PREFACE

Not another textbook for neuropathology! Yes, we hear you and feel your pain. In fact, that was our initial response when we were approached to write the book you are now holding. In surveying the expanse of currently available neuropathology textbooks, we felt there was a place for a book that could combine our career experiences of trying to discern what is known (and knowable) with the perennially proposed question, "What do we *need* to know?" Together we tried to produce a book that would be practical, understandable, and to the point (minimizing reading time during intraoperative consultation). We have concentrated our efforts on elucidating important neuropathologic entities that fall outside of general surgical pathologic practice. Conversely, we have given short shrift to disease entities falling well within the purview of the general surgical pathologist, but which also tend to involve the nervous system. Despite using this mental targeting to bring coherence and a sense of purpose to our writing, we believe this book will also prove helpful to pathology, radiology, and neurosurgery residents and staff as well as to others interested in a practical histopathologic approach to neurosurgical diseases.

We have found that much of the anxiety related to surgical pathology revolves around several major themes:

1. It is generally believed that though one can do without much of one's liver or colon, every neuron counts. Therefore, we are sometimes asked to make very big diagnoses on very small amounts of tissue.
2. This request usually comes as an intraoperative consultation, where time is of the essence, and technical aspects of the preparations may be less than ideal.
3. Everything looks pink.

Our publishers helped us with this last problem by insisting on black and white photographs. We initially protested, noting that many recent textbook reviews seemed to be primarily guided by whether illustrations were in color (good) or black and white (bad). However, upon further reflection we accepted this mandate as a blessing in disguise, allowing the reader to focus on differences in morphology, rather than tincture, as a guide to correct diagnosis. In fact, one of us (M.C.) has always been a fan of black and white photography, both in histologic atlases as well as in the immortal photographs of artists ranging from Ansel Adams to Diane Arbus. Within this framework, we have attempted to produce a user-friendly guide to the exciting world of neuropathologic diagnosis. Although Chapter 1 covers intraoperative neurosurgical diagnosis in general, we never strayed far from the frozen section room, either in body or in spirit, as we attempted to elucidate the neuropathologic entities comprising the remainder of the book. Though we realize that it is neither possible nor desirable to remove all anxiety from surgical neuropathologic diagnosis (after all, it *is* brain surgery), we hope that *Practical Differential Diagnosis in Surgical Neuropathology* will help focus the reader's energy toward optimizing our common goal: the care of the patient.

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2 Gliosis

ONE OF THE MOST CHALLENGING differential diagnostic problems encountered in the setting of surgical neuropathology is distinguishing between gliosis or reactive astrocytosis and a low-grade glial neoplasm. Gliosis is the brain's way of reacting to injury, insult, or "something" that should not be there (e.g., a tumor). Therefore, it is common to observe at least some degree of reactive astrocytosis adjacent to and associated with a tumor. This problem is further magnified by the paucity of material that is typically available for evaluation, particularly in this age of stereotactic biopsies. Compound this with all the artifacts and limitations one can encounter in the setting of intraoperative consultation, and the distinction between gliosis and an infiltrating, low-grade glioma often tops the list as one of the more difficult challenges of diagnostic neuropathology.

Before one even looks at the biopsy, basic clinical and radiographic information should be available or sought out. Information with regard to the age of the patient, precise location of the lesion or lesions seen radiographically, a prior history of central nervous system disease or disease that may potentially involve the central nervous system, and some sense of the time course of the disease process in question, are all important and potentially useful pieces of information. A previous history of radiation therapy or trauma involving the brain should alert one to expect to see some gliosis. All too frequently, the pathologist is asked to interpret a biopsy, given nothing more than an age on a requisition form (which may or may not be always accurate!), a "useful" site designation, and clinical information such as "brain," "lesion," or "tumor." This form of communication is woefully inadequate.

The radiographic appearance of the lesion is of critical importance. The presence of a mass or tumor radiographically most certainly does not represent simply a reactive astrocytosis. Unfortunately, there are a variety of nonneoplastic conditions, such as infarct, demyelinating disease, or infection (abscess), that may radiographically mimic a tumor and most certainly will demonstrate areas of astrocytosis. However, most of these other conditions are characterized by features that generally allow for their recognition. The presence of prominent numbers of macrophages, which are commonly encountered in an infarct or demyelinating condition, are distinctly uncommon in most fibrillary astrocytomas *(1,2)*.

Reactive astrocytosis, similar to gliomas, may involve both gray and white matter. Areas of astrocytosis associated with tumors tends to be most noticeable at the infiltrating edge of the lesion and may be accompanied by edema, particularly in a higher grade neoplasm. Gliosis often results in parenchyma that is firm in consistency, a feature that does not prove very useful in the routine evaluation of small biopsy specimens. Likewise, many of the gross and radiographic features of a tumor such as microcystic degeneration or calcification are not going to be grossly appreciable in a small biopsy core.

