

## **Blessing, Chapter 3**

### **Anatomy of the Lower Brainstem, part 1**

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*Check what Cajal has said before you begin working on any part of the nervous system.*  
Advice from Le Gros Clark, cited in the foreword to Swanson's translation of Cajal's  
*Histology of the Nervous System*

Many of the brainstem nuclei mediating alerting, nociceptive, cardiovascular, respiratory, ingestive, and visceral homeostatic functions, form part of the region traditionally referred to as the reticular formation. Because of uncertainty surrounding that term, this chapter includes a detailed critique of the various concepts of the reticular formation. Most of the brainstem nuclei and pathways relevant to the functions discussed in this book are reviewed. For a more complete account of the relevant neuroanatomy in a number of species, excellent atlases and detailed descriptions are available, for humans, by Olszewski and Baxter (1949) and Paxinos (1990); for rats, by Paxinos and Watson (1986) and Swanson (1992); for rabbits, by Meesen and Olszewski (1949); and for cats, by Berman (1968) and Mannen (1988). Relevant chapters in Loewy and Spyer (1990b) and Paxinos (1995) also contain valuable accounts of the neuroanatomy of experimental animals, particularly rats. Cajal's *Histology of the Nervous System*, now available in English translation (Cajal, 1909), takes the reader directly to the microscopic appearance of the various medullary transections.

A series of low-power darkfield photomicrographs of freshly cut unstained transverse sections through the brainstem of the rat, from the spinomedullary junction to the caudal midbrain, are presented in Figure 3.1A-H. The detail in these micrographs reflects regional variations in the optical density within each section, a property largely determined by the amount of myelin. In the darkfield views, myelinated regions appear lighter, and unmyelinated regions appear darker. Perikarya of individual neurons can sometimes be discerned because there is little or no myelin around the cell body. Thus, individual motoneurons are apparent in the hypoglossal nucleus in Figure 3.1B. The fibers of the tractus solitarius, which are myelinated, lose their sheaths as they enter the nucleus tractus solitarius, so the nucleus appears as a relatively dark area in the dorsomedial medulla in Figure 3.1B. The same region has a quite different appearance after a Nissl stain (see Fig. 3.10). The views of the rat brainstem can be compared with the the Nissl and Weil stains of paired transverse sections from the human brainstem, together with magnetic resonance images for orientation (see Fig. 8.2A-P).

The darkfield views of unstained sections emphasize the complexity of the interrelationships between neuronal perikarya and fiber pathways. The labeling on the photomicrographs is conservative, with no attempt to draw boundaries around nuclear configurations. Such an approach is helpful in reassessing the concept of the reticular formation.

**Figure 3.1** A-H, Darkfield photomicrographs of unstained transverse (30  $\mu\text{m}$ ) frozen sections through rat medulla, pons, and caudal midbrain. The sections were mounted in glycerol, coverslipped, and photographed with an Olympus BH2 microscope fitted with a Kodak digital camera. Individual photographs were pieced together and processed with image analysis software (Adobe Photoshop and Canvas). Images were labeled and printed directly from the computer using a Kodak dye-sublimation printer. Dr Gai Weiping contributed to the construction of this rat atlas. Abbreviations listed on pages xiii-xiv.

## **Naming in Neuroanatomy**

As noted in Chapter 1, we can imagine that the "stem" of the brain was so named to contrast it with the cerebral hemispheres, the "flower" of the brain. Most neuroanatomical names and classifications were bestowed before natural, functionally relevant subdivisions of the nervous system were defined (see Swanson, 1992, for a helpful discussion of this matter). This somewhat arbitrary assignment of terms was essential, but we need to be mindful of prejudices that may have been engendered. Thus the baby born with an intact brainstem but no forebrain will presumably always be referred to as "anencephalic" in spite of the misleading impression created by the term.

When the brainstem was initially subdivided, the emphasis was on gross embryology and on external appearance. The various flexures and enlargements, the opened fourth ventricle, the extensive middle cerebellar peduncle (the pontine bridge), the cerebellum, and the prominent superior and inferior colliculi, all played important roles in the definition of medulla, pons, and midbrain. The terms are helpful, but excessive emphasis on these somewhat arbitrary subdivisions can complicate our understanding. The term tectum (roof), for example, refers to the dorsal portion of the midbrain without indicating any functional or structural unity. There is no fundamental natural distinction between medulla and pons so that whether the facial nucleus is in the rostral medulla or in the caudal pons is an arbitrary verbal question. Transverse sections through the midbrain include thalamic structures such as the medial and lateral geniculate nuclei, even though the thalamus is part of the forebrain. The study of sagittal and horizontal brainstem sections helps to place arbitrary subdivisions in context, thereby helping us build up a unified picture of the whole brainstem.

Definitions of individual brainstem nuclei have also been greatly influenced by neuroanatomical methodology. Cajal's use (1909) of the Golgi method, in conjunction with Nissl and myelin stains, as well as various degeneration techniques, gave him a feel for the connectivity of the various brainstem nuclei. Brodal (1957) also considered evidence from the various techniques, with emphasis on retrograde degeneration procedures in young animals. In contrast, Olszewski concentrated virtually exclusively on the Nissl method, so that his accounts of brainstem anatomy (Olszewski and Baxter, 1949; Meessen and Olszewski, 1949; Olszewski, 1954), invaluable as they are, place major emphasis on the definition of brainstem nuclei in terms of "cytoarchitectonic findings," that is, on the structure and arrangement of nerve cells in terms of their size, shape, and configuration. As we shall see, Olszewski's probably excessive use of subdividing lines reflected his eagerness to emphasize the presence of definable brainstem nuclei in the supposedly (by others) undifferentiated reticular

formation. Since the 1970s, histochemical, immunohistochemical, and tract tracing studies have added to the criteria by which nuclei are defined and further subdivided.

Gene-based embryological studies are also beginning to make a contribution. Embryological development of the vertebrate cranium involves iterative segmentary processes. Although the contributions of the various embryonic tissues (especially neuroepithelium and mesoderm) are still uncertain, foci of rapidly proliferating cells form a series of transient rostrocaudal swellings within the neural tube shortly after neurulation. These segmentary elements, known as rhombomeres in the hindbrain, are under control of homeobox genes generally similar to those responsible for segmentation in *Drosophila*. Chick hindbrain rhombomeres have been shown to be associated with formation of cranial nerves V, VII, and IX, as well as cranial nerve VIII. The rhombomeres may be units of cell lineage restriction, with living descendants of a single dividing cell being confined to their original rhombomeric unit. The rhombomeres are illustrated in Figure 3.2. Their definitions and histories are discussed by Lumsden and Keynes (1989), Simon and Lumsden (1993), Lumsden (1990), Northcutt (1993), and Gilland and Baker (1993).

**Figure 3.2** Segmental rhombomeres (r1-r8) transiently expressed in the chick hindbrain. Roman numerals indicate cranial nerves. Branchial arches are indicated by b1-b4. (Modified from Lumsden, 1990.)

### **The Reticular Formation of the Brainstem**

At the symposium held in the Canadian Laurentian mountains, Olszewski (1954) reminded his colleagues of the conventional anatomical definition of the reticular formation. The term refers to those parts of the brainstem appearing as an interlacing network of fiber bundles in myelin stains, with neurons scattered among the fiber bundles. Brodal (1957), who also emphasized the traditional definition of the reticular formation, assures us that the early neuroanatomists held no special theoretical concepts concerning the specificity or otherwise of the neuronal connections made by reticular neurons. The accounts of the reticular formation by Cajal (1909) and Herrick (1948), for example, were simple and cautious.

