathology comprise two of the Part 4 chapters: one describes what is important to include in regulatory submissions (from the viewpoint of regulatory officials), the other provides useful suggestions for navigating the various regulatory guidelines pertinent to the conduct and interpretation of neurotoxicity studies involving pathology. Additionally in Part 4 are chapters on neuropathology in veterinary and medical practice, a chapter on diagnostic neuropathology (primarily of spontaneous diseases), and a guide to training personnel, primarily technical staff, who will be involved in the conduct of studies with neuropathological endpoints. Finally, there is a chapter on the neuropathology report. Since everyone has his or her own style and notions of what comprises a great report, this chapter is likely to be controversial. But even if only useful for stimulating debate, a chapter on reporting was needed.

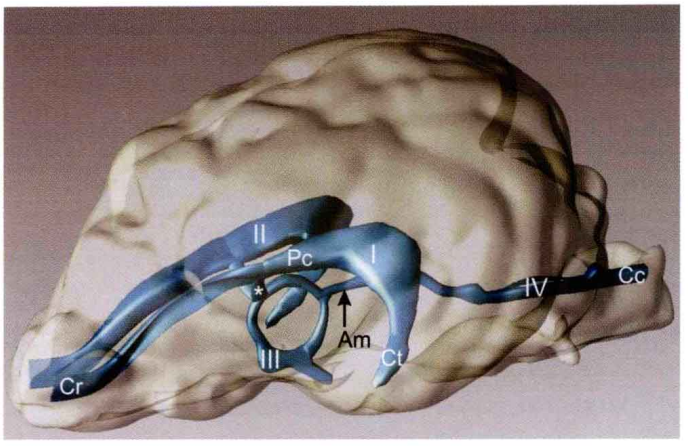
Finally, Part 4 ends with a chapter on the future of neuropathology. It will be particularly interesting to dust off this first edition in 20 years and see how close the authors were in predicting changes in the dynamic field of toxicological neuropathology.

The morphological examination of the nervous system is the task of the neuropathologist. Coordinating that pathologist with all the other contributing scientists is the task of the researcher and/or study director. That is not an easy job. For all those involved in neurotoxicology in general and toxicologic neuropathology in particular, this book seeks to better inform you, to make your career even more interesting, and to provide you with an increased opportunity for success in gathering and interpreting the data necessary to make good decisions.

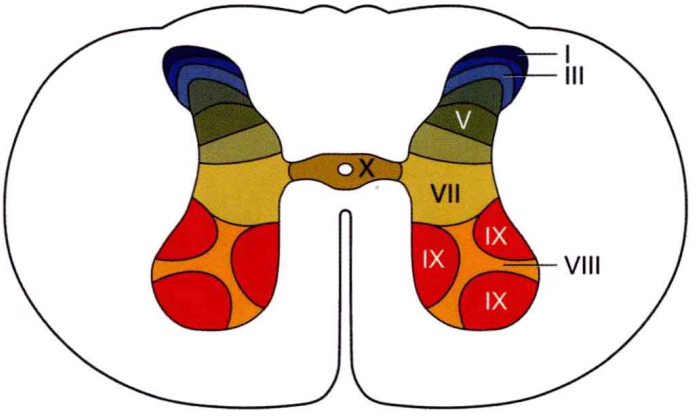
We hope that this book will be a boon to both experts and novices in toxicological neuropathology, and that this information will assist all those engaged in protecting the health of humans and animals from the devastating damage that can follow genetic, degenerative, physical, and toxic injury to the nervous system.