Microscopically, similar to low-grade tumors, astrocytosis may result in a slight increase in cellularity (Figs. 2-1 and 2-2). The increased cellularity associated with reactive astrocytosis is generally evenly distributed from microscopic field to field, in contrast to tumors, where the increased cellularity is generally unevenly distributed. Again, in a small biopsy or smear/crush preparation, this distinction may be subtle or not evident. Care must be taken in the setting of the biopsy which appears hypercellular, but which lacks any appreciable atypia or cells with prominent eosinophilic cytoplasm; this picture may be seen in a thickly cut biopsy of normal parenchyma. Both astrocytosis and infiltrating glioma result in some degree of cytologic "atypia" or cellular alteration. However, there are some differences between the cytologic alterations in these processes. Reactive astrocytes frequently have a slightly enlarged nucleus, which is generally eccentrically

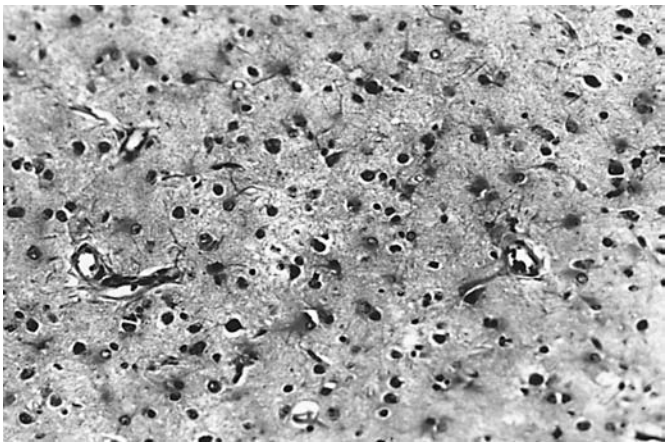

Fig. 2-1. Increased, evenly distributed cellularity in reactive astrocytosis.

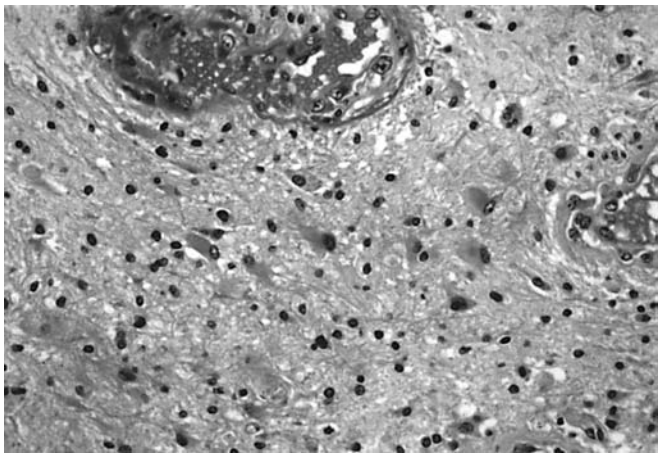

Fig. 2-3. Reactive astrocytes with abundant eosinophilic cytoplasm.

placed and often associated with prominent eosinophilic cytoplasm and stellate cytoplasmic processes *(3)* (Fig. 2-3). Nuclear contours in reactive astrocytes are generally rounded or slightly oval and cells are generally monomorphic in their appearance. Binucleate cells are not uncommon. The atypia encountered in a low-grade astrocytoma is characteristically different *(4)*. Cells generally have a high nuclear to cytoplasmic ratio (i.e., they contain little or no discernible cytoplasm). The nuclei are enlarged in the order of two to three times the size of normal astrocytic nuclei. Nuclei have markedly irregular contours with indentations and irregularities. Nuclear chromatin often is more clumped and unevenly distributed. Nuclei are generally more hyperchromatic or darker staining. Oligodendroglial cells are characterized by round nuclei with scant cytoplasm.

Distinction of gemistocytic astrocytes in a gemistocytic astrocytoma from reactive astrocytes, particularly at the infiltrative edge of a tumor, may be more difficult. Gemistocytic astrocytoma cells tend to have shorter and thinner cytoplasmic processes, in contrast to the longer, tapering processes of reactive astrocytes. These subtle differences may not be readily apparent on routine hematoxylin–eosin staining and may require a cytologic preparation or immunostains such as glial fibrillary acidic protein stain (GFAP) to visualize *(5)* (Fig. 2-4).