### **The Views of Cajal and Herrick**

Cajal's concept of the reticular formation is best understood in relation to his overall account of the medulla oblongata. As the central canal of the spinal cord widens into the fourth ventricle, structures dorsal to the canal become displaced laterally and ventrally (as shown in Fig. 3.1). The equivalent of the spinal dorsal horn occupies a majority of the grey matter associated with the fourth ventricle, also divided into two columns. The dorsal sensory column receives fibers from the vestibulocochlear and intermediate nerves and most of the sensory fibers associated with the glossopharyngeal and vagus nerves. The ventral column (spinal nucleus of V) corresponds to the substantia gelatinosa, as well as the head and neck of the dorsal horn. The spinal ventral horn is converted into medullary motor nuclei lying dorsomedially, whereas the sensory nuclei (extensions of the dorsal horn) come to lie dorsolaterally. Cell groups that are adjacent in the spinal grey become separated by fiber tracts in the

medulla. Thus the two major cell clusters in the motor horn become distinct columns of motoneurons in the medulla (dorsomedial and ventrolateral). Finally, spinal grey matter associated with the intermediate horn (neurons in the interstitial nucleus and the funicular cells of the ventral horn) is replaced in the medulla by large interstitial neurons. Together with the medullary white matter, these neurons, Cajal notes, are known as the *reticular formation*.

Cajal divided the reticular nuclei into raphe and medial and lateral groups, although he was not entirely convinced of the usefulness of the medial-lateral distinction, which was based largely on the greater predominance of fiber bundles, and generally larger neurons, in the more medial region. Cajal noted that fibers descending from the neocortex do not innervate cranial nerve motoneurons. He suggested that the descending fibers synapse on some of the reticular neurons, which might therefore be "intermediary between the pyramidal tract and brainstem motor nuclei" (Cajal, 1909: 788). Cajal cautiously considered that reticular neurons might also function as third-order sensory neurons. Inputs to both motor and sensory components of the reticular formation derive (so Cajal suggested) from the spinal cord, from second-order sensory neurons, from other reticular neurons, and from other brain regions such as neocortex, cerebellum, and tectum. There is nothing in Cajal's account to suggest that cells in the reticular formation have the same function and the same nonspecific connections.

Herrick's concept of the reticular formation was similar to that of Cajal's. In his classic study, *The Brain of the Tiger Salamander* (1948), Herrick recognized three basic longitudinal divisions in the brain and spinal cord. There is a dorsal sensory input zone, a ventral motor output zone, and an intermediate zone for coordination and integration of inputs and outputs. In the hindbrain, boundaries between the intermediate zone and the other two zones are blurred, especially in the more ventral regions. The motoneurons and the coordinating interneurons, with similar morphologies, are difficult to distinguish unless a conveniently visualized axon exiting in motor roots defines a given cell as a motoneuron. Herrick refers to the region containing the coordinating interneurons as the reticular formation. In the tiger salamander this interneuronal region contains relatively few neurons, reflecting the relatively stereotyped and rigid behavior patterns that they integrate.

In the process of evolution, as stereotyped responses give way to more complex and more flexible motor patterns, there is, Herrick (1948:65) notes, a corresponding increase in the numbers of neurons in the reticular formation and, presumably, an increase in the complexity of their interconnections: "The final result is that in the human brain the apparatus of intermediate-zone type has increased so much that it comprises more than half the weight of the brain, for both cerebral and cerebellar cortices are derivatives of this primordial matrix." By including the neocortices in his concept of the human reticular formation, Herrick emphasizes the connective specificity of the constituent neurons.

A number of authors (including Ramón-Moliner and Nauta, 1966) claim Herrick's study as support for the idea that the reticular formation of more primitive animals is a primordial diffuse nonspecific net. Herrick does introduce the salamander brain as a "primitive and relatively unspecialized web of tissue." However, as noted, he offers a detailed anatomical account that contains nothing to suggest that either the individual neurons or their connectivity is qualitatively different from the neurons that

constitute the brains of higher vertebrates. The concept of a primordial diffuse net suggests that an animal with such a nervous system would lack the capacity for highly differentiated actions. Yet Herrick recognizes the tiger salamander as "a predacious and voracious terror" to all humbler inhabitants of the world in which it lives.

### **Contributions of Moruzzi, Magoun, and the Scheibels to the Concept of the Reticular Formation**

A fundamental paradigm shift in the concept of the reticular formation occurred when Moruzzi and Magoun grafted their "ascending reticular activating system" onto the traditionally conceived Cajal-type concept of the reticular formation (see Chapter 6 for references and further discussion of the ideas of Moruzzi and Magoun). In fact, it was simply *assumed* that large regions of the brainstem consist of nonspecifically interconnected neurons whose output functions as a kind of volume control for the level of arousal and consciousness. This system of reticular neurons was considered to be driven by abundant collaterals from the classic lemniscal- or spinothalamic-specific sensory pathways. The assumption was that, since diverse inputs can modify the level of arousal, the anatomical pathways mediating these changes must be nonspecifically interconnected. Figure 3.3A, from Magoun (1954), summarizes the theoretical neuroanatomical arrangement, seen as consisting of a series of ascending polysynaptic relays (mediated by short-axoned neurons). The neuronal system, by virtue of its polysynaptic relays, was hypothesized to be especially sensitive to the action of anesthetic agents (French et al., 1953b).

**Figure 3.3** A, Schematic representation of the ascending reticular activating system, with its proposed inputs and forebrain projections. (Modified from Magoun, 1954.) B, Drawing of a Golgi silver-impregnated neuron in the brainstem of a 2-day-old rat. (Modified from the drawing by Scheibel and Scheibel, originally prepared for the book by Brazier, 1968.)

At the Henry Ford Hospital Symposium, Scheibel and Scheibel (1957) presented their concept of the structural characteristics considered to mediate the integrative actions of the brainstem reticular core. Their study "grew out of our need to understand a little more of the structural substrates possibly involved in the delusional and hallucinatory phenomena with which our psychotic patients daily baffled us in the psychiatric clinic. Our hope has been to construct some kind of total image of the core of the brain stem." In symposia, in abstracts, and in book chapters (1951, 1955, 1955, 1957, 1967, 1980, 1984), the Scheibels presented Golgi studies depicting long-axoned neurons, such as the one shown in Figure 3.3B, which, paradoxically, are conventionally considered as providing a neuroanatomical framework for the theories proposed by Moruzzi and Magoun. In responding to the Scheibels' presentation at Henry Ford Hospital, Kuypers observed that the renewed use of the Golgi method could mark the beginning of a new era in neuroanatomy. As Brodal noted, the early Golgi studies of Cajal had largely been forgotten.

The Scheibels' major points are summarized below (quotations are from the references listed above).

1. Dendrites of reticular neurons radiate maximally in the dorsoventral plane, with little or no projection in the rostrocaudal plane. The dendrites are long and relatively unramified, thick at the somal junction and tapering toward the distal end. The dendritic trees are arranged into discrete units in the longitudinal axis, like spheres flattened antero-posteriorly into structures reminiscent of poker chip stacks. The dendritic domain of a single reticular cell is so large that it transcends cyto-architecturally determined nuclear boundaries. Dendrites of reticular neurons stream into each other's fields of interaction quite indiscriminantly. Activation of a particular poker chip unit may change the activity of nearby units via dendrodendritic interactions.
2. Ascending spinal systems emit brainstem collaterals perpendicular to their longitudinal course. These collaterals therefore enter the reticular formation in a plane perpendicular to the long axis of the brainstem, paralleling the dendritic orientation. Phylogenetically older afferent and efferent systems (spinothalamic and extrapyramidal) contribute more collaterals than do newer tracts such as the medial lemnisci, the pyramids, and cerebellar efferents. The degree of overlap of the collateral afferent plexuses is so great, especially in the lower brainstem, that "it is difficult to see how any specificity of input can be maintained." The output of each reticular element (each chip) reflects the net summation of the diverse inputs in such a manner that the specific informational content of individual afferent sources is lost; the reticular formation functions as a volume control for the level of arousal. The output of the reticular formation describes "not the pageantry and colour of the passing parade, but the loudness of the shouting that accompanies it." Axons of reticular neurons were seen to innervate all the cranial nuclei (sensory and motor), with the resulting excitation "having a general rather than a specific informational content."
3. There are few if any short-axoned Golgi type II cells in the reticular formation (see Hobson [1980] for examples of Golgi type II cells). Axons of reticular neurons project long distances particularly through the "cell-fiber maze" of the reticular formation itself. Axons emit numerous collaterals throughout their course. Closed loops of any length, and of tremendous complexity, can be built up. Both ascending and descending collaterals occur, travelling at least a substantial way along the length of the brainstem and "tying together" the dendritic arbors belonging to individual chips. The reticular formation is so interconnected that an impulse pattern can probably describe any conceivable path within it. Activity may travel along the brainstem in a series of lateral and ascending "tacks. "
4. Under certain fortunate conditions in single sagittal sections, axons from the same perikaryon can be traced from the medulla to the forebrain and from the medulla to the spinal cord.

A striking example of a reticular neuron demonstrated by the Golgi method neuron is reproduced in Figure 3.3B. This cell and other similar cells are famous, appearing in many textbooks (e.g., Kandel et al., 1991).

A cautious supporting analysis of the reticular formation was provided by Ramón-Moliner and Nauta (1966) based on their extensive anatomical experience and on their own Golgi-Cox preparations. While acknowledging that no one characteristic reliably distinguishes reticular from nonreticular neurons, Ramón-Moliner and Nauta were impressed by the cytological polymorphism and the

extensive, relatively straight, dendrites of brainstem reticular neurons and by the manner in which these dendrites intermingle with passing fiber bundles. The concept of the isodendritic core of the brainstem was introduced, the territory largely, but not completely, overlapping with the territory of the reticular formation. Such isodendritic neurons were hypothesized to be less likely to be recipients of specialized types of inputs. In agreement with the Scheibels' concepts, the neurons were thought to "offer a more optimal substratum for integrative functions." Thus the view emerged that isodendritic core-reticular neurons constitute a simple, phylogenetically early form of neuropil that serves as a kind of nonspecific background for the actions of the circumscribed, highly organized, discriminating neurons constituting the more recently evolved portions of the nervous system.

### **The Reticular Formation in Contemporary Views of the Brainstem**

In a more recent discussion in the Handbook of Physiology, Scheibel (1984) considers new evidence for differentiation of the reticular formation derived from connectivity studies and from newer histochemical and immunohistochemical procedures. As nuclei such as the lateral reticular nucleus, the raphe, the locus coeruleus, and other noradrenaline-containing groups became better characterized, there was a natural tendency for them to be withdrawn from the reticular formation. Scheibel proposed that all these nuclei continue to be regarded as belonging to the brainstem reticular core "without prejudicing the present and future role of any item in the subset." The Handbook of Physiology review concludes by acknowledging the functional and anatomical specificity that may characterize "the polysensory characteristics of reticular afferent patterns and the diversity of axonal trajectories." Nevertheless, Scheibel insists that "the general concept of the reticular core as a pool of interneurons with a pluri-potentiality of functions undoubtedly remains intact." As the Scheibels hoped, their theory became the "total image of the core of the brain stem," an image that continues to influence many studies of brainstem structure and function.

Some contemporary neuroanatomists still conduct their studies of the brainstem within a framework embodying aspects of the Scheibel tradition. In an important chapter in a key book, Jones (1995), whose own work demonstrated that extremely few reticular neurons project to both diencephalon and spinal cord, still adheres to the idea that "the distinct structure of the reticular formation thus provides a network for massive integration of polymodal input and polyvalent output." Jones questions the appropriateness of the term nucleus, as employed by Olszewski and others, for describing the Nissl appearance of brainstem reticular regions. She prefers the term *field*, citing Berman (1968), who used it when demarcation into obvious nuclei on Nissl cytoarchitectonic grounds was prevented by the loose neuronal arrangement. Jones offers no precise definition of the criteria used to delineate her fields. The regional differences seem to depend on Nissl cytoarchitectonics taken in conjunction with homologies to particular Rexed laminae of the spinal cord. In the medulla, from medial to lateral, the defined fields reflect the proposed distribution of radially orientated columns of neurons associated with somatic motor, visceral motor, and somatic sensory cranial nerve nuclei.

The holistic concept of the reticular formation is still employed by many neurologists, neurosurgeons, neuroendocrinologists, and psychiatrists in their attempt to understand the brainstem. Modern clinical neurology textbooks (e.g., McLeod et al., 1995) still use variations of the Moruzzi-Magoun-Scheibel

schematization of the reticular formation to explain how arousal and consciousness are regulated. The most recent edition of Gray's Anatomy (Williams, 1995) includes a very "conventional" account of the reticular formation, noting that it contains ill-defined collections of neurons with diffuse, difficult to define, polysynaptic connections: "a continuous isodendritic core traversing the whole brainstem." In recent years, Steriade and colleagues have completed sophisticated cellular neurobiological work concerning the role of specific brainstem nuclei in the control of awareness and the sleep-wake cycle (see Chapter 6) without specific reference to reticular theories. Yet even Steriade (1993) continues to invoke the concept of the reticular core. In a similar vein, the reticular formation is still subtly invoked as a kind of power supply for the brainstem, as in the current model of the respiratory network proposed by Richter and colleagues (see Chapter 4). Thus a contemporary critique of the anatomical and physiological concepts of the reticular formation is still relevant. It is by no means a strawman assignment.

### **Evaluation of the Scheibel Concept of the Reticular Formation**

Olszewski (1954), noting the confused and theoretically committed way in which physiologists were beginning to vary the traditional concept of the reticular formation, proposed that the term be abandoned. For Olszewski, the Nissl appearance of the brainstem proclaimed its neuroanatomical specificity:

The most striking feature of the cytoarchitecture of the lower brain stem is the great variety of cell types which are found in a few cubic centimeters of volume of the mesencephalon and rhombencephalon. This variety is greater than in any other part of the central nervous system. The cells vary not only in regard to their size, shape and intensity of staining but particularly in regard to the arrangement of the Nissl substance and position of the nucleus in the cell body.... The second prominent feature of the cellular morphology of the lower brain stem is the fact that the different cell types occurring there are not haphazardly scattered over the whole area but that each cell type is limited to a given region and occurs there, either alone, or in combination with other definite cell types. This type of cell arrangement allows the subdivision of all grey masses of the lower brainstem into individual nuclei. This applies particularly to those regions of the lower brainstem which are usually included in, and described as, the reticular formation. Accordingly the reticular formation cannot be looked upon as a morphological unity, or as a sort of ill-defined, uniform network in which, here and there, some "nuclei" formed accumulation of nerve cells can be recognized. Instead the reticular formation must be considered as a collection of nuclei of very different structure. Therefore it is our opinion that the term "reticular formation" could advantageously be dropped from both anatomical and physiological parlance, and that when speaking of any particular region of the brain stem reference should be made to the nucleus or nuclei which comprise it.

Following these prescient remarks, Olszewski continued his contribution to the Laurentian symposium presentation by outlining his account of human brainstem neuroanatomy, published as one of his two wonderful atlases of the brainstem (Olszewski and Baxter, 1949; Meessen and Olszewski, 1949). However, Olszewski's recommendations seemed to fall on deaf ears. The concept of the nonspecific reticular formation flourished, so that Brodal (1957) soon noted that the authors of physiological papers were portraying the reticular formation as a diffuse structural entity, with its own functional principles. Similarly, Ramón-Moliner and Nauta (1966) lamented that the reticular formation had become an ill-defined anatomical concept "submitted by the anatomist at the request of the physiologist."

Brodal's own carefully documented, detailed neuroanatomical analysis (1957) is replete with demonstrations of specific organization and regional heterogeneity in the reticular regions of the brain. Brodal concluded that the reticular formation is organized into distinct, but functionally interacting, groups of neurons. He encouraged neurophysiologists to pay closer attention to the structural aspects of their studies, repeating (1957:74) Lorente de Nó's admonition that "in the absence of detailed anatomical information the interpretation of brain potentials is fraught with dangers and difficulties." The later distillation of his wisdom in the third edition of his textbook (Brodal, 1981) includes a heroic reassessment of the anatomical and physiological evidence concerning the reticular formation. Unfortunately, Brodal's creative and critical input just preceded the modern era of neuroanatomy so that, as he realized, his assessments concerning the reticular formation lacked decisiveness.

Now that we have the benefit of numerous studies using modern neuroanatomical methods, it is timely to reevaluate the Scheibels' modifications to the traditional concept of the reticular formation.

### **The extent of the dendritic tree establishes neither the nonspecificity of the inputs nor the presence of dendro-dendritic interactions**

Dendrites of cranial nerve motoneurons, impeccably nonreticular, may extend beyond the apparent boundaries of the nucleus. Cajal noted, for example, that hypoglossal motoneurons have dendrites that project far into the longitudinal fibers of the adjacent white matter (Fig. 3.4).

**Figure 3.4** Drawing of Golgi-stained hypoglossal motoneurons. Dendrites extend from the hypoglossal nucleus into the adjacent reticular formation. (Modified from Cajal, 1909:575.)

Herrick (1948) also noted that the dendrites of motoneurons are widely spread, intermingling with those of the interneurons. Modern studies of the nucleus ambiguus (Bieger and Hopkins, 1987; Altschuler et al., 1991a; Shapiro and Miselis, 1985b) indicate that dendrites of these motoneurons may also extend into the neighboring reticular formation. The Scheibels (1970) even considered that their theories of dendrodendritic interaction might apply to the dendrites of spinal motoneurons, also impeccably nonreticular.

The orientation of the dendrites implies neither interactivity nor a poker chip type of functional organization. Dendrodendritic interactions could not be responsible for the coordination of actions

such as swallowing because the relevant neurons are distributed within a number of widely separated cranial nuclei. It may be that dendrodendritic interactions are important, but this needs to be established by appropriate experimental studies.

The Bötzing group of respiratory cells and the C1 premotor sympathetic vasomotor neurons in the rostral ventrolateral medulla both occur in reticularis lateralis or in paragigantocellular lateralis (see discussion later in this chapter). The dendritic morphology and long axonal projections of these neurons characterize them as typical neurons of the reticular formation, as defined by the Scheibels. Neurons from the two populations intermingle extensively. Yet, as is detailed in Chapters 4 and 5, the connectivity, transmitter content, inputs, and discharge patterns of these neurons are quite distinct, a conclusion supported in a study directed specifically to this issue (Kanjhan et al., 1995). Moreover, evidence is against the coordination of either Bötzing or C1 neuronal discharge by dendrodendritic interactions (see Chapters 4 and 5)

Modern ultrastructural studies of neurons in reticular regions (e.g., Milner et al., 1988b; Shapoval et al., 1991; Chan et al., 1995), show extensive conventional synaptic inputs to soma and dendrites. So far there is no morphological evidence that extensive dendrodendritic interaction is an obvious general feature of reticular neurons. Chan and colleagues (1995), for example, tell us that in their ultrastructural analysis of medullary catecholamine neurons they "occasionally observed" tyrosine hydroxylase-immunoreactive dendrites with membranes not segregated by intervening astrocytic processes in the rostral (C1) group of neurons, but not in the caudal (A1) group.

### **Dendrites of reticular neurons have various orientations**

Grzanna and Molliver (1980b) considered the question of dendritic orientation by analyzing their Golgi-like reticular images of central noradrenaline neurons obtained with the immunohistochemical procedure. Dendritic orientation was different for different catecholamine neuronal groups. Most of the noradrenaline cells have long thin dendrites, with few branches. Those of the A1 cells are mainly in the dorsoventral plane. The dendrites of the A5 cells are wrapped around the dorsolateral border of the superior olive. Those of the A7 cells extend mainly laterally, interspersed within the fibers of the lateral lemniscus. Dendrites of the most rostral locus coeruleus neurons radiate in all planes.

Subsequent detailed studies of the locus coeruleus, including Golgi preparations (Grzanna and Molliver, 1980a; Swanson, 1976) indicate that neurons in the A4 (caudal) portion of the locus have dendrites with a predominantly longitudinal orientation. Those of the ventral division of the locus coeruleus radiate in all directions, and those of the locus coeruleus proper have prominent medially and laterally directed dendrites.

Leontovich and Zhukova (1963) performed extensive Golgi studies that confirmed the idea that dendrites of reticular neurons are long, sparse, and poorly ramified, but their studies do not specifically address the question of the orientation of the dendrites. Newman (1985a,b), who correlated the Golgi appearance of reticular neurons with their definition by retrograde intra-axonal transport of HRP, noted marked variations in the dendritic arborization patterns of different brainstem neuronal subgroups. A modern study of the cat brain (Mannen, 1988) includes detailed drawing of brainstem neurons from many different regions. The various Golgi images emphasise the diversity of

dendritic orientation in brainstem regions traditionally assigned to the reticular formation. Valverde (1961, 1962) noted a predominant mediolateral orientation of both perikarya and dendritic trees in Golgi preparations from the ventromedial pons at the level of the superior olive (Fig. 3.5A).

**Figure 3.5** A, Drawing of Golgi-stained neurons in the ventral pons at the level of the superior olivary nucleus in a newborn kitten. (Modified from Valverde, 1961.) B, Drawing of Golgi-stained neurons in the nucleus tractus solitarius and the dorsal motor nucleus of the vagus. (Modified from Cajal, 1909:603.) Abbreviations listed on pages xiii-xiv.

Neurons with a similar mediolateral orientation of dendrites in the region can be demonstrated with 5-HT immunohistochemical markers and by transneuronal transport following application of Herpes simplex virus to the vagus nerve (Blessing et al., 1991).

The mediolateral orientation of the ventromedial pontine neurons may simply reflect the physical effects of the abundant fiber bundles decussating at this rostrocaudal level. Cajal (1909) noted that the shape of a cell, including the orientation and number of its dendrites, is related to its structural neighborhood, not just to its synaptic connectivity. The neuron

fits comfortably in large expanses of grey matter, where it is polygonal or triangular and its dendrites radiate in all directions. However, if a neuron is compressed between fascicles of white matter, it changes shape to accommodate them; it may, for example, become fusiform with two opposing dendritic trees, it may become piriform with all of the dendrites arising from one side, and so on. (1909:791).

The orientation of neuronal perikarya and dendrites medial to the tractus solitarius (Fig. 3.5B) may also represent a mechanical effect of the fiber pathway. The manner in which A5 catecholamine neurons are stretched around the dorsolateral border of the superior olive presumably reflects similar mechanical factors.

Simple inspection of the ventral pons suggests that the superior olive has displaced the neighboring A5 neurons dorsally. One rarely (never?) observes an A5 catecholamine neuron within the confines of the superior olive. A similarly strict boundary occurs between the dorsal motor nucleus of the vagus and the hypoglossal nucleus, a boundary clearly apparent in connectivity studies and in darkfield views, but not so obvious in Nissl preparations. At present we have little understanding of the principles underlying these divisions. They could reflect embryological developmental events (see brief description at the beginning of this chapter) -instances of the boundaries that form as a result of "repulsive forces between the neuroepithelial cells of odd and even numbered rhombomeres" (Simon and Lumsden, 1993).

### **Individual reticular neurons do not have inputs from virtually all sources**

The Scheibels proposed that spinothalamic rather than lemniscal sensory pathways provided the major input to the reticular formation, although the Moruzzi-Magoun diagram (Fig. 3.3A) suggests

inputs from lemniscal pathways to all levels of the brainstem. Cajal (1909:778) had already noted that the medial lemniscus issues collaterals in the pons, not in the medulla, an observation confirmed by recent studies (Tracey and Waite, 1995). As will be obvious throughout this book, what is striking is the highly organized manner in which the inputs to the various reticular regions are arranged. As discussed in Chapter 6, the protagonists of the nonspecific reticular formation theory, in their own neurophysiological study (Scheibel et al., 1955), failed to support the fundamental assumption that each reticular neuron can be driven by a wide variety of inputs.

### **There may be short-axoned (Golgi type II) neurons in the reticular formation**

In a review for the *Handbook of Physiology* (Scheibel, 1984:227), we are told that the length of reticular formation neurons ranges "from relatively limited trajectories (but not true short-axoned cells) to the great majority of intermediate length elements." Presumably the axon length of neurons in the brainstem reticular regions is variable, and the distinction between Golgi types I and II is arbitrary. But even if, for the sake of argument, we accept the classification, there may be short-axoned Golgi type II neurons in the brainstem. Holmes and colleagues (1994) note that certain GABA-synthesizing neurons are likely candidates. Reticular formation lesions diminished the number of dense GAD-positive varicosities within the region of cell loss but not at any distant location. Type II neuronal morphology in the ventral medulla has been demonstrated by Mason and Fields (1989) after intracellular filling of probable nociceptive neurons (see Fig. 6.11 in Chapter 6). GABA-ergic inhibitory vasomotor neurons, with a short projection from the caudal to the rostral ventrolateral medulla (see Chapter 5), may also be Golgi type II neurons. These details are not vitally relevant to the Scheibels' overall theory, but the debate emphasizes the limitations of conclusions based on a single technique.

### **The Scheibels' Golgi neurons**

As mentioned, the illustration in Figure 3.3B is commonly reproduced in textbooks to illustrate the cytology of the reticular formation. The Scheibels' diagrams were prescient in that they emphasized the presence of long ascending and long descending axons of reticular neurons. Such projections had already been established by degenerative techniques, but the Scheibels' Golgi images were much more dramatic. The cell in Figure 3.3B was drawn from a preparation in a young rat and first published in a book (Brazier, 1968). Now that modern axonal tracing procedures are available, it is reasonable to wonder as to the identity of the depicted neuron. The perikaryon is in nucleus reticularis gigantocellularis. Jones (1995) notes that most reticular neurons within the medial and intermediate reticular regions give rise to either long descending or long ascending projections, not to collateralized long descending and long ascending projections as suggested by the Scheibels. Less than 2% of the reticular neurons project to both diencephalon and spinal cord (Jones and Yang, 1985; Waltzer and Martin, 1984). Similar findings have been reported for neurons in the rat ventrolateral medulla, another reticular brainstem region (Tucker et al., 1987).

In the absence of subsequent evidence for the existence of neurons with the anatomical projections depicted in Figure 3.3B, we might wonder how such a cell was observed. Both ascending and

descending stem axon collaterals, as well as numerous branches, are depicted as being present within the single sagittal section. There is no indication in the legend or description of methods concerning the thickness of the section. Concerning the distal projections of reticular neurons, Cajal was much more cautious. He thought that most ascending axons might end in pontine nuclei or in the tectum. Insofar as Cajal studied long pathways by following individual axons in Golgi preparations, his ideas were "established in the mouse rather than in the human (or even the dog, cat or rabbit) in whom distances are too great" (1909:791).

### **Criticism of the field subdivision of the brainstem suggested by Jones**

There are many examples illustrating how the fields designated by Jones blinker our conceptions of the neurons they contain. Why, for example, should preganglionic parasympathetic neurons be assigned to fields? Yet these neurons, apart from those in the well-defined dorsal motor nucleus of the vagus and external nucleus ambiguus (and thereby excluded from the reticular formation), are scattered through the more rostral parvocellular field and the rostral intermediate field (Jones terminology), as demonstrated by Contreras and colleagues (1980). Neuronal groups, defined on the basis of their transmitter neurochemistry, may extend through different fields. The ventrolateral extension of the group of 5-HT neurons, for example, is found in gigantocellular field and in gigantocellular field, ventral part. Catecholamine neurons in the ventrolateral medulla occur in the intermediate field, in the ventrolateral intermediate field, and in the lateral paragigantocellular field. Markers for acetylcholine, L-glutamate, GABA, and nitric oxide occur in virtually all fields, as illustrated in Jones' own work (Jones, 1990; Jones et al., 1991; Holmes et al., 1994). Similarly, the fields fail to subdivide neurons according to their axonal projections. The intermediate, ventrolateral intermediate, and lateral paragigantocellular fields all give rise to descending axons that innervate preganglionic sympathetic neurons in the spinal cord. Raphe neurons, as well as nearby cells in the parapyramidal and more dorsal regions (gigantocellular, ventral part and gigantocellular fields) also innervate neurons in the spinal cord. Premotor neurons projecting specifically to hypoglossal, facial, and trigeminal motoneurons occur between the hypoglossal nucleus and the dorsomedial portion of spinal V (in dorsal portions of both intermediate and parvocellular fields), as discussed later in this chapter.

Thus, even if Jones' use of the term field is restricted to the Berman concept (see earlier), we may object that the approach still has the unfortunate consequence of de-emphasizing the wealth of information now available for describing particular classes of neurons based on connectivity and transmitter neurochemistry criteria. However, Jones (1995:155) implies that her field concept also reflects the brainstem organization proposed by the Scheibels. The fields are "organized as sectors of the reticular network across which there are overlapping dendritic and axonal domains." Thus the term field seems to be used in a more dynamic sense, suggesting spheres of functional influence. Such an undefined usage of the term is to be strongly discouraged. It reintroduces some of the poorly characterized interactive properties assigned to the reticular formation by the Scheibels. Hinting at mysterious underlying organizational principles is easy, but ultimately sterile. Presenting a testable

theory (e.g., the rhombomere theory) that interacts with our rapidly expanding knowledge of the actual structure and function of the different brainstem regions will prove much more fruitful.

### **Problems With Olszewski-Type Cytoarchitectonic Classifications of the Reticular Formation, With Special Reference to the Region of the Medulla Referred to as the Paragigantocellularis Nucleus**

As indicated, Olszewski's painstaking efforts were motivated partially by his desire to demonstrate the specificity of neuronal organization in the reticular formation. Unfortunately his principal tool could not do justice to the neuroanatomical reality. The cytoarchitectonic method hardly does justice to itself when used in conjunction with Nissl stains, given the failure to demonstrate dendritic morphology. It may even be that cytoarchitecture, particularly neuronal orientation, is not a major determinant of neuronal function (see Cajal's views cited earlier in this chapter).

