DIAGNOSTIC PATHOLOGY

Neuropathology

SECOND EDITION

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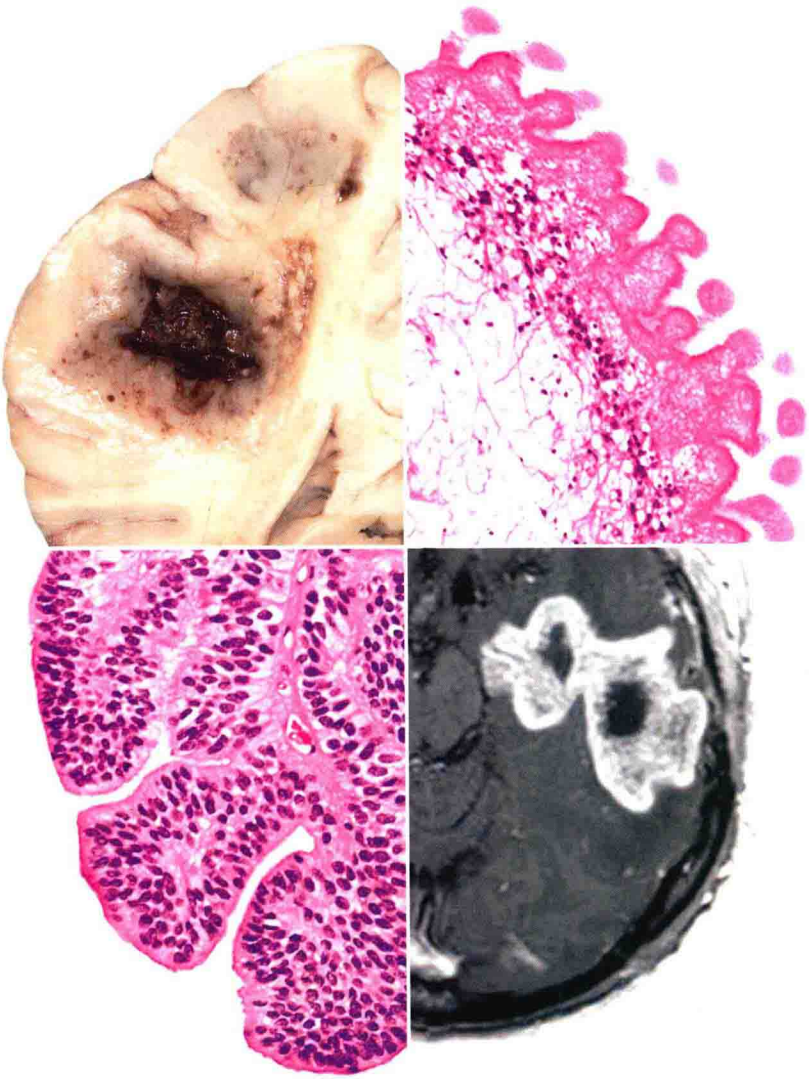

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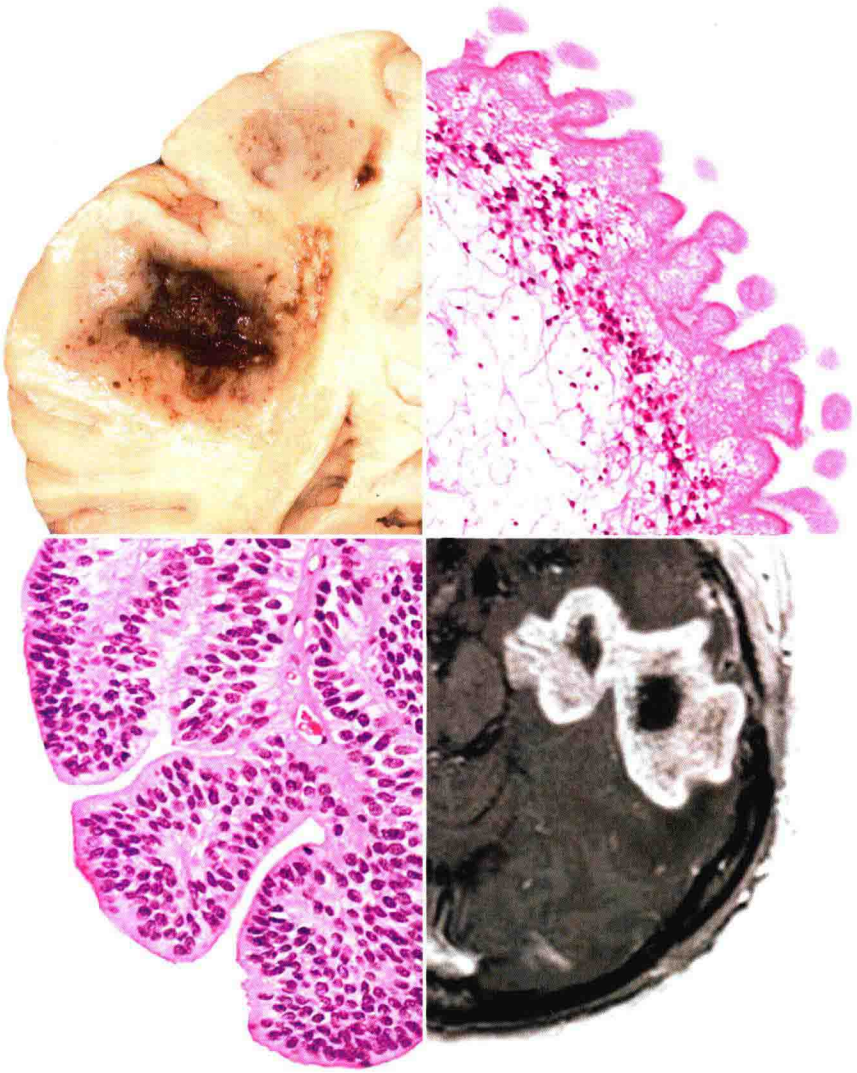