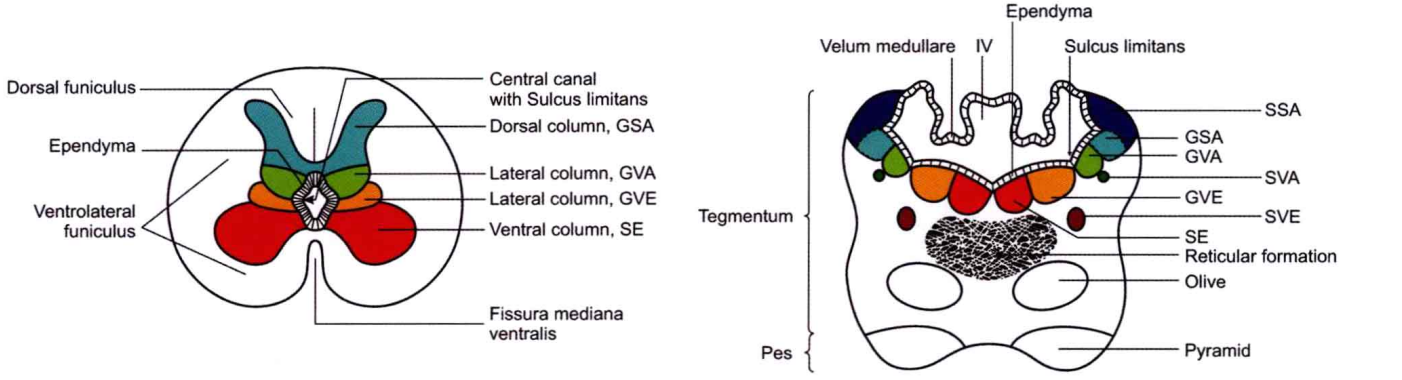

**CHAPTER 2, FIGURE 3** Development of the cauda equina. Early in gestation (small image on left), the spinal cord segments are aligned with the corresponding vertebrae. After birth (large image on right), allometric growth of the spinal cord and vertebral column results in progressive cranial displacement of spinal cord segments relative to the corresponding vertebrae. 5–7, Lumbar spinal cord segments 5 through 7; 1–3, sacral spinal cord segments 1 through 3; V–VII, lumbar vertebrae V through VII; I–III, sacral vertebrae I through III.



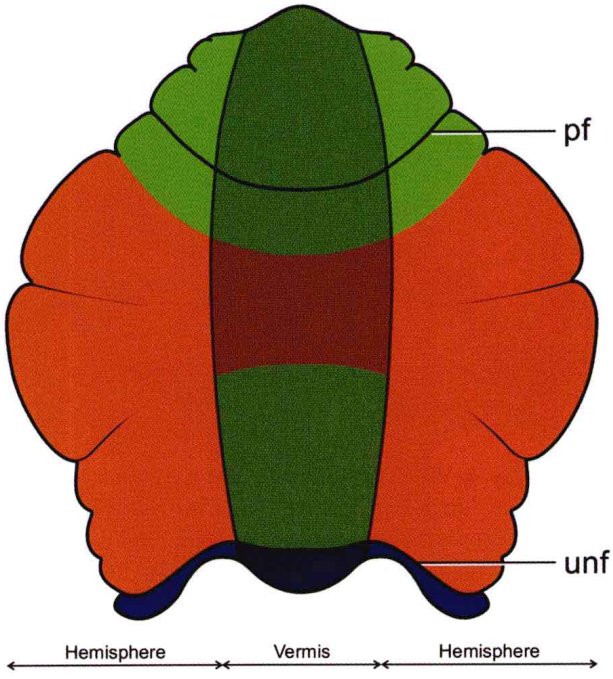

**CHAPTER 2, FIGURE 2** Mammalian ventricular system (modeled after the dog). I, II, Lateral ventricles (with Pc, pars centralis; Cr, cornu rostrale; Ct: cornu temporale); III, third ventricle (circling the interthalamic adhesion); Am, aqueductus mesencephali; IV, fourth ventricle; Cc, canalis centralis of the spinal cord; *, foramen interventriculare.



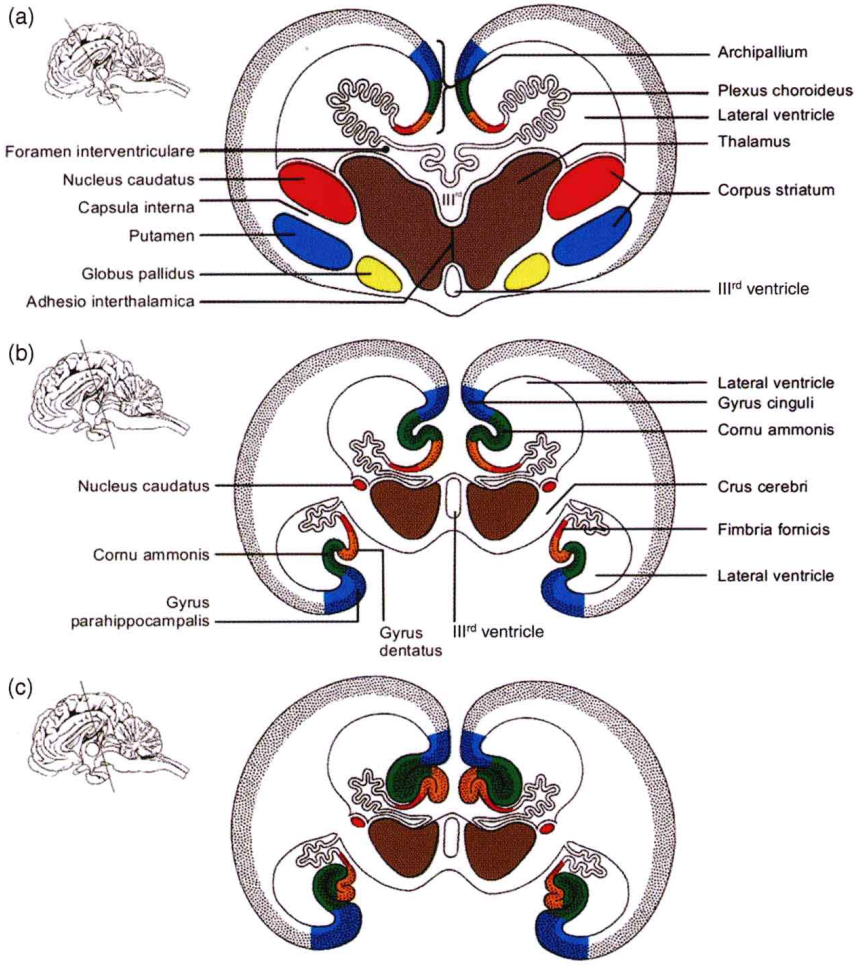

**CHAPTER 2, FIGURE 4** Laminar arrangement of spinal cord gray matter, according to Rexed. Laminae I to VI receive sensory input from pseudounipolar neurons, whereas visceral somatic efferents originate from layers VII to IX. Layer X contributes fibers to the spinoreticular and spinothalamic tracts. (Courtesy of Enke Verlag in MVS Medizinverlage Stuttgart GmbH & Co. KG.).



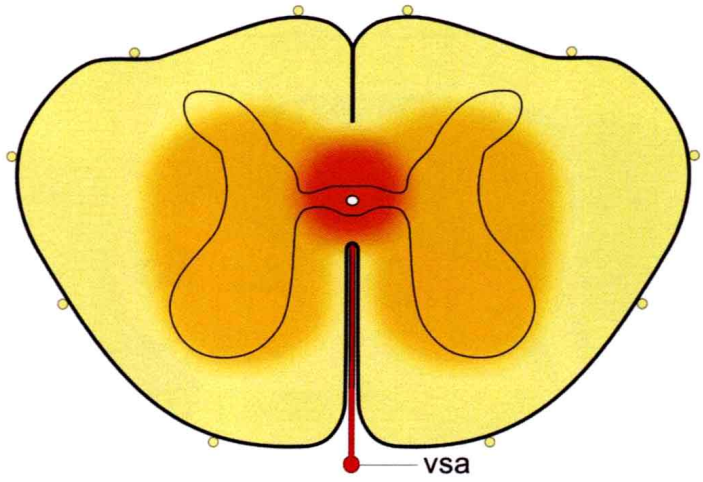

**CHAPTER 2, FIGURE 5** Functional organization of gray matter in the mammalian spinal cord (a) and rhombencephalon (b). As a consequence of the flattening of the rhombencephalon, dorsoventral alignment of modalities as seen in the spinal cord is modified into a lateromedial sequence. Nuclei dealing with the special modalities that are unique to the head are added at the lateral aspect (SSA) and deep to the general modalities in the tegmentum (SVA, SVE). GSA, General somatic afferent; GVA, general visceral afferent; GVE, general visceral efferent; SE, somatic efferent; SSA, special somatic afferent; SVA, special visceral afferent; SVE, special visceral efferent; IV, fourth ventricle.



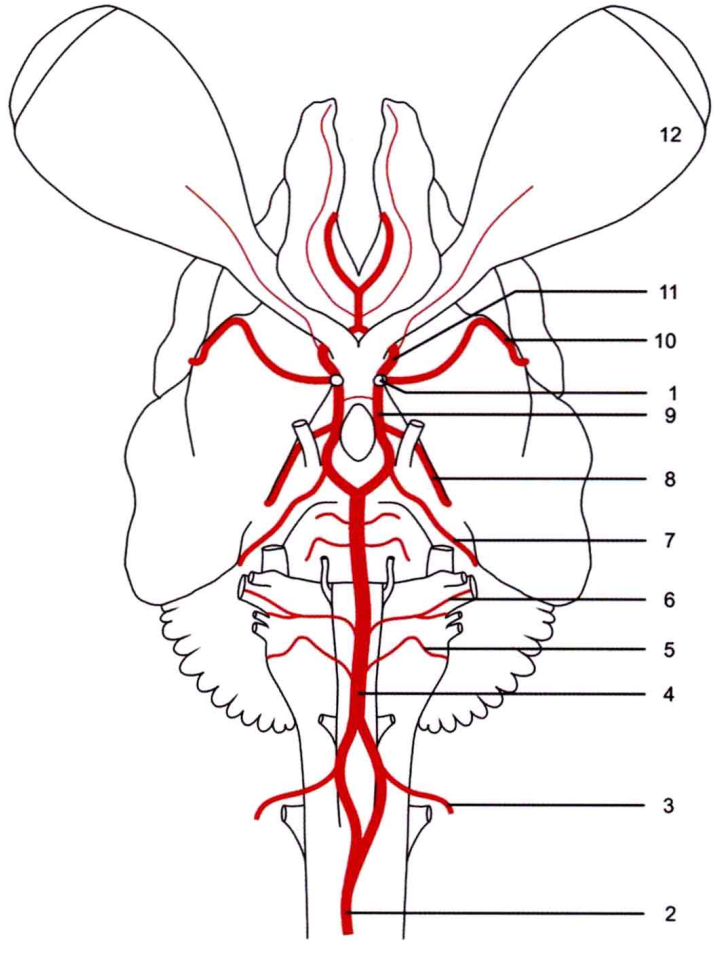

**CHAPTER 2, FIGURE 6** Morphological and functional subdivisions of the cerebellum. The vestibulocerebellum consists of the flocculonodular lobe (dark blue) and deals with input from the vestibular apparatus. The spinocerebellum (green) receives proprioceptive (and exteroceptive) information. The cerebrocerebellum [s. pontocerebellum (brown)] is involved in processing collateral information on corticofugal motor activity. pf, Primary fissure; unf, uvulonodular fissure. (Courtesy of Enke Verlag in MVS Medizinverlage Stuttgart GmbH & Co. KG.)