Given that those who use the "cytoarchitectonic method" rarely specify the precise criteria that subdivide nuclei, we may wonder how the method actually works. One suspects that, in practice, groups of Nissl-stained neurons define themselves as nuclei by forming gestalts in the mind of the experienced neuroanatomist. A group of cells looks like a nucleus and is so defined. Thus, in the discussion section of her valuable Nissl study of the cat brainstem, Taber (1961) informs us that "a well-circumscribed arrangement of cell bodies of neurons is readily defined as a nucleus"; a little disingenuous perhaps, but fundamentally honest.

A good example of the process of cytoarchitectonic subdivision of reticular regions (in the Olszewski tradition) is provided by the studies of the nucleus paragigantocellularis lateralis (PGi) in the cat by Taber (1961) and in the rat by Andrezik and colleagues (1981a,b). In the cat study, apart from the general explanation (cited above), there is no specification of the criteria used to define PGi. In the rat study, we are told that the boundaries of the PGi were defined by "neuronal orientation, staining qualities and myeloarchitecture." However, the particular orientations, the particular staining qualities, and the particular myeloarchitectural criteria are never specified. We are then told that the distribution of neurons within the nucleus is not uniform, with heterogeneity of neuronal size and packing density suggesting subdivision into a more caudal portion (caudal to the facial nucleus) and a more rostral portion (medial to the facial nucleus). Further heterogeneity of neuronal size, shape, and dendritic orientation was considered to indicate the presence of at least eight neuronal types within the two subdivisions.

Once the rat PGi was defined by these (unspecified) cytoarchitectonic criteria, some attempt was made to characterize PGi neurons in terms of neurotransmitter anatomy. It was noted that some PGi neurons were likely to synthesize 5-HT, but the relationship of the PGi to the C1 phenylethanolamine-N-methyltransferase (PNMT)-positive cells (Hökfelt et al., 1974) was not discussed by Andrezik and colleagues (see below). Unfortunately the study of PGi inputs (Andrezik et al., 1981b) was marred by the manner in which unconjugated HRP is taken up by fibers of passage. There was no consideration of the efferent projections of the PGi or any recognition that it might contain bulbospinal neurons, as had already been documented for the cat (Amendt et al., 1978,

1979; Tohyama et al., 1979a; Kuypers and Maisky, 1975) and for the rat (Satoh et al., 1977; Satoh, 1979).

Now that we appreciate that the C1 group of PNMT-positive neurons (including bulbospinal sympathetic premotor cells) is located in the general region of the PGi, it is instructive to see how the two categories of neurons have been dealt with in subsequent studies. One analysis of the distribution of PNMT neurons in the cat medulla (Ruggiero et al., 1986) assigns them to an intermediate segment of the PGi, as defined by Andrezik and colleagues, but notes that the region is distinct from PGi as defined by Taber. In the case of the rat, Ross and colleagues (1984a) note that PGi guidelines do not encompass the distribution of C1 spinally projecting PNMT neurons. Similarly for the rat, Kalia and Fuxe (1985) (who seem to use a different definition of PGi, without reference to Andrezik and colleagues) conclude that the overlap between the C1 group and the PGi "does not seem to be very remarkable," and a more detailed analysis from these colleagues even excludes most of the C1 neurons from the PGi (Kalia et al., 1985b). Respiratory neurons, especially those in the Bötzing group, are mostly slightly dorsal to the C1 cells in the rat, but some are intermingled with C1 cells, as are some neurons of the nucleus ambiguus (Blessing et al., 1985; Ellenberger et al., 1990b; Pilowsky et al., 1990b; Sun et al., 1994; Kanjhan et al., 1995). Yet many anatomical studies of the region, especially those with a focus on the C1 PNMT-positive neurons, still basically accept the existence of the PGi as a definite nucleus around which it is possible to draw a boundary (see Fig. 3.6, taken from Van Bockstaele et al., 1989), even though the functional heterogeneity of the enclosed neurons and their rostrocaudal neighbors may be recognized (Van Bockstaele et al., 1993).

**Figure 3.6** Photomicrograph of rostral ventrolateral medulla of the rat, with nucleus paragigantocellularis (PGi) outlined. (Modified from Van Bockstaele et al., 1989.) Abbreviations listed on pages xiii-xiv.

Dampney, McAllen, and colleagues (see a recent account and references in Polson and colleagues, 1992) consider that, in the cat rostral ventrolateral medulla, neurons with a cardiovascular function are grouped into a definite nucleus, definable by Nissl appearance. The investigators note that this subretrofacial nucleus does not fit nicely into the PGi framework defined by Taber. The subretrofacial nucleus contains a concentration of bulbospinal neurons and a concentration of catecholamine cells, so that tyrosine hydroxylase (TH)-positive cells, which constitute over half the subretrofacial nucleus, are "virtually absent" from regions immediately surrounding the retrofacial nucleus, thereby validating the concept of the subretrofacial nucleus as an anatomical unity. However, as noted by Polson and colleagues (1992) for TH-positive neurons in their own study and acknowledged for PNMT-positive cells in their review of previous studies, catecholamine neurons also occur dorsal to the subretrofacial nucleus, in the region medial to the retrofacial nucleus (nucleus ambiguus) (Ruggiero et al., 1986; Kitahama et al., 1986; Reiner and Vincent, 1986). Whether these neurons are displaced subretrofacial cells or whether they belong to different functional subclasses of neurons has not been determined. There are similar tensions between the various definitions of nuclei constituting the more caudal region of the medulla oblongata, where the distribution of A1 noradrenaline-

synthesizing neurons overlap with respiratory neurons and neurons of the nucleus ambiguus (see discussions by Ellenberger and Feldman, 1990b, and Ellenberger and colleagues, 1990b; see also Chapters 4 and 5).

The preceding comments are not meant to disparage work that has proven an important contribution to our understanding of brainstem structure and function. The point is that in neither the rat nor the cat have the relevant neurons been demonstrated on cytoarchitectonic, neurochemical, or connectional grounds to be sufficiently similar to one another, and sufficiently different from neurons in surrounding regions, to enable the PGI to be defined as a separate nucleus.

Referring to the PGI as a nucleus suggests a neuroanatomical unity that has placed unnecessary restraints on subsequent anatomical and physiological studies. Nevertheless, the concept of the PGI (as a nucleus) is widely adopted in studies of the medulla oblongata directed toward the function of the presympathetic motoneurons in the region, as exemplified in cardiovascular studies by Guyenet and colleagues and in arousal-nociception studies by Aston-Jones and colleagues (see Chapter 6).

### **Conclusion Concerning the Scheibels' Views on Reticular Neurons: Time To Abandon Both the Concept of the Reticular Formation and Its Rigid Nuclear Subdivisions**

The observation that many brainstem neurons have long, relatively unbranching dendrites is correct. However, the orientation of the arborization is variable. In those instances in which the architecture is predominantly dorsoventral there is nothing to suggest any poker chip arrangement. Nor do any of these findings provide any basis for the Scheibels' concept of dendrodendritic interactions resulting in one poker chip influencing its neighbor. Dendrites of reticular neurons do arbour in the region containing the fibers from which they receive synaptic input, but this is hardly surprising. The Scheibels' findings actually have little to say concerning the specificity or otherwise of inputs to brainstem neurons in so-called reticular regions.

These neuronal populations are gradually, on the basis of multiple criteria, being characterized as groups of anatomically and functionally specific neurons, with specific neuronal connections. There probably are no brainstem neurons with nonspecific connections corresponding to those postulated by the Scheibels to be characteristic of the reticular formation. The term is so theoretically tainted that it is time for it to be discarded. Scheibel himself (1984:241) contemplated the possibility of using nuclei of the brain stem core, or perhaps an item-by-item muster. Brainstem core is not a suitable substitute. There is no core in the brainstem, there are just cells, arranged into various subgroups. An item-by-item muster of defined nuclei is to be encouraged.