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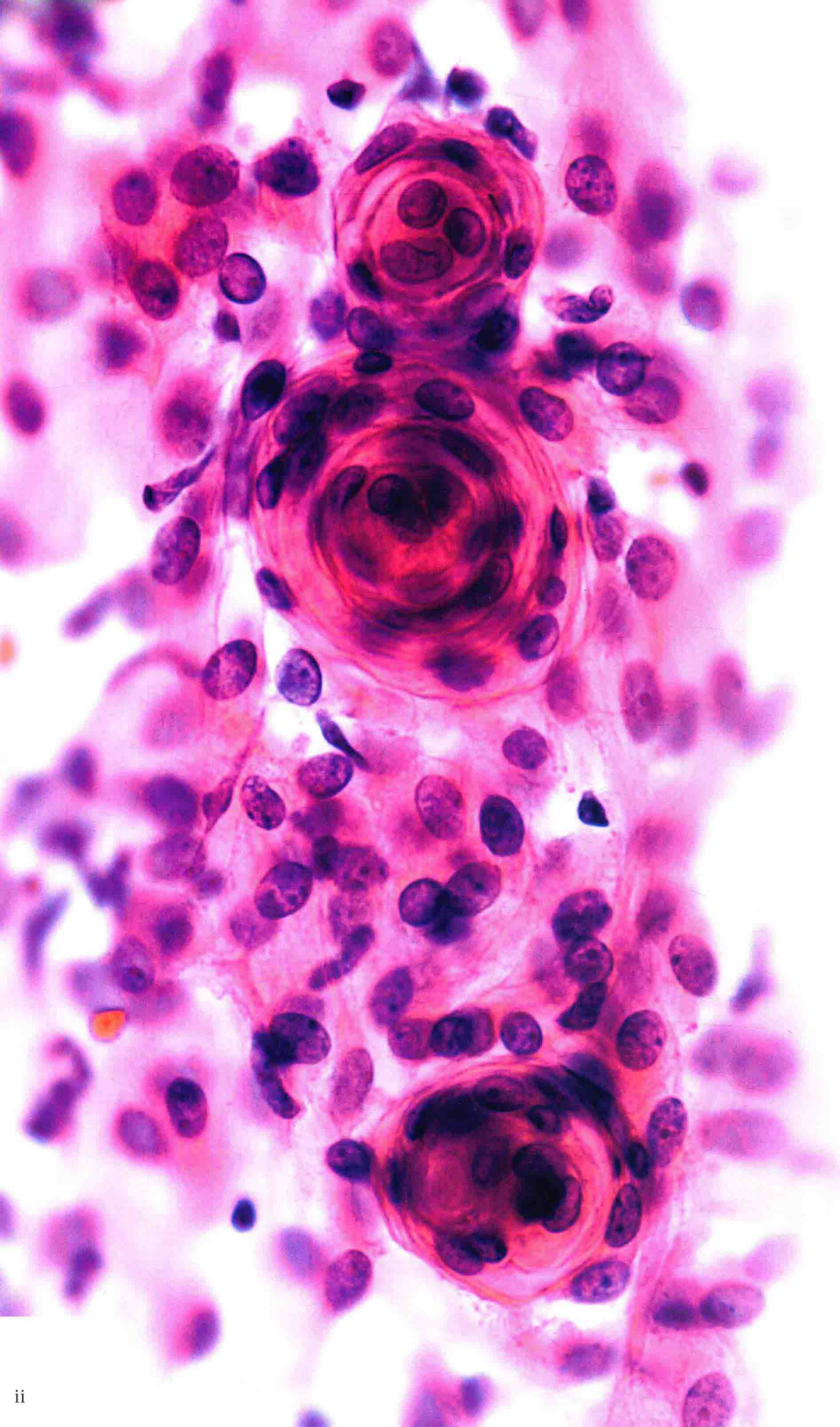

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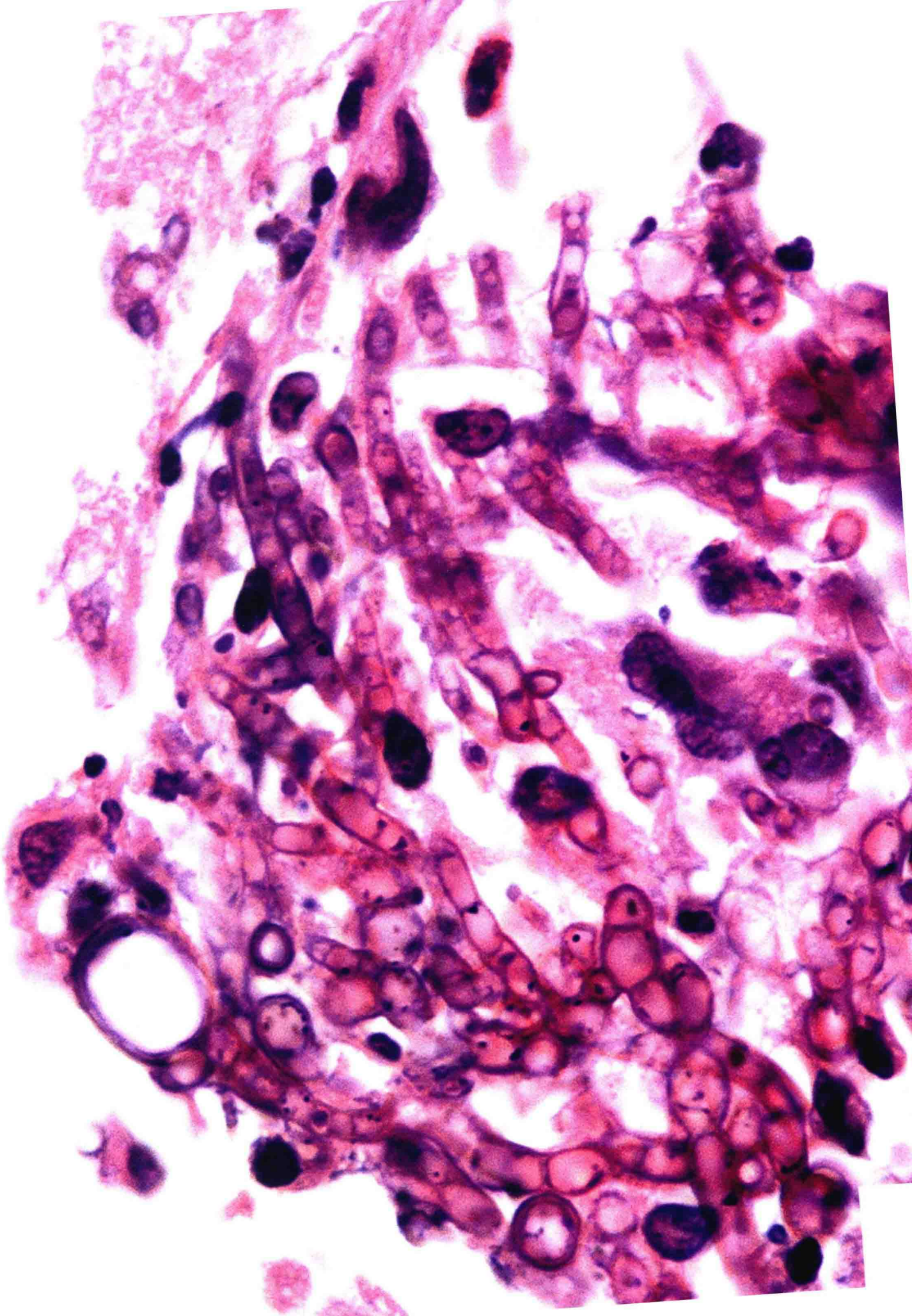


Dedications

The bell rings, and it is teaching time!!
The little porcelain bell chimes with a soft melodious tone, and everyone around the six-headed microscope is aware of the impending words of wisdom that hardly come out of the master's lips at other times. The ensuing statement, whether advice or an observation, better be recorded in your mind's hard drive since it will be of use many times as you face the same challenges in your own ventures. This little bell has accompanied all the sign-out sessions of Dr. Peter C. Burger at Johns Hopkins Hospital since the time I began working with him as an assistant professor in 1997. Many years later, the bell still chimes and brings awe and smiles to all those around that microscope. It has been a unique privilege to have worked with Peter C. Burger, undoubtedly one of the giants and keen observers of surgical neuropathology. Hundreds of publications, numerous books, lectures, and other scholarly works can only underscore a part of an academician's life that has inspired, motivated, provoked, and enticed numerous pathologists and other scientists.

There is little need to reiterate the timeline and accomplishments of Dr. Burger here but much necessity to pay tribute to my quiet mentor, who does not like to be in the limelight nor cares to talk about himself or his accomplishments. An occasional jape about his prowess on correct diagnosis or uncanny observational skills is all you can hear from him about decades of hard work. This whimsical statement often compels you to remember the crucial issues in a particular case and recall how he reached the diagnosis that may have eluded many skilled diagnosticians.

My entire career in neuropathology is a dedication to my Captain, as he has forced us to be far better than we can be. I have to tell him that none of the cups of coffee along with the good wisdom we have shared have been forgotten. This book is still the product of Peter C. Burger and Bernd W. Scheithauer to the very last sentence. Their vision, teachings, and passion for diagnostic neuropathology drives all of us to be worthy of the high standards they have established. Despite all the gloom and doom in this world, the efforts my two mentors have put into this book represent our faith in the good of humanity and our desire to see our patients cured of their ailments.

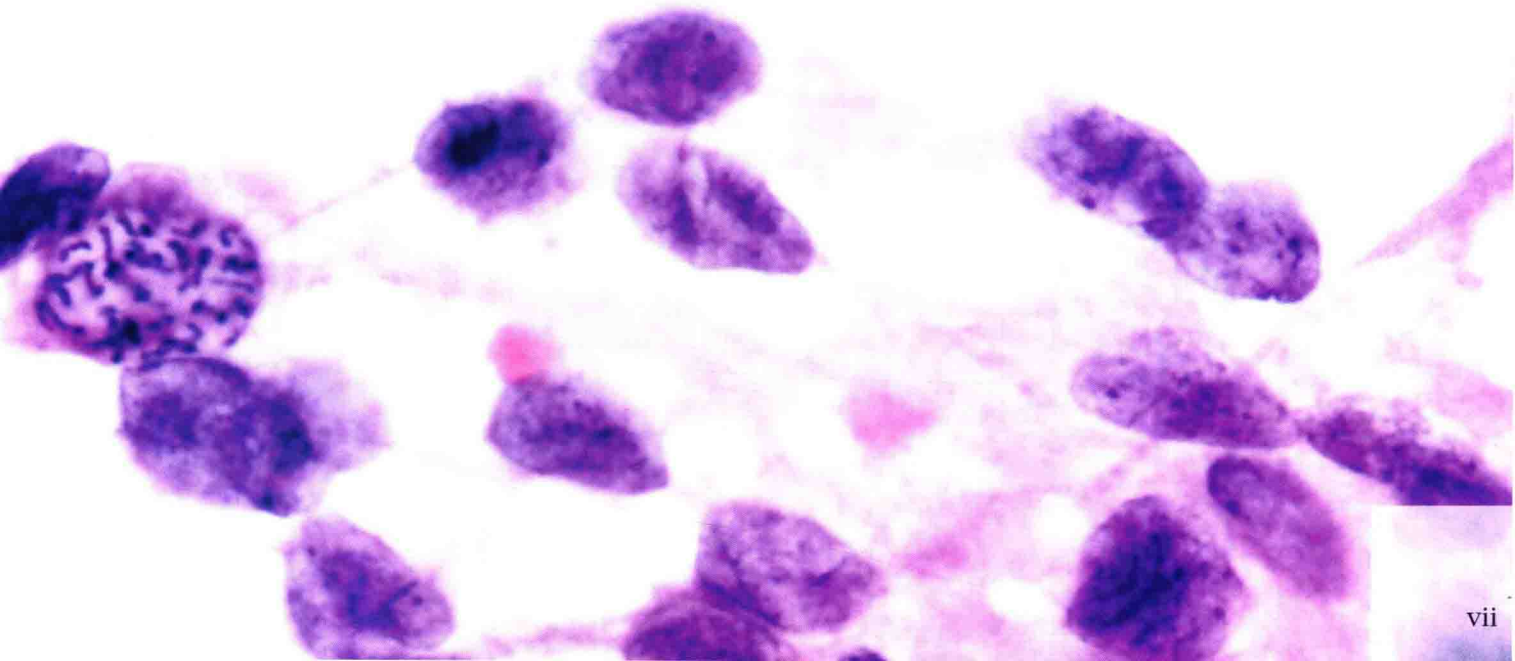
TT

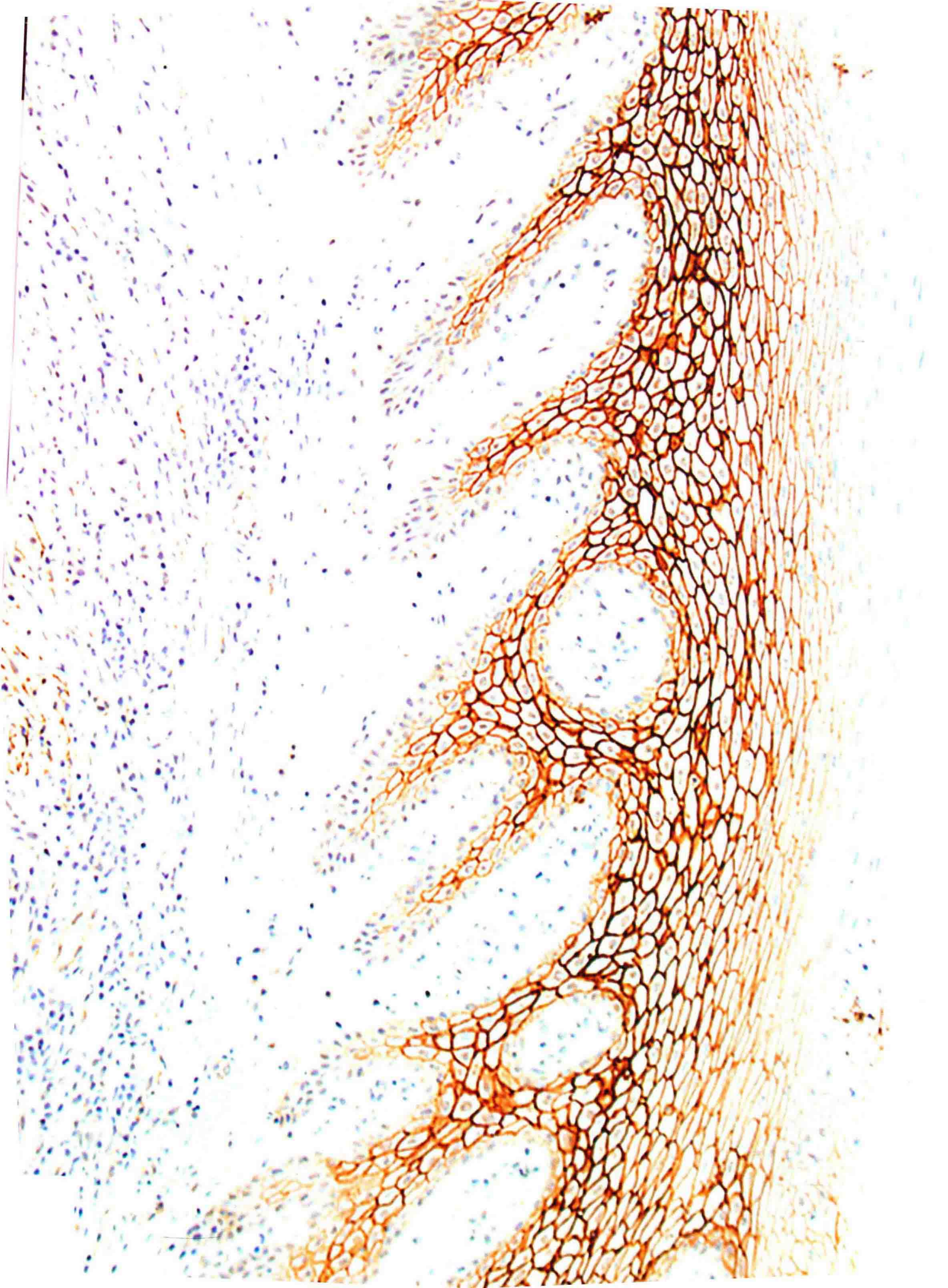
It has been an enormous pleasure to participate in this project started by two extraordinary men, who had an enormous influence in shaping how I practice medicine today. Bernd had a consistent presence during my formative years in pathology and neuropathology, an energetic motivator with his boundless enthusiasm for diagnostic neuropathology. Peter is a wonderful colleague and mentor and a continuous source of wisdom and advice in my professional and nonprofessional life. We are proud to preserve their voice and teachings as we carry this evolving project into the future and incorporate the recent exciting developments that are transforming our daily practice.

FJR

The original "footprints" of Peter Burger and Bernd Scheithauer, the initial senior authors of this text, remain throughout this second edition of their book. While I have never had the privilege of working directly with either Peter or Bernd, their "walk" has been directly extended by two of their most talented "academic descendants" (a.k.a. trainees), Tarik and Fausto. Together, the three of us have attempted to leave what was perfect in the first edition but update what was necessary in the current edition. We did this work as a direct tribute to both Peter and Bernd; we hope the reader will be pleased with the result and find the information useful in their practice.

BKKD





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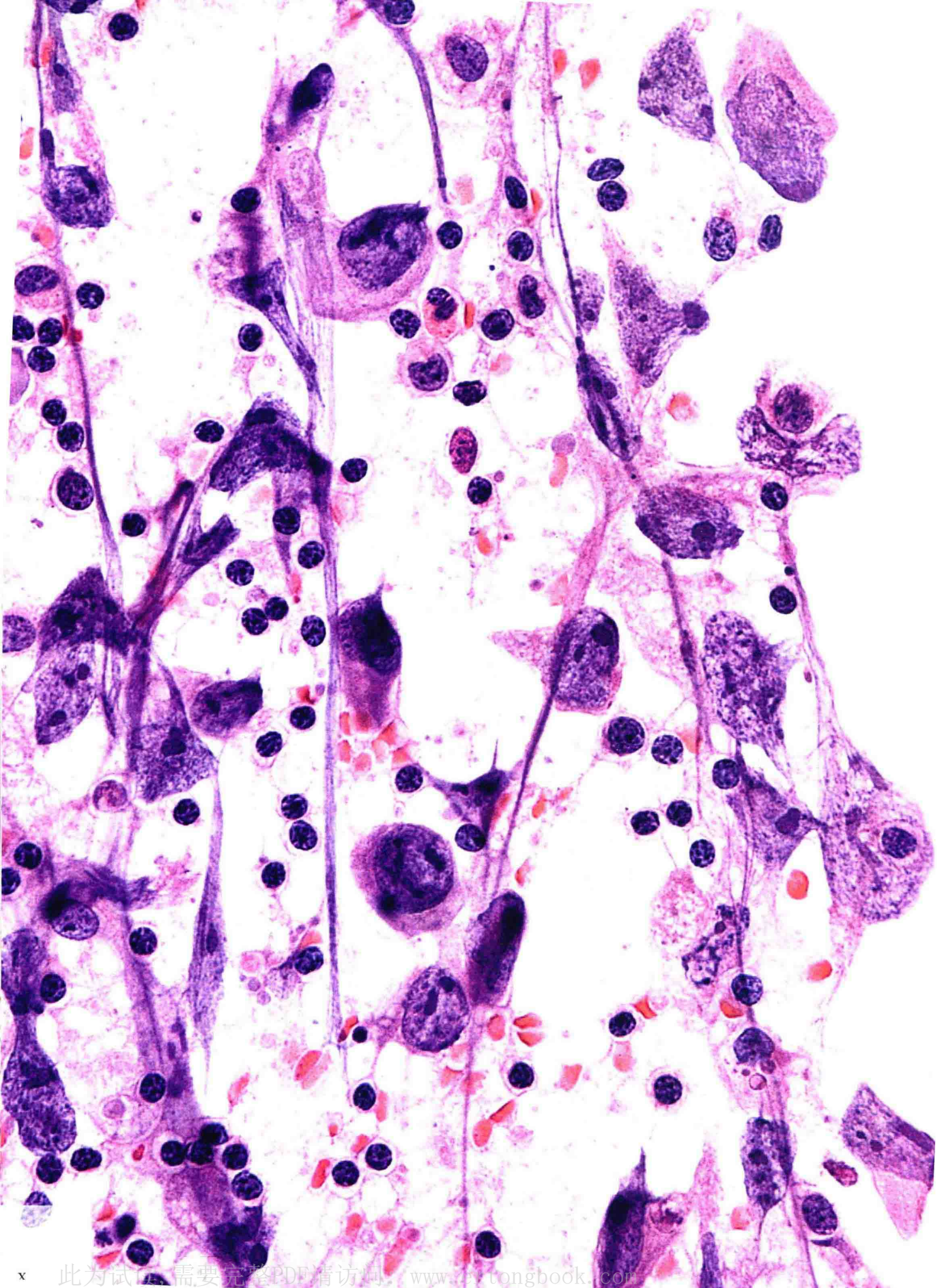

Preface

Until only two decades ago, it was quite sufficient to diagnose surgical neuropathology material based on routine hematoxylin and eosin (H&E)-stained sections, and the information gleaned from these sections was often sufficient to characterize tumors and categorize nonneoplastic processes. This practice has been sufficient for the clinicians in a majority of the diseases. The routine H&E stain still constitutes the critical starting point for surgical neuropathology today.

Yet, the explosion of new methods and models, advances in radiological, clinical, morphological, and molecular aspects of diseases, as well as the increasing options for different treatment modalities require frequent updating of "classical" textbooks and revision of diagnostic algorithms. The revision of this book was prompted by this necessity and the desire to continue the remarkable works of two giants in diagnostic neuropathology. Like the original work, the collaborative effort of the authors provides a pragmatic, visually satisfactory, and user-friendly reference for the everyday surgical pathologist.

Much is changing in the world of CNS neoplasia, and the modifications in this book reflect the changing times and the adoption of the "integrated diagnosis" that merges the old with the new methodology to provide a better guide for our colleagues.

Many chapters have been substantially updated, and all have been revised with new images and additional information. There is a new contributor to many chapters, and the readers will notice a change in the listing of authors for chapters with extensive revisions. This book remains the product of collaborative work, hours of deliberation, and careful consideration of the practical facts and key issues that will immediately attract the reader's attention. Our goal was to provide a reference that can be used in daily signout sessions and for teaching activities of our colleagues. We hope that the practicing pathologists at all levels—residents, fellows, academicians, and private practitioners—will find this work equally fun and useful and easy to navigate.

We are, as we always will be, grateful to our mentors, whom we owe the ability to carry on their journey with the hopes that our students will see even wider horizons. We are also grateful to all those countless workers in our divisions and in Elsevier, who tirelessly tried to make this book come alive. The search for better understanding and cures continues.

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What Is New and WHO Is Changing

There have been a number of discoveries since 2007 that are likely to be added in the next revision of the WHO classification of CNS tumors, and some are highlighted below. Some changes are significant, while others are minor but helpful developments. Furthermore, the use of "integrated diagnosis" that incorporates molecular pathological findings is being proposed as the standard reporting format.

Diffuse Astrocytomas

There seems to be a distinct difference between the molecular characteristic of adult and pediatric (age < 15) diffuse astrocytomas, and they will need to be considered in separate categories.

A. Adult Diffuse Astrocytomas; grouped into two distinct categories based on the presence of *IDH1/2* mutation

- **a. *IDH1/2* mutant diffuse astrocytomas**
  - **i.** Often coexist with ATRX mutation or loss of protein expression (on immunohistochemistry) and *TP53* mutation
  - **ii.** IDH mutant grade IV glioblastomas were shown to have better prognosis than IDH wild-type anaplastic (grade III) astrocytomas
  - **iii.** No significant prognostic difference was found between *IDH1/2* mutant WHO grade II and grade III diffuse astrocytomas
  - **iv.** *IDH1/2* mutant glioblastomas correspond to secondary glioblastoma
- **b. *IDH1/2* wild-type diffuse astrocytomas**
  - **i.** Uniformly have worse prognosis compared to all other diffuse gliomas
  - **ii.** Harbor genetic alterations more typical of glioblastomas (e.g., *EGFR* amplification &/or *PTEN* deletion)
  - **iii.** Often have intact ATRX expression and wild-type *TP53* gene
  - **iv.** *IDH1/2* wild-type glioblastomas correspond to primary glioblastoma
  - **v.** Frequently have *TERT* promoter mutations
- **c. Granular cell diffuse astrocytomas behave as glioblastoma, regardless of histological grade**

B. Pediatric Diffuse Astrocytomas and Glioblastomas

- **a. Pediatric high-grade astrocytomas (anaplastic astrocytomas, glioblastomas) lack *IDH1/2* mutation and mostly lack EGFR and PTEN alterations**
  - **i.** Most diffuse intrinsic pontine gliomas behave adversely, regardless of histological grade; many have mutations in genes encoding histone proteins (*H3F3A*, *HIST1H3B*, others)
  - **ii.** *H3K27M* increasingly identified in midline gliomas, especially thalamic and brainstem, as well as some spinal cord, in both children and adults; can be tested by IHC

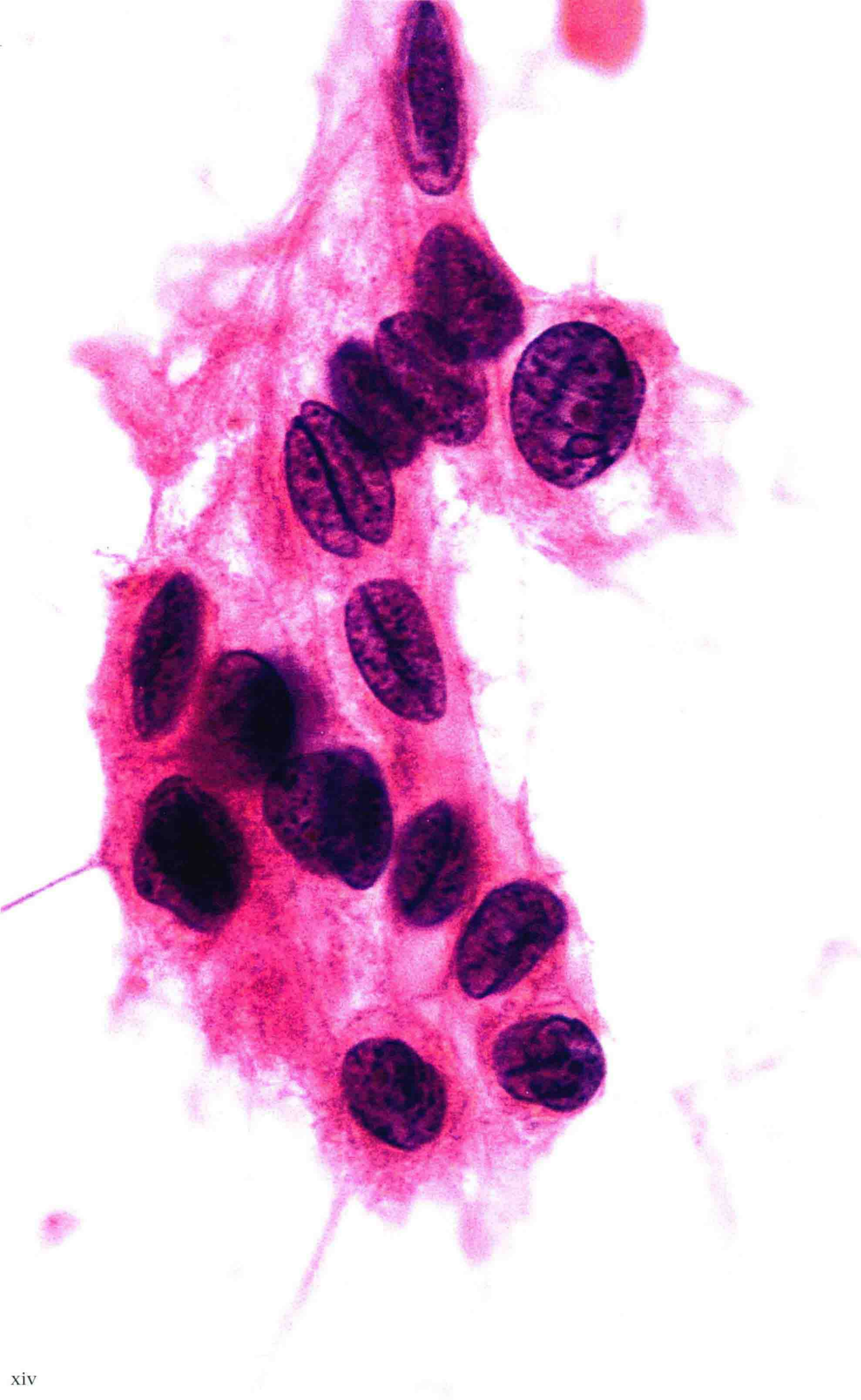
Oligodendrogliomas

Oligodendroglial tumors are defined by presence of both co-deletion of chromosomes 1p and 19q and *IDH1/2* mutations.

- It has been suggested that tumors formerly classified as glioblastoma with oligodendroglioma component by the WHO that also harbor 1p/19q co-deletions be considered anaplastic oligodendroglioma, WHO grade III
- Diagnosis of mixed oligoastrocytoma is discouraged (based on data showing almost all are either genetically oligodendroglioma (i.e., *IDH1/2* mutant, co-deletion of 1p, 19q, no ATRX mutation [i.e., no loss of nuclear ATRX by IHC] OR *IDH1/2* mutant, no co-deletion, ATRX +/- *TP53* mutations, not both and not an admixture of cells with both)
- Frequent *TERT* promoter mutations
- There are rare tumors in the pediatric population histologically similar to adult oligodendrogliomas without the above molecular changes; their nature is yet to be understood
- A distinct group of tumors currently termed "diffuse leptomeningeal oligodendroglial-like neoplasms" or DOLN harbor *KIAA-BRAF* duplications and 1p deletion, and may be considered a new entity

Other Pertinent Developments

- Pilomyxoid astrocytoma still remains a variant of pilocytic astrocytoma, but grading has been questioned, and a suggestion to omit WHO grading has been proposed
- Primitive neuroectodermal tumor no longer recognized terminology: Tumors formerly designated supratentorial or CNS PNET are now designated Embryonal Tumor, NOS
- Peripheral neuroectodermal tumor no longer recognized terminology: Tumors formerly designated pPNET are now simply Ewing sarcoma
- Chordoid glioma now recognized to express nuclear TTF-1, similar to other infundibular region lineage tumors (pituicytoma, spindle cell oncocytoma, granular cell tumor of neurohypophysis)
- Some supratentorial ependymomas are characterized by C11orf95-RELA fusion (testing may be performed by PCR or FISH for break-apart probes) and aggressive behavior; these tumors also show strong L1CAM positivity on immunohistochemistry
- TTF1 nuclear positivity is shared by pituicytoma, spindle cell oncocytoma, granular cell tumor of neurohypophysis, which suggests a common origin
- SOX10 positivity is seen in melanocytic and peripheral nerve sheath tumors and is useful in distinguishing them from other mesenchymal neoplasms
- STAT6 nuclear IHC expression (parallels STAT6:NAB2 fusion) in solitary fibrous tumor/hemangiopericytoma family of neoplasms distinguishes them from other spindle cell tumors, such as meningiomas or schwannoma
- SSTR2A strong diffuse positivity is somewhat better than EMA positivity in the diagnosis of meningiomas
- SF-1 (steroidogenic factor 1) now defines gonadotroph adenoma, distinguishes it from hormone negative SF-1 negative null cell adenoma
- Pit-1 expression in pituitary adenomas links all types of GH, PRL, TSH, and admixed hormonal combinations



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