There are other features which are more variably present in tumors, but can serve as soft clues in this differential diagnosis between gliosis and glioma. Identification of a mitotic figure in an astrocytic cell is evidence in support of a neoplastic process. Caution should be taken not to confuse a mitotic figure in a vessel wall or in coexistent granulation tissue as indicative of tumor. An atypical mitotic figure is most certainly indicative of a neoplasm. The formation of granulation tissue is relatively uncommon in the central nervous system, as compared with other organ systems, where this is a common pattern of injury repair. Granulation tissue observed in the brain or

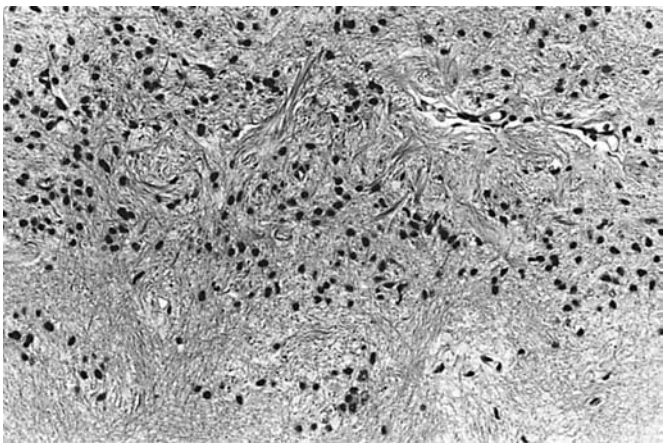

Fig. 2-2. Reactive astrocytosis and gliosis in a region adjacent to infarct.

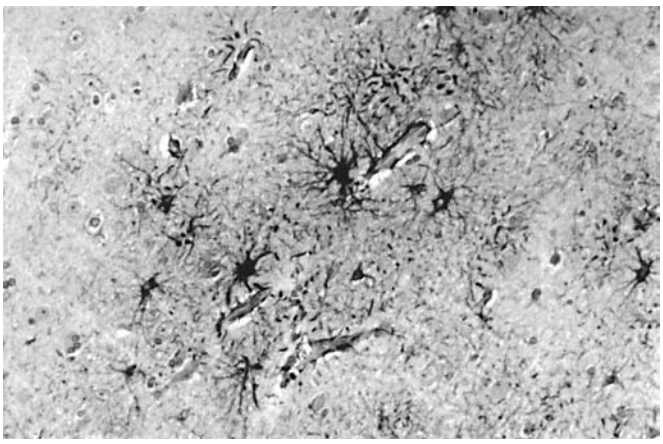

Fig. 2-4. Glial fibrillary acidic protein stain highlighting long, tapering processes in reactive astrocytes.

Table 2-1.
Gliosis Versus Glioma

	Gliosis	*Glioma*
Age	Any	Peak 3rd to 5th decade, but can occur at any age
Location	Gray or white matter	White > gray matter
Gross	Firm	Firm; obliterate gray-white junction, may be cystic
Hypervascularity	Evenly distributed	Unevenly distributed
Atypia	Binucleate cells, more eosinophilic cytoplasm with long tapered processes	High nuclear/cytoplasmic ratio, hyperchromatic, nuclear irregularity and pleomorphism
Mitoses	Usually absent	May be present
Calcification	–	±
Microcystic change	–	±
Satellitosis	–	±
Distribution	Generally focal	Diffuse infiltration

spinal cord develops from fibroblasts and mesenchymal cells normally encountered around vessels and in the leptomeninges.

The presence of true microcystic degeneration is strongly indicative of a neoplastic process, rather than simply reactive astrocytosis. Care should be taken not to interpret the pseudomicrocystic change one can generate as an artefact at frozen section intraoperative consultation as true microcystic degeneration. One should also not misinterpret cystic degeneration in an area of remote infarct or demyelinating disease as being suggestive of a tumor. Both of these processes will show prominent numbers of reactive astrocytes.

Microcalcifications may be seen in up to 15% of fibrillary astrocytomas and in the vast majority of oligodendrogliomas *(6)*. Calcifications are generally not part of the gliosis process, although calcification may develop in association with other processes in which gliosis is a prominent feature, including remote ischemic injury or organized hematoma.

Satellitosis is a particularly common occurrence at the gray-white interface, where oligodendroglial cells normally arrange themselves around neurons. Occasionally, satellitosis of tumor cells around preexisting structures such as neurons or vessels may be seen at the infiltrating edge of astrocytomas (secondary structures of Scherer) *(7)* or of oligodendrogliomas. Reactive astrocytes do not typically arrange themselves around other structures. The presence of eosinophilic Rosenthal fibers or granular bodies, although more typically thought of as being associated with low grade neoplasms such as pilocytic astrocytoma or ganglioglioma, may on occasion be observed in areas of long-standing reactive astrocytosis and in a variety of non-neoplastic conditions. Care should be taken not to confuse piloid gliosis with a pilocytic astrocytoma *(8)*.

Table 2-1 summarizes features that may be useful in differentiating gliosis from a low-grade glioma. Often times, the single most useful parameter histologically is the quality of cytologic atypia. Specific issues surrounding reactive changes as they pertain to radiation therapy will be discussed in Chapter 6.

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