The fields defined by Jones, and some of the nuclei defined in the Olszewski tradition, should also be abandoned. The neuroanatomical reality often defies the best subdividing lines. We can accept that neurons with different connectivity, different neurotransmitters, and different functions can be intermingled. If theorists wish to subdivide particular regions, or to group them together, then the relevant criteria should be clearly stated and supported with appropriate experimental evidence. Subdividing lines may initially aid our efforts, but eventually they hinder our mature grasp of the neuroanatomical organization.

We need theoretically neutral terms to refer to the heterogeneous populations of neurons in particular brainstem regions. When there is no nucleus apparent in the particular brainstem region under study, perhaps we could refer to premotor and interneuronal groups, the plural terminology reminding us to ask "which group of premotor or interneurons in which region?" This is as it should be. In the case, for example, of the ventrolateral medulla, I think it is wisest to refer to general regions (e.g., caudal, intermediate, and rostral ventrolateral medulla), with each study specifying, in as much detail as possible, the location and properties of the particular subpopulations of neurons under investigation. Findings from the new techniques and disciplines are already suggesting nuclear classifications that transcend old boundaries so that it is important to remain flexible in our definitions of particular nuclei and their subdivisions. As the detailed embryology of the brainstem becomes apparent, there will be important new criteria for defining the various classes of neurons in the brainstem. We need not rush to draw "definitive" nuclear boundaries or to subdivide brainstem neurons into "definitive" classes. Our categories can be changed as advancing knowledge confirms the definition of new structural and functional units. I consider that the best atlas for appreciating the neuroanatomy of the rat brainstem is that of Swanson (1992). There the concept of the reticular formation stands squarely in the theoretical tradition of Cajal, Herrick, Olszewski, and Brodal. Swanson's subdivisions are extremely conservative, the faintly dashed subdividing lines almost inviting future modification. In a penetrating essay, Hobson (1980) notes that our human tendency to "reticularism" is one aspect of our need to make a unitary sense from the complexity of the nervous system. But, as recognized by Hobson, this need does not entitle us to take shortcuts whereby we reach grand theoretical conclusions concerning classification of brainstem neurons without doing the necessary research. We need to replace "black arrow" pathways with actual pathways.

### **A More Useful Classification of Lower Brainstem Neurons**

A still useful approach classifies brainstem nuclei according to a framework that emphasizes the central connections of the cranial nerves. The traditional classification of the efferent cranial nerves, such as that adopted by Ranson and Clark (1959), reflects the distinction between striated muscles derived from segmented mesoderm (somatic muscles) and those derived from branchial mesoderm (visceral muscles) so that neurons innervating the two types of muscle are placed in fundamentally different categories, emphasized by their dorsomedial and more ventrolateral locations.

Anomalies resulting from this classificatory system are discussed in a very informative account of the evolution of the cranial nerves (Székely and Matesz, 1993). We can agree, for example, that it is difficult to argue for the "visceral" nature of either the muscles of facial expression and mastication, the auditory muscles, or the muscles innervated by the accessory nerve. The "somatomotor" tongue muscles move an actual viscus. However, the tongue is so intimately involved in chewing and swallowing that control of its movement must be closely integrated with facial and jaw movements. Assigning the hypoglossal cells to a totally different class of motoneurons needs additional justification.

It is clearly paradoxical to classify trigeminal afferents as general somatosensory neurons while trigeminal efferents are classified as visceromotor neurons. Finger (1993) argues that the term special

visceral sensory appears without foundation when applied to gustatory systems. Theories of the embryological origin of the various head components, including the muscles associated with branchial arches, are currently being revised, with the role of homeobox genes in head segmentation beginning to be appreciated (as discussed at the beginning of this chapter). We can expect new theoretical bases for classifications. Meanwhile, it is wise to emphasize communalities as well as possible differences between somatic and visceral components of cranial nerves.

Most sensory neurons with direct inputs from the periphery (secondary sensory neurons) are arranged into nuclei easily recognizable in Nissl stains. The same holds for most motoneurons. However, some motoneurons (e.g., the accessory motoneurons of V and VII, as well as parasympathetic preganglionic neurons in the pons and upper medulla) require identification by tracing studies (not available for humans) or by neurochemical content.

Neurons not directly connected with the periphery (i.e., not secondary sensory neurons and not motoneurons) can be classified as interneurons. Premotor neurons, all presumably possessing extensive axonal collateralization, can be regarded as a subclass of interneurons. Thus the C1 sympathetic premotor cells in the rostral ventrolateral medulla (see later in this chapter) possess axon collaterals that project to the nucleus tractus solitarius (nTS). Some interneurons, such as those in the olives and in the lateral reticular nucleus, are obvious and well characterized. Others, including most of the monoamine-synthesizing cells, require definition by connectivity or neurochemical criteria, not simply by location or Nissl appearance. Neurons with primary afferent input may also function as interneurons and sometimes as premotor cells (e.g., those in the central nucleus of the nTS, see later in this chapter). The complex realities of neuroanatomy suggest the necessity of a flexible approach to classification.

Tables 3.1 to 3.4 classify the nerve cells present in the lower brainstem in a manner that avoids use of the term *reticular formation*.

The remainder of this chapter gives more details concerning selected subgroups from this classification. The anatomy of the peripheral nervous system is not dealt with in this book. A summary of some of the more difficult lower cranial nerve anatomy, including salivary and taste pathways, is shown in Figure 3.7. References to more complete neuroanatomical accounts are given in the introduction to this chapter.

**Figure 3.7** Diagram of lower cranial nerves containing parasympathetic efferent fibers and gustatory afferent fibers. Roman numerals refer to cranial nerves. The preganglionic cell bodies are shown in the medulla and upper pons. The central termination site of the gustatory afferents are shown in the region of the rostral nucleus tractus solitarius. (Modified from Miller, 1985)

### **Somatic Motoneurons (Excluding the Nucleus Ambiguus)**

These neurons are dealt with in the atlases referenced at the beginning of this chapter. The relevant nuclei in the rat brain are labeled in Figure 3.1. Their location in the human brainstem is given in Figure 8.2.

## **Somatic Premotor Neurons**

Although cranial nerve XII innervates structures derived from mesodermal segmental somites, its neurons functionally relate to the motoneurons of V, VII, IX, and X, which innervate structures derived from branchial arch muscles. Discharge of the relevant motoneurons must be coordinated during activities such as swallowing.

There are no collateral projections whereby this might be achieved, and the wide spatial separation of the various nuclei excludes dendrodendritic interactions. Although direct neocortical projections from the precentral gyrus to cranial motoneurons exist in primates (Kuypers and Lawrence, 1967), in other experimental animals there are probably no direct inputs to the motoneurons from regions rostral to the midbrain (Travers and Norgren, 1983).

In the cat, for example, projections from the region of the motor cortex concerned with jaw movements terminate in pontine "reticular" regions known to contain trigeminal premotor neurons (Yasui et al., 1985a). Thus, as Cajal and Herrick emphasized (see earlier in this chapter), certain regions of reticular formation contain extensive groups of somatic premotor neurons that may also collateralize and function as interneurons to coordinate the discharge of cranial motoneurons.

These premotor neurons have been localized by studies of the source of axonal inputs to V, VII, nucleus ambiguus, and XII cranial motoneurons (Borke et al., 1983; Mizuno et al., 1983; Travers and Norgren, 1983; Takada et al., 1984; Aldes, 1990; Ter Horst et al., 1991a; Li et al., 1993, Mogoseanu et al., 1993, 1994) and, in the case of XII, by transneuronal transport of live viruses, including Herpes simplex (Ugolini et al., 1987) and rabies (Ugolini, 1995). There are bilateral projections to these nuclei from the region lateral to XII, between this nucleus and the dorsomedial border of the spinal nucleus of the trigeminal nerve (Vsp) (see PHA-L injection site in Fig. 3.8). Travers and Norgren (1983) note that these neurons overlap the medial gigantocellular and lateral parvicellular reticular formation subdivisions previously established by cytoarchitectural analysis. What is remarkable is how limited and specific are the innervation targets defined by anterograde transport from the region containing a concentration of the premotor neurons (Yu et al., 1996a). As shown in Figure 3.8, the projection in the rabbit seems to be almost entirely to V, VII, and XII, a finding consistent with the retrograde transport observations of Travers and Norgren in the rat. The projection from the premotor region lateral to XII is specifically to the portions of VII that contain motoneurons controlling the orofacial muscles involved in ingestion, chewing, and swallowing. Neuroanatomical studies demonstrating similarly specific connections are available for pre-motor neurons that coordinate eye movements (Olivier et al., 1993) and those that integrate vestibular reflexes (Kitama et al., 1995).

## **Premotor Phrenic and Thoracic Respiratory Motoneurons**

Neurons projecting directly to phrenic and thoracic spinal respiratory neurons occur in the Kölliker-Fuse nucleus and other parabrachial nuclei, in the ventrolateral medulla, and in the ventrolateral nTS. The evidence for this is summarized in Fig. 4.3.

**Figure 3.8** A, Position of retrogradely labeled neurons (filled circles) after deposition of tracer in the hypoglossal nucleus in the rat. (Modified from Travers and Norgren, 1983.) B, Anterograde transport of *Phaseolus vulgaris* leucoagglutinin after deposition of tracer just ventrolateral to the rostral hypoglossal nucleus and medial to the dorsal portion of the spinal nucleus of the trigeminal nerve in the rabbit. The projection is specifically directed toward motoneurons in V, VII, and XII, indicating that the injected area probably contains somatic premotor neurons controlling swallowing. (Modified from Yu, et al., 1996.) Abbreviations listed on pages xiii-xiv.

**Table 3.1** Classification of Secondary Sensory Neurons (CNS Neurons with Primary Afferent Inputs)

| <i>Peripheral Origin of Primary Afferent</i>                          | <i>Location of Primary Perikarya</i>  | <i>Cranial Nerve</i> | <i>Brainstem Nucleus in which Primary Afferents Terminate</i>                               |
|---|---------------------------------------|----------------------|---|
| General cutaneous from anterior two-thirds of head                    | Cavum trigeminale                     | V,IX,X               | Principal sensory nucleus of V  |
| Joint position sense  | In pons and midbrain                  | V                    | Mesencephalic nucleus of V  |
| Nociception, temperature anterior two-thirds of head                  | Cavum trigeminale                     | V,IX,X               | Spinal nucleus of V, possibly nucleus tractus solitarius                                    |
| Hearing and vestibular function                                       | Spiral and vestibular ganglia         | VIII                 | Dorsal and ventral cochlear nuclei; medial, lateral, superior, and spinal vestibular nuclei |
| General cutaneous from posterior one-third of head and rest of body   | Dorsal root ganglia                   | Spinal dorsal roots  | Gracile and cuneate nuclei  |
| Gustation   | Geniculate VII, petrosal IX, nodose X | VII,IX,X             | nTS, spinal nucleus of V, and paratrigeminal islands  |
| Baro-, chemoreceptors, receptors in heart, lung, and abdominal organs | Petrosal IX, nodose X                 | IX,X                 | nTS, spinal nucleus of V, and paratrigeminal islands  |

**Table 3.3** Classification of Somatic Motoneurons

| <i>Peripheral Striated Muscle Innervated</i>                                      | <i>Cranial Nerve</i> | <i>Brainstem Nucleus</i>                        |
|---|----------------------|---|
| Extraocular muscles   | III,IV,VI            | Edinger-Westphal, trochlear, abducent           |
| Jaw muscles   | V                    | Principal trigeminal motor nucleus              |
| Mylohyoid, anterior digastric, tensor tympani, stapedius                          | V                    | Accessory trigeminal motor nucleus              |
| Stylohyoid, posterior digastric   | VII                  | Accessory facial nucleus                        |
| Facial expression   | VII                  | Main facial nucleus                             |
| Swallowing and phonation (muscles of pharynx, larynx and upper part of esophagus) | IX,X                 | Nucleus ambiguus (excluding external formation) |
| Tongue  | XII                  | Hypoglossal                                     |
| Stenomastoid and trapezius  | XI                   | Accessory                                       |

**Table 3.2** Classification of Interneurons, including Premotor Neurons

| <i>Type of Neuron</i>  | <i>Brainstem Nucleus</i>  |
|--|---|
| Interneurons with no primary afferent input and no direct projections to motoneurons | Inferior olive, lateral reticular nucleus, cerebellar nuclei, vestibular nuclei, nuclei pontis, arcuate nuclei, superior olive, nucleus intercalatus, prepositus hypoglossi, locus coeruleus and subcoeruleus, dorsal tegmental nuclei, A7 cells, parabrachial, Kölliker-Fuse, pedunculopontine and cuneiform nuclei, periaqueductal gray |
| Premotor cells for cranial somatic motoneurons                                       | Neurons in various regions of the pons and medulla; many still undefined  |
| Premotor cells for cervical (phrenic) and thoracic spinal respiratory neurons        | Some Kölliker-Fuse and parabrachial neurons, Bötzing complex neurons, rostral inspiratory and more caudal expiratory neurons in the ventrolateral medulla, some cells in nucleus tractus solitarius, raphe magnus, parapyramidal and more caudal raphe neurons  |
| Presympathetic motoneurons   | Paraventricular nucleus of hypothalamus, A5 catecholamine cells, C1 catecholamine cells and other intermingled noncatecholamine cells, raphe magnus, parapyramidal and more caudal raphe neurons  |
| Preparasymphathetic motoneurons (cranial outflow)                                    | See details in this chapter   |
| Preparasymphathetic motoneurons (sacral spinal outflow)                              | Raphe and parapyramidal nuclei, rostral ventrolateral medulla, A5 region, Barrington's nucleus, and paraventricular and preoptic nuclei of the hypothalamus   |
| Premotor cells for hypothalamic magnocellular neurons                                | A1 and A2 catecholamine-synthesizing neurons and possibly some midbrain raphe neurons   |

**Table 3.4** Classification of Parasympathetic Motoneurons

| <i>Peripheral Target</i>           | <i>Final Motor Neuron</i> | <i>Cranial Nerve</i> | <i>Brainstem Nucleus</i>                                |
|------------------------------------|---------------------------|----------------------|---|
| Ciliary and iris muscles           | Ciliary ganglion          | III                  | Edinger-Westphal nucleus                                |
| Lacrimal gland                     | Sphenopalatine ganglion   | VII,IX               | Neurons dorsal to rostral portion of facial nucleus     |
| Salivary and mucosal glands        | All cranial ganglia       | VII,IX               | Neurons dorsal to rostral portion of facial nucleus     |
| Cranial blood vessels              | All cranial ganglia       | VII,IX               | Probably with salivary and lacrimal preganglionic cells |
| Lower airways and lung             | Ganglia in airways        | X                    | Nucleus ambiguus, dorsal motor nucleus of vagus         |
| Heart                              | Cardiac ganglia           | X                    | Nucleus ambiguus (external formation)                   |
| Stomach and other abdominal organs | Enteric neurons           | X                    | Dorsal motor nucleus of the vagus                       |