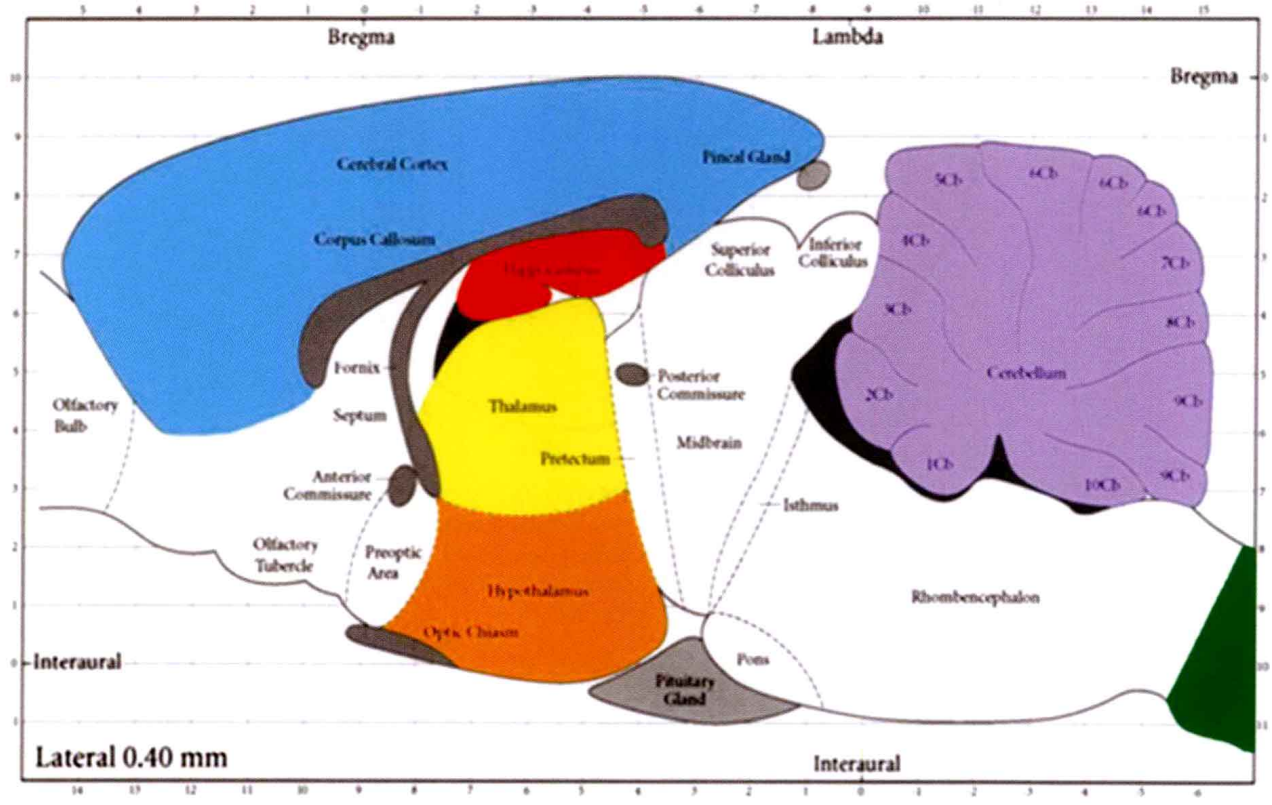

**CHAPTER 2, FIGURE 7** Embryonic development in the mammalian prosencephalon. Section at the level of the interventricular foramen (a), and sections caudal to the interthalamic adhesion at an early (b) and at a later stage (c) of development. (a) The basal nuclei include the nucleus caudatus, the putamen, and the globus pallidus. They develop from an originally compact mass of gray matter which is later split into separate nuclei by the entrance of axons that comprise the internal capsule. (b, c) The archipallium extends as a band along the medial border of either brain vesicle, dorsal to the choroid plexus of the lateral ventricle. (a) During further development (b, c), the archipallium is invaginated into the lateral ventricle, thus forming the cornu ammonis (hippocampus proper). (Courtesy of Enke Verlag in MVS Medizinverlage Stuttgart GmbH & Co. KG.)



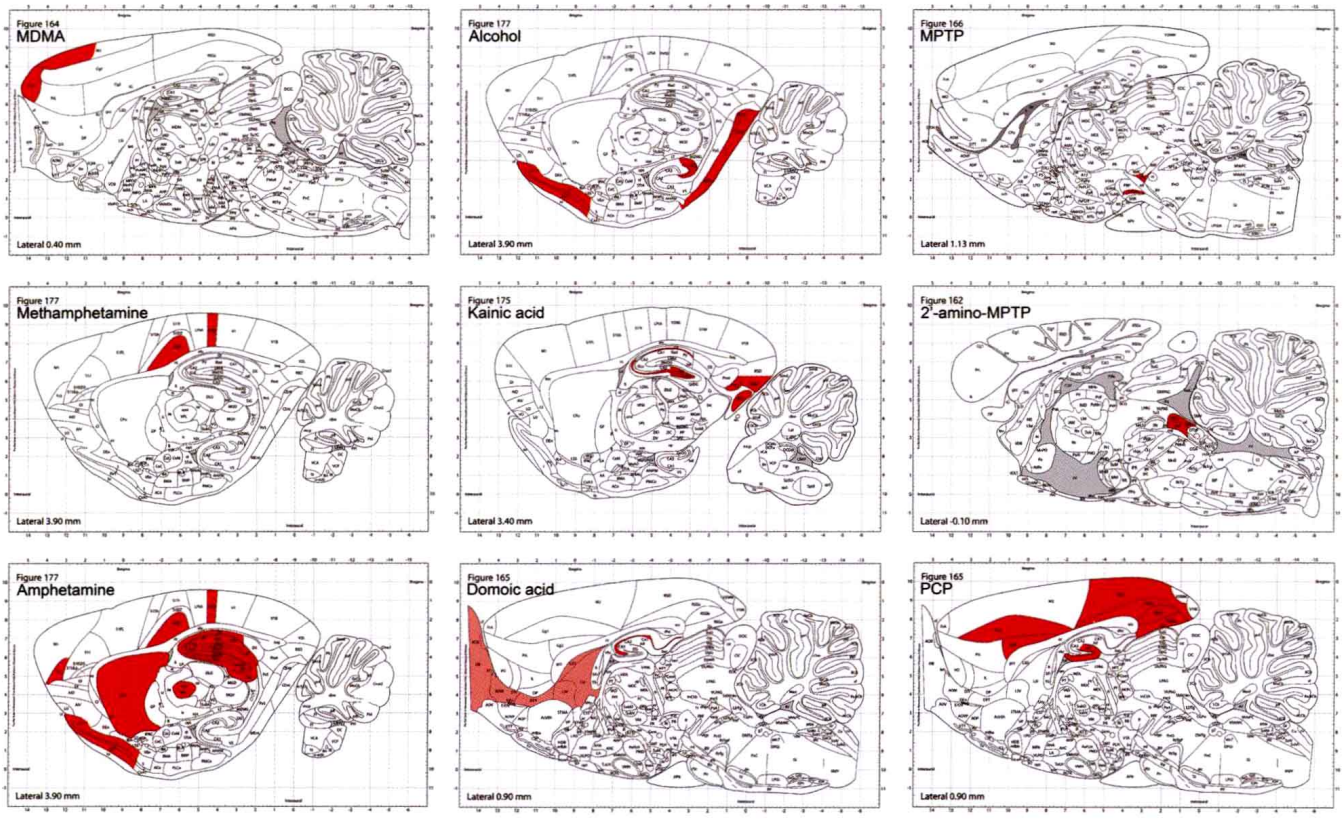

**CHAPTER 2, FIGURE 8** Blood supply to the spinal cord. The innermost zone (dark orange) is fed by branches arising from the ventral spinal artery (vsa), which enters the gray matter from the ventral fissure. The outer zone (yellow) depends on blood supplied from vessels penetrating the nervous tissue from the outer surface. The intermediate zone (pale orange) is supplied by both routes. (Courtesy of Enke Verlag in MVS Medizinverlage Stuttgart GmbH & Co. KG.)




**CHAPTER 2, FIGURE 9** Blood supply to the mammalian brain. 1, internal carotid artery; 2, ventral spinal artery; 3, vertebral artery; 4, basilar artery; 5, caudal cerebellar artery; 6, labyrinthine artery; 7, rostral cerebellar artery; 8, caudal cerebral artery; 9, caudal communicating artery; 10, middle cerebral artery; 11, rostral cerebral artery; 12, left eye. (Courtesy of Enke Verlag in MVS Medizinverlage Stuttgart GmbH & Co. KG.)




**CHAPTER 9, FIGURE 3** Major subdivisions of the brain shown in sagittal section: this single level (and there are many more levels) shows the complexity of brain organization.




**CHAPTER 9, FIGURE 5** Areas of the brain affected by nine known neurotoxins; note that some of the areas are quite small and easily missed in all but the most thorough brain sectioning scheme.