

History of Cortical Cytology

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1. The Discovery of Cortical Neurons

It is difficult to ascertain who first *saw* a neuron in the cerebral cortex. It seems evident from modern studies which have attempted to duplicate the conditions of Malpighi's (1666) experiments that the "glands" he described in the human cerebral cortex cannot have been cells (Clarke and Bearn, 1968). Similarly, the often-reproduced figures of Gennari (1782) and Baillarger (1840) that accompanied their descriptions of the laminar structure of the cortex are based upon alternating patterns of gray and white matter as detected with the naked eye or with a hand lens. Cells were obviously not visualized.

Ehrenberg (1833, 1836), an early microscopist, appears to have been aware of neurons in the cerebral cortex of man and animals, referring to them as "granules" or "globules," but he did not illustrate them. Clearer descriptions of nucleated "ganglion bodies" in the cortex are given by Valentin (1836) and Remak (1841). Remak also detected bundles of axons ascending from the white matter and deflecting horizontally especially near the surface of the brain. Remak makes it clear that he felt he could see myelinated fibers in continuity with the processes emanating from the ganglion cells in the cortex, as he had in the spinal and sympathetic ganglia.

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The early observations on the cortex were made on tissue that was unfixed, or, at best, poorly fixed in alcohol; usually it was compressed in water under a cover glass, rather than sectioned, and it was unstained. Fixation in chromic acid was introduced by Hannover in 1840 and the use of carmine as a stain for nerve cells not until 1858 (Von Gerlach, 1872). Between the discovery of the "ganglion cells" in the cortex and the introduction of carmine, von Kölliker (1849) was able to make some crude sketches of cells some of which he called "pyramidal" (Fig. 1). The idea was also gaining acceptance that the myelinated fibers of the white matter were probably continuations of nerve cell processes (reviewed e.g., in Liddell, 1960). But in 1860 von Kölliker still felt obliged to say: "although the connection of the fibres entering into the cortical substance with nerve cells has not, as yet, been actually demonstrated, still I do not hesitate in affirming it; and I regard the cortical substance as the place of origin of all the nerve fibres of the hemispheres and *corpus callosum*." Final confirmation of the original statement by Remak in the cerebral cortex and elsewhere had to await the work of Dieters in 1865. Even by 1905, however, Campbell could still believe that some fibers in the cortex might be "autochthonous."

Von Gerlach in 1858 stained sections cut from material fixed in potassium dichromate with ammoniacal carmine. In the same year, Berlin (1858) applied

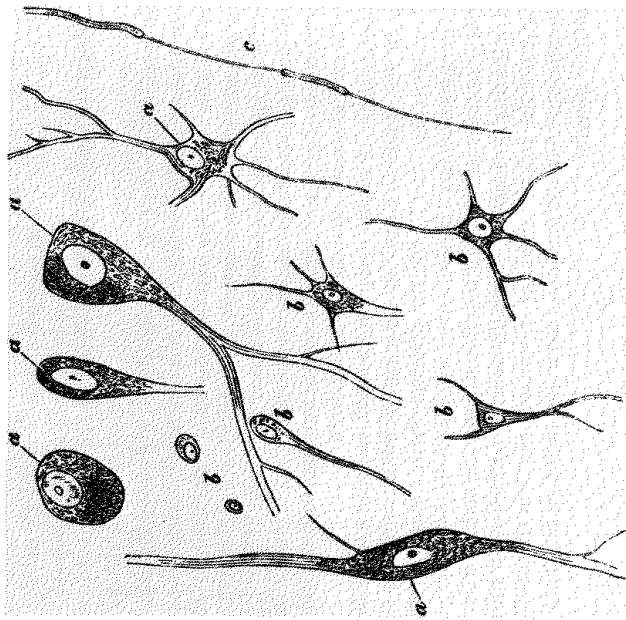


Figure 1. Drawings of cells from the deeper parts of the cortex of the human brain; probably from chromic acid-fixed but unstained material. Cell a at top center is a "pyramidal cell." Reproduced from von Kölliker (1860); drawn in 1852 or earlier for the second edition of his textbook.

the new method to the cerebral cortex for the first time and was able to distinguish not only its arrangement in layers but also several forms of cells that he called pyramidal, granular and spindle-shaped or fusiform (Fig. 2). The originality of these names is, perhaps, questionable since von Kölliker (1852) had already referred to triangular, round, and spindle cells in addition to pyramidal cells in the cortex.

2. Laminar Patterns in the Cortex

Making his first studies on the brains of bats, but later extending them to man and other animals, Meynert (1867–1868, 1869–1872) provided the first systematic descriptions of cortical layering (Fig. 3). His preparations were sections of material fixed in potassium dichromate, stained with carmine, dehydrated in alcohol, and cleared in oil of cloves. To him, the commonest type of cortical stratification, covering the surface of much of the human brain, was a five-layered one (Fig. 3A), consisting of an outer "neuroglia layer" containing a few angular nerve cells, a second layer of small pyramidal cells, a third layer of large pyramidal cells, a fourth layer of multimorph or granular cells, and a fifth layer composed of large short pyramids and deeper spindle-shaped cells. His fifth layer, obviously, includes both our layers V and VI. Meynert was also able to detect what he called projection fibers and association fibers entering and leaving the cortex and to trace some of them in continuity with the axons arising from pyramidal cells. The radial fasciculi of the cortex were also his discovery.

Meynert noted three additional layers in the cortex of the calcarine sulcus (Fig. 3B). Examining his drawings, one can see that he merged layers II and III of the five-layered cortex, recognized the three divisions of what many workers now call layer IV in the primate visual area, noted a distinct layer V containing the large solitary pyramidal cells that now bear his name, and divided our layer VI into superficial and deep parts.

The next significant series of studies on cortical lamination were made by Lewis (1878a) and his collaborator, Clarke (Lewis and Clarke, 1878). In the intervening years, Betz (1874) had discovered in the motor cortex of man, dog, and monkey the large pyramidal cells that have come to bear his name.

Lewis gives an account of his methods in the same volume of *Brain* (Vol. 1) that carries his paper on the comparative structure of the cortex in man, sheep, and cat (Lewis, 1878b). He cut unfixed brain tissue on a small freezing microtome, freezing thin blocks in less than 20 sec by the use of an ether spray. They were then cut (at an unspecified thickness) into water. From there, they were mounted on glass slides, fixed in 0.1–0.2% osmium tetroxide and stained with 0.25% aniline black. Before mounting in Canada Balsam, they were dehydrated in sulfuric acid vapor to avoid leaching of the stain by alcohol. Apart from superior staining, Lewis rightly considered that his method of preparation resulted in far less shrinkage of the cortex than occurred after prior dichromate fixation.

The paper by Lewis and Clarke (1878) is devoted to the human motor cortex, as delimited from a comparison with Ferrier's (1874) stimulation maps in mon-

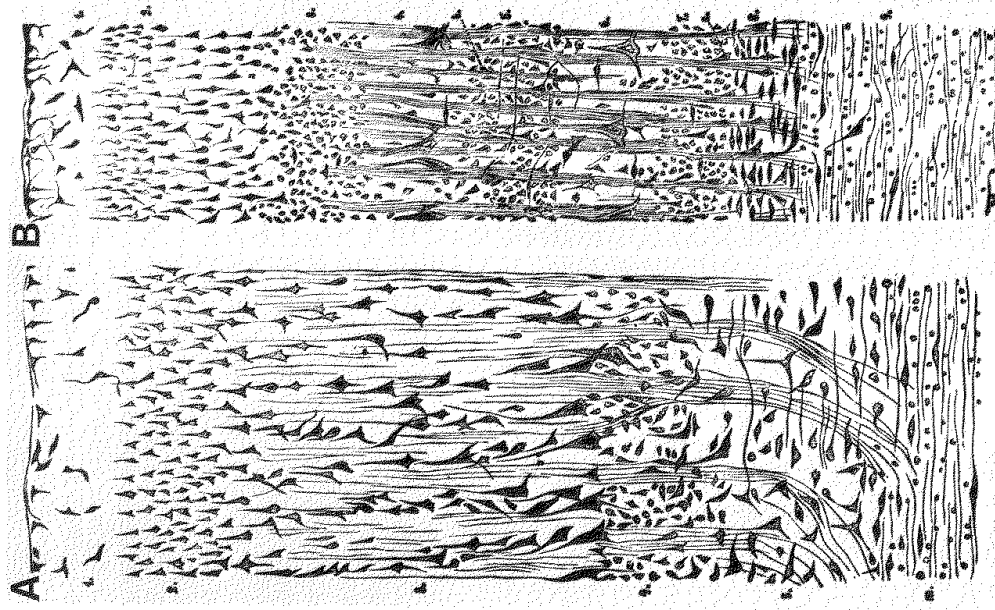


Figure 3. (A) Meynert's drawing of his typical five-layered cortex, from the frontal lobe. (B) Meynert's drawing of "the cortex of the calcarine fissure," showing four additional layers but fusion of layers 2 and 3. From Meynert (1884).

keys. In this, they illustrated the human Betz cells for the first time* and noted that the motor cortex was five-layered. But in his subsequent paper on the comparative anatomy of the cortex, Lewis (1878a) took issue with Meynert and concluded that, apart from the motor area, the cortex was fundamentally six-

* Betz did not illustrate them in 1874, nor in his more comprehensive account of 1881.

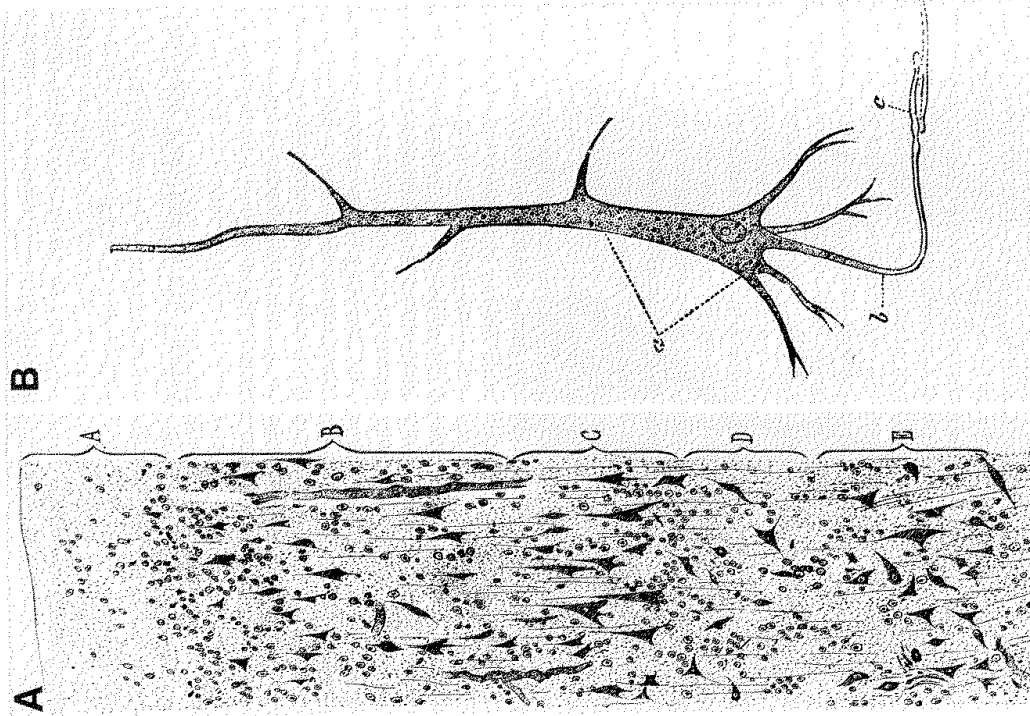


Figure 2. (A) Drawing of part of a section of the cerebral cortex from the brain of a "simpleton," stained with carmine probably after fixation in chromic acid, showing the five layers (A-E) of Meynert with pyramidal, small angular, and fusiform cells. From Dejerine (1895); said to be from an earlier work of Vignal. (B) Pyramidal cell, probably from fixed but unstained material. From Bastian (1880); said to be from an earlier work by Charcot.

layered (Fig. 4). Layer I was regarded as containing no nerve cells. Layers II and III formed a continuum of pyramidal cells of increasing size. Layer IV he regarded as a further layer of small pyramidal cells, exactly similar to those of layer II. This layer he regarded as absent from the motor area. Layer V was the ganglionic layer and layer VI the spindle cell layer. In his later work, seemingly published only as part of the enlarged second edition of Ferrier's work *The Functions of the Brain* (1886), Lewis more clearly identified the granule cells of layer IV in the monkey brain (Fig. 5) and noted seven layers in the visual cortex, the additional layer being formed by a splitting of layer IV.

The subsequent history of cortical lamination has been often told (see Chapter 2). During his brief career, the Swedish worker Hammarberg (1895) sampled a number of cortical regions in man and described laminar variations among

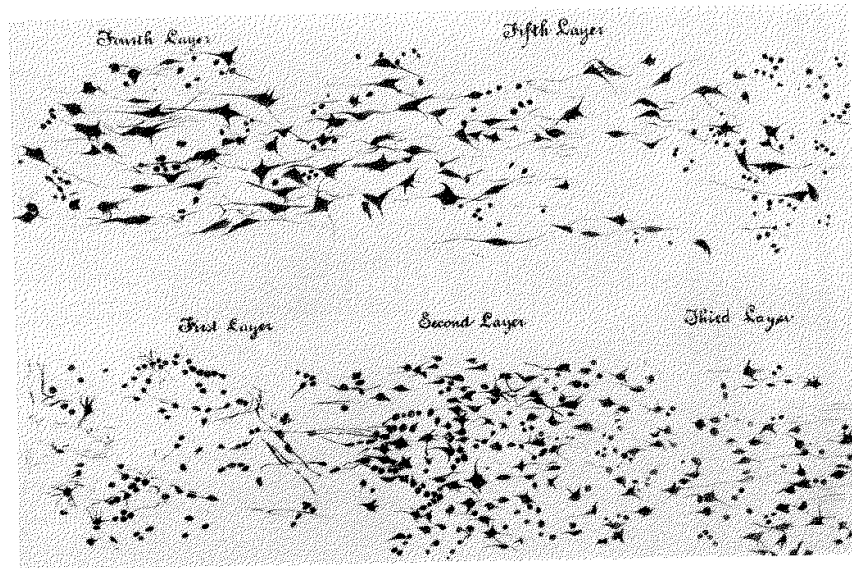


Figure 4. Lamination of the motor cortex of a sheep; fresh frozen sections, fixed in osmium and stained with aniline black. From Lewis (1878a).

them, mainly in terms of a five-layered plan, the internal granular layer being termed layer 4 and described as a layer of small irregular cells.

The first complete description based upon cytoarchitectonic criteria of the extent of a single cortical area was that of Bolton (1900) who delimited the human visual cortex with remarkable accuracy. He numbered the layers only I through 5 and though fusing our layers II and III, he clearly identified the three components of layer IV, naming them the outer granular layer, the stria of Gennari, and the inner granular layer (Fig. 6).

Campbell (1905), in the first comprehensive architectonic work on the cortex of man and animals, adopted a seven-layered scheme derived from that of Ramón y Cajal (1904) and seemingly obtained from German translations of Ramón y Cajal's earlier Spanish works (1900–1906). The scheme is not fundamentally different from the six-layered plan of Lewis, the seventh layer being obtained simply by a division of Lewis's (and our) layer III into an outer layer of medium-sized pyramids and an inner layer of large pyramids. Campbell relied upon thionin-stained,* celloidin sections from brains fixed in Müller's fluid, and in addition to pyramidal cells, he observed what he called stellate cells in layer 5 (our layer IV) and spindle-shaped or fusiform cells in layer 7 (our layer VI) (Fig. 7). In the visual area he described two layers of stellate cells in the equivalent of our layer IV.

The idea of six layers as the fundamental cortical pattern became rooted in the literature as the result of its adoption by Brodmann (1903, 1909, 1912) and his teachers, C. and O. Vogt (1919; O. Vogt, 1903). Brodmann's principal reason for adopting this plan stemmed from his belief that it represented the fundamental embryological and evolutionary scheme of cortical organization. The cell types that Brodmann and the Vogt school identified on the basis of Nissl staining were: granular, pyramidal and triangular or fusiform but they made little point of these, their principal emphasis being on the laminar structure as a means of cytoarchitectonic parcellation. By adhering rigidly to a six-layered scheme, they found it necessary in areas like the visual cortex to divide certain layers such as layers IV and VI into sublayers (Fig. 8). These are with us to this day and have often led to endless confusion, especially when cross-species homologies are involved.

As the years passed, the architectonicists of the German school came to place more and more emphasis on myelin stains as a means of delineating cortical areas (Mauß, 1908; Vogt and Vogt, 1919). The Weigert method based on hematoxylin staining, had been introduced in 1882 and the modification of Wolters was used to survey cortical lamination in the human brain by Kaes (1893) who was warmly praised for his observations by Campbell (1905). From Kaes's studies and from the later ones of Edinger (1896), Bechterew (1894), Flechsig (1898), Ramón y Cajal (1909–1911), Campbell (1905), and Brodmann (1909) some of whom used the Pal variant of the stain, a nomenclature relating to the fiber lamination of the cortex emerged (Fig. 8). At the surface is the zonal or plexiform

* Nissl had introduced his aniline dye stain in about 1885 but it was not perfected for several years (Nissl, 1903).



Figure 5. Later drawings by Lewis showing cortical lamination in the monkey. From Ferrier (1886). (A) Occipital lobe; (B) temporal lobe; (C) frontal lobe (probably area 6); (D) motor area; (E) hippocampus; (F) entorhinal area.

layer, consisting of a rather dense plexus of horizontal myelinated axons usually thought by the early workers to arise mostly from Martinotti cells. A thick but lightly myelinated supraradiary plexus corresponds to layers II and III of Nissl stains. In some areas, a thin stria of Kaes-Bechterew may occupy the upper part of layer II. The external band of Baillarger (sometimes called the stria of Gennari

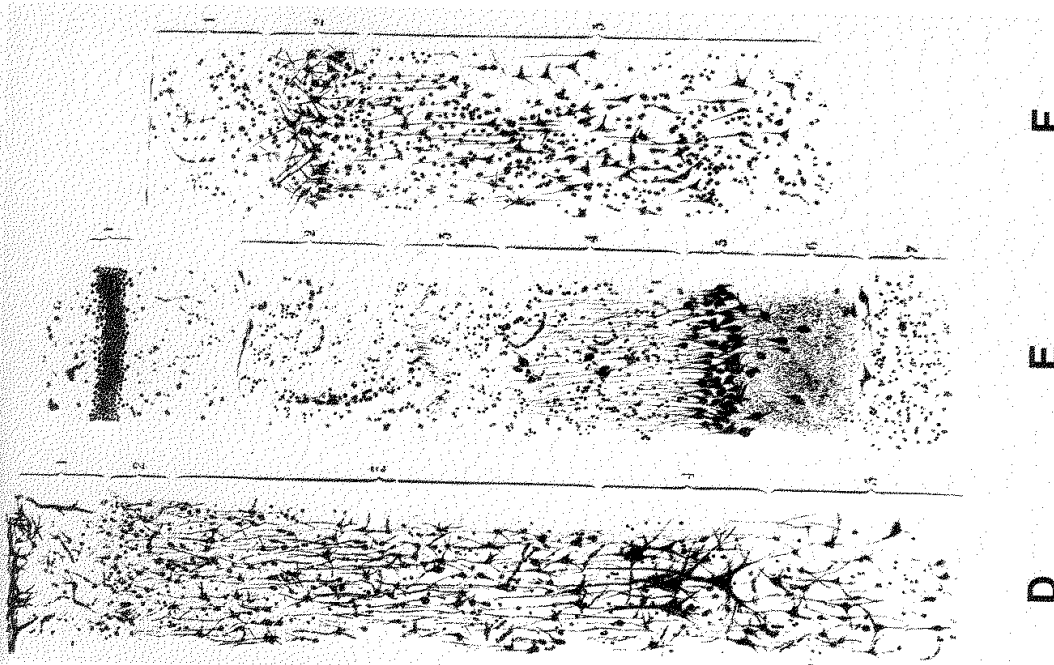


Figure 5. (continued)

even outside the striate area, e.g., by Campbell) corresponds to layer IV and is composed of a dense horizontal plexus. The internal band of Baillarger, another dense horizontal plexus, lies deep in layer V separated from the external band by a lightly myelinated, intrastriate layer. Layer VI often has several strata of horizontal fibers, the most obvious being at the border of the white matter.

TABLE SHOWING THE RELATION TO ONE ANOTHER OF THE VARIOUS PUBLISHED CLASSIFICATIONS OF "OCIPITAL" LAMINATION.

YEAR.	1872.	1876.	1881.	1893.	1895.	1896.	1900.	YEAR.
OBSERVER.	MEYNERT.	KRAUSE.	BETZ.	LEONOVA.	HAMMARBERG.	SCHLAPP.	CAJAL.	OBSERVER.
1.	1	1	1	1	1	1	1	1.
2.	2	2	2	2	2	2	2	2.
3a.	3	3	3	3	3	3	3	3a.
3b.	4	4	4	4	4	4	4	3b.
3c.	5	5	5	5	5	5	5	3c.
4.	6	6	6	6	6	6	6	4.
5.	7	7	7	7	7	7	7	5.

Figure 6. Bolton's (1900) comparative table of schemes of lamination for the human visual cortex. His own layers are placed at left and right.

Traversing the horizontal layers of myelinated fibers are the vertical radiations of Meynert, with the intervening, delicate, interradiary plexus of Edinger.

The myelin stains naturally, however, added no information in the area of cellular morphology. Relatively little was contributed by the reduced silver or neurofibrillar stains either. The first of these was introduced by Bielschowsky in 1902 and perfected in 1904. In 1905, he and Brodmann published a joint paper on the application of silver staining to the human cerebral cortex (Fig. 9). Ramón y Cajal used the method to complement some of his observations made with the Golgi technique, particularly on the nature of the axonal endings around pyramidal cells. However, in requiring the use of relatively thin sections and in staining, unlike the Golgi or methylene blue method, every soma and every process present, the reduced silver methods made it very difficult to build up a satisfactory three-dimensional picture of individual cells. Ramón y Cajal (1954), who stated that he first used neurofibrillar stains in 1903, remarked that the method was also unsatisfactory for staining short-axon cells.

Some of the early studies of connectivity on the cortex were also made during the heyday of architectonics. Many of these are referred to in Chapter 16. Several

workers had by about 1910 clearly recognized that retrograde degeneration of Betz cells ensued after spinal cord lesions or long-standing amputations (e.g., Campbell, 1905; Holmes and Page May, 1909), thus leading to the belief that the infragranular layers of all cortical areas were efferent and the supragranular layers receptive or associative (e.g., Bolton, 1910). It was to be many years, however, before the details or even an outline of efferent and afferent connections of the cortex was established. Retrograde degeneration (e.g., Nissl, 1913;



Figure 7. Campbell's (1905) drawings of thionin-stained, celloidin sections from the human postcentral gyrus (A) and superior parietal lobule (B). The layering scheme is that of Ramón y Cajal and the cells are all drawn as small pyramids.

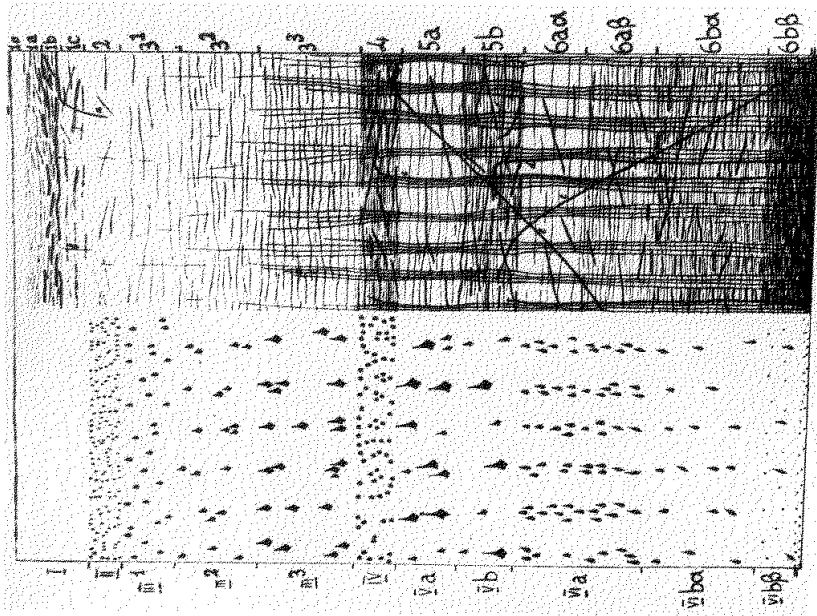


Figure 8. Vogt's scheme of the fundamental plans of cellular (left) and fiber (right) layering in the cerebral cortex. Fiber layers 4 and 5b are the bands of Baillarger; the stria of Kaes–Bechterew when present is layer 1c. From Vogt and Vogt (1919).

von Monakow, 1914; Walker, 1938), the Marchi method (e.g., Polyak, 1932), the Nauta methods (e.g., Brodal, 1969), and electrophysiology (e.g., Fulton, 1949) eventually gave us a fairly thorough understanding of the broad organizational plan of efferent and afferent connections in the cortex but the exact origins and terminations of efferent and afferent fibers in cellular terms had to await studies carried out in the last 7 or 8 years.

3. Staining of Individual Cell Types

Although the broad distinction between pyramidal and nonpyramidal cell types was evident in the earliest studies utilizing carmine as a stain, full recognition of the variety of cell types and the extent of the ramifications of individual

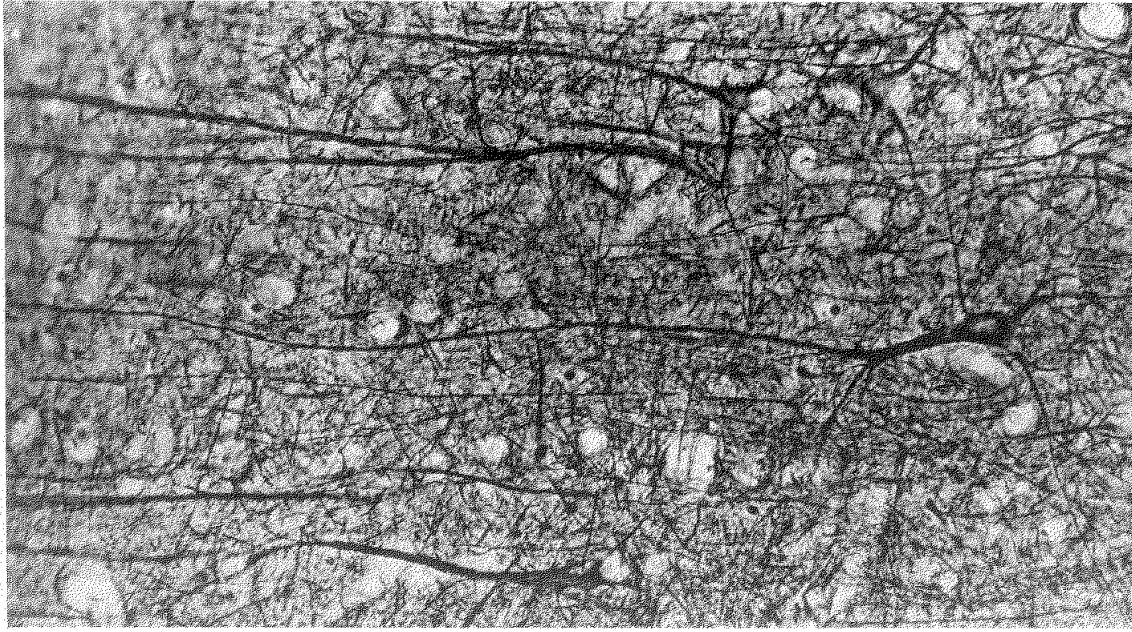


Figure 9. Pyramidal cells from the human precentral gyrus stained with Bielschowsky's neurofibrillar stain. From Bielschowsky and Brodmann (1905).

cells only emerged with the application of the Golgi and methylene blue stains. Golgi discovered the silver stain that bears his name in 1873 and by 1874 had applied it to the cerebellar cortex. When he first used it to examine the cerebral cortex is difficult to ascertain but by 1883, he had described both pyramidal cells and large star-shaped cells in some detail (see Chapter 5). According to Ramón

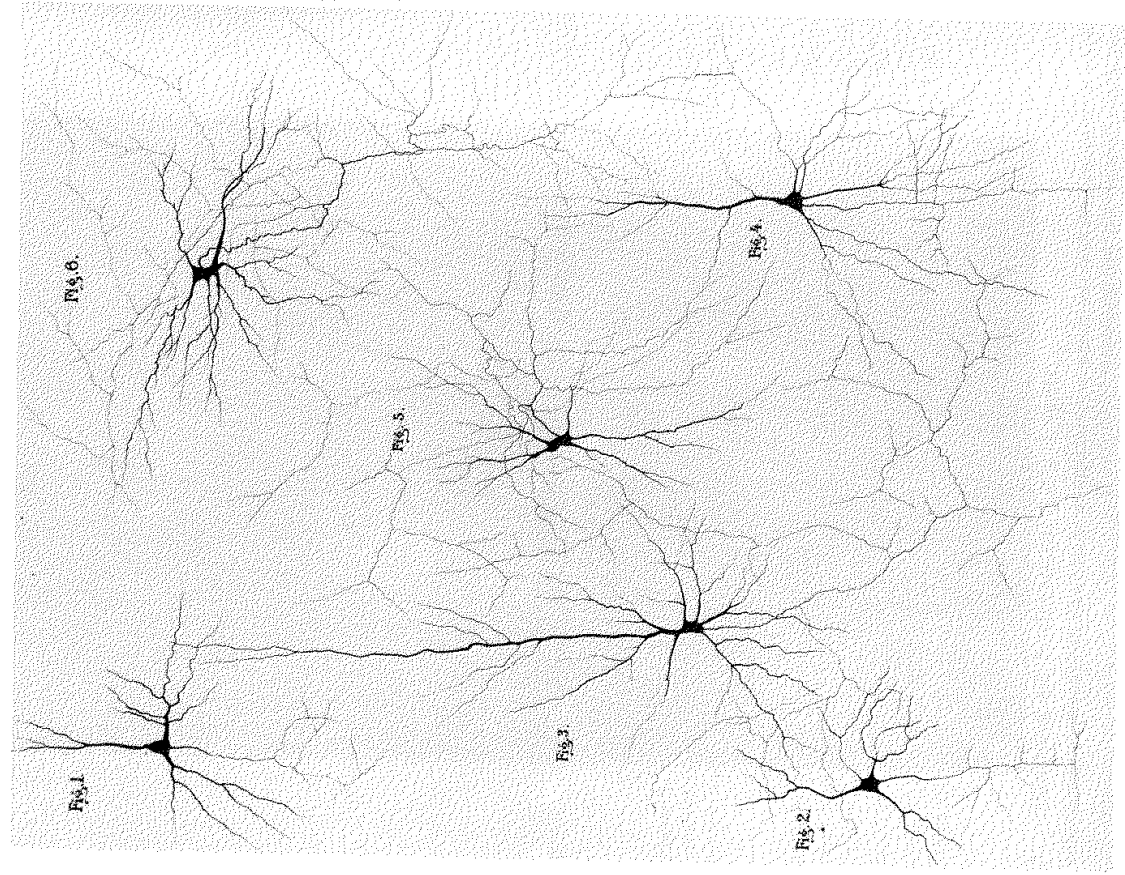


Figure 10. Drawings by Golgi of pyramidal and nonpyramidal cells from the human cerebral cortex. The original drawing showed axons in red. From Golgi (1883b).

y Cajal (1954), one of Golgi's chief contributions at this stage was to indicate that the dendrites ended freely, not by anastomosing with one another. Probably Golgi should also be credited with the first clear distinctions between axons and dendrites in the cortex, though Deiters had indicated this much earlier in other regions. Golgi was able to stain the axons of many of the cortical cells and observed collateral branches, probably for the first time (Fig. 10). He did not draw spines on the dendrites of any cells though Ramón y Cajal, who first described them on pyramidal cells in 1891, stated (1954) that Golgi must have seen them.

Between 1883 and publication of Volume 2, Part 2 of the original Spanish version of Ramón y Cajal's *Histologie du Système Nerveux*, in 1904, there were several excellent studies of the cerebral cortex made by using the Golgi method particularly by Golgi himself (1884, 1885, 1886, 1894), by Ramón y Cajal (1891, 1894, and other references in his books of 1904, 1911, and 1954), and by Retzius (1893, 1896). Many others dabbled with the staining of cortical cells (Fig. 11), but by far the most comprehensive surveys of cortical cell types are those of Ramón y Cajal and of Retzius (Fig. 12), who in general concurred with most of Ramón y Cajal's descriptions. A further readable and well-illustrated account, also in line with that of Ramón y Cajal, is the one published by von Kölliker

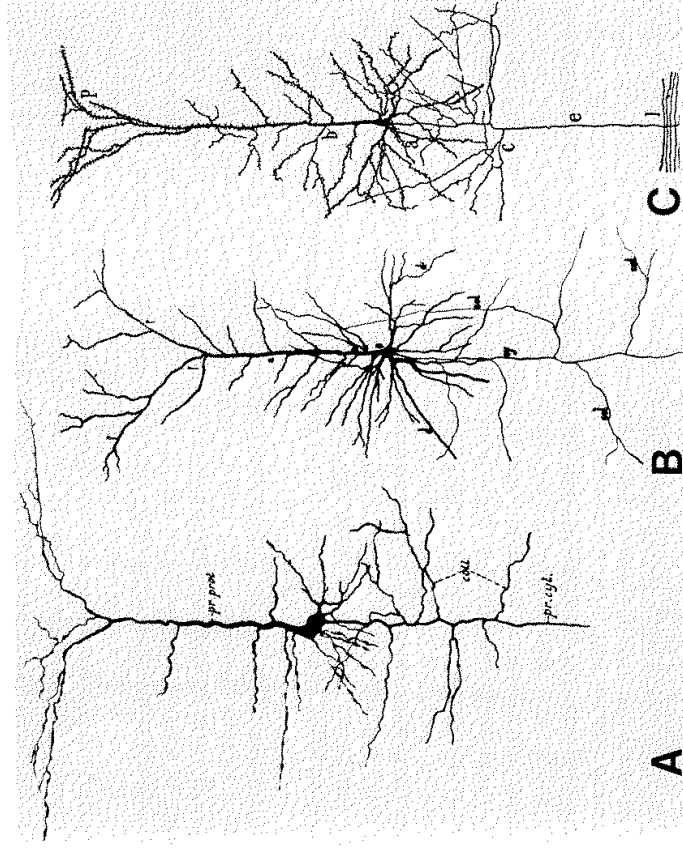


Figure 11. Drawings of Golgi-impregnated pyramidal cells from the cortex of a 9-day-old mouse (A), adult man (B), and a mouse of unspecified age (C). By Van Gehuchten (1897, A), by Ramón y Cajal's translator, Azoulay (from Dejerine, 1895, B) and by Ramón y Cajal himself (1909–1911, C). All indicate the axon and its collaterals. (B) and (C) show dendritic spines.

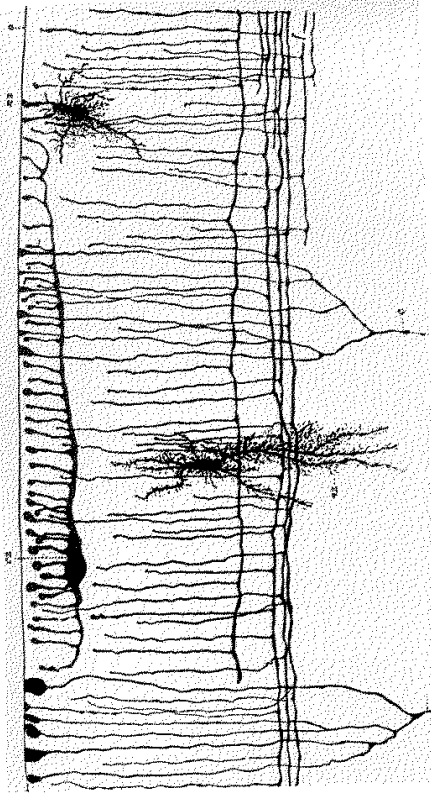


Figure 12. Drawing by Retzius (1893) of a Golgi-impregnated Cajal-Retzius cell, tangential fibers, astrocytes, and radial glial processes from layer I of the temporal cortex of a human fetus.

(1896) in the sixth edition of his *Handbuch der Gewebelehre des Menschen* (Fig. 13). This was based on a series of studies carried out as the result of his "discovery" of Ramón y Cajal and Ramón y Cajal's preparations at the meeting of the German Anatomical Society in Berlin in 1889 (Ramón y Cajal, 1937).

Ramón y Cajal based his studies not only on Golgi preparations but also on those stained with methylene blue (Figs. 14, 15) introduced by Ehrlich in 1868, and like the Golgi method staining only a small proportion of the neurons present but in their entirety. He stated (Ramón y Cajal, 1954), however, that he found methylene blue less satisfactory than the Golgi method, except for demonstrating the large fusiform cells.

Ramón y Cajal described the cells of the cortex systematically, layer by layer, both in general terms and in selected specific areas such as the visual and auditory. His emphasis was on the human brain and he made extensive use of preparations from human infants, supplemented by some material from cats, dogs, and rodents. Later in life he was to make a detailed study of the visual cortex of the cat alone (Ramón y Cajal, 1922). His basic classification is into pyramidal cells and cells with short axons (Fig. 14; and see Chapter 6). He thought that the number of short-axon cells increased greatly in the human brain and he saw this feature as one of the keys to understanding the functional complexity of the brain of man. He recognized the similarity between pyramidal cells of all layers, despite considerable variations in size. But he also detected subtle differences in their dendrite branching patterns and in the patterns of collateral branching of their axons. Among the cells with short axons, he detected a number of different varieties based on dendritic and/or axonal arborizations. Unfortunately, he was not always consistent in his naming of these, sometimes using several synonyms for the same cell type and sometimes giving the same name to clearly different kinds of cells. His use of the term *double bouquet cell*,

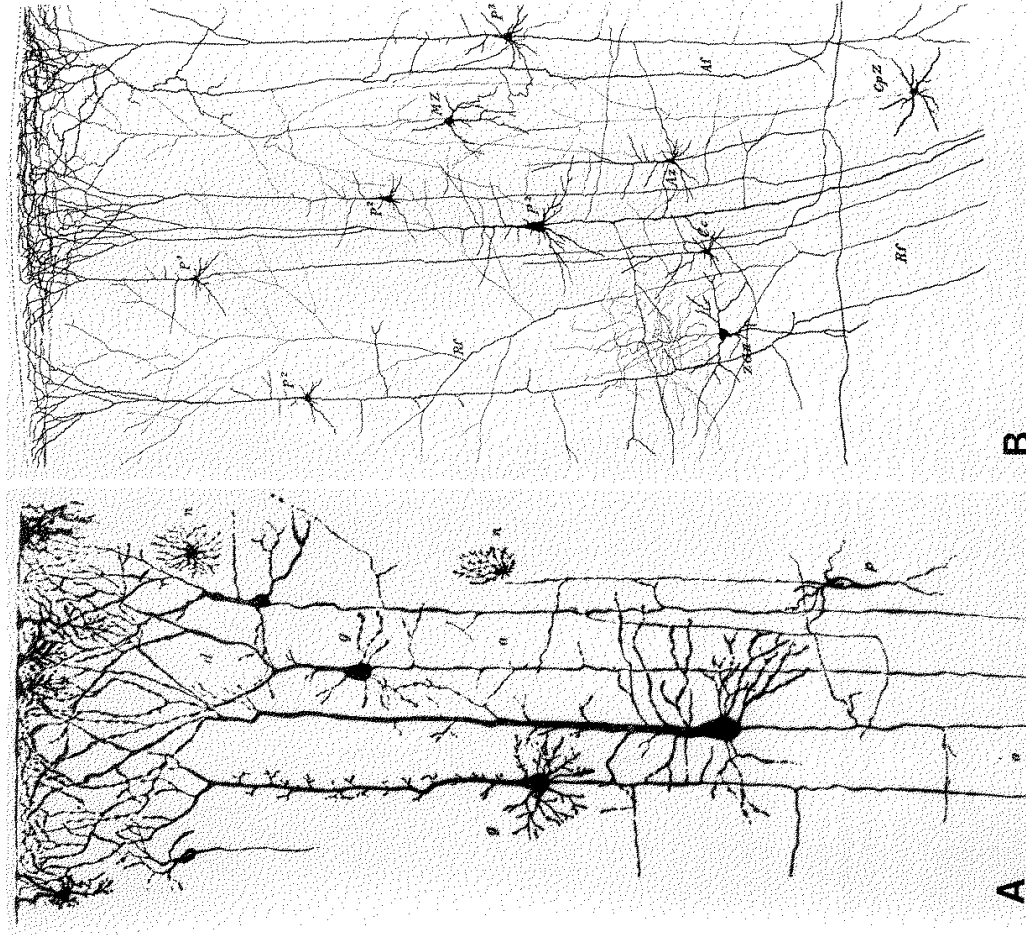


Figure 13. (A) Drawing by Retzius (1896) of Golgi-impregnated neurons and glial cells in the cerebral cortex of a young rabbit. (B) Drawing by von Kolliker (1896) summarizing his view of cortical organization, as based on Golgi preparations of mice and rabbits. Af: ending of a callosal or association fiber; Az: association cell; Cc: cell of corpus callosum; CpZ: cell of corpus striatum; MZ: Martinotti cell; P: pyramidal cells; Rf: "Ramón's centripetal sensory fiber"; ZGII: Golgi type II cell. The original drawing showed axons in blue or red.

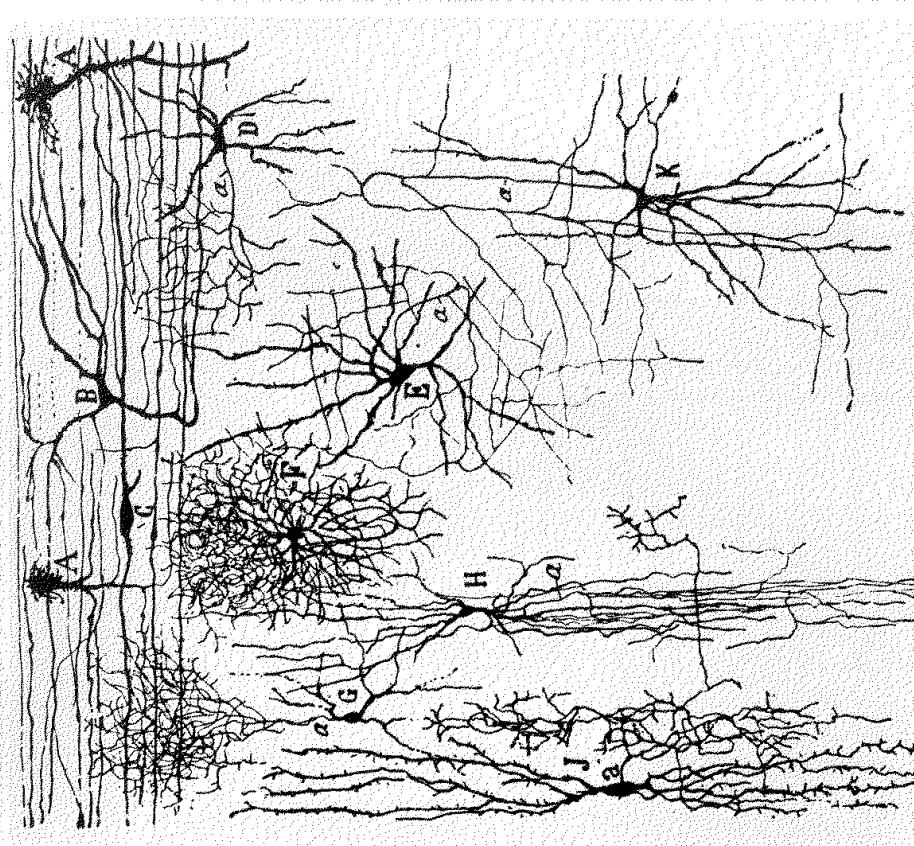


Figure 14. Drawings by Ramón y Cajal (1911) of Golgi-impregnated short-axon neurons in the superficial layers of the motor cortex of a human infant. A–C: “horizontal cells”; D–F: “short-axon cells”; G: “cell with ascending axon”; H, J: “double bouquet cells”; K: “large bouquet cell.”

for example, is notoriously inconsistent, sometimes being based on dendritic characteristics, sometimes on one kind of axonal characteristic, and sometimes on another (see Chapter 6). This may be one reason why until recent times Ramón y Cajal’s terms did not come into common usage, his followers such as Lorente de Nó (1922, 1949) preferring to use the term *short-axon cell* to cover all forms.

Generally speaking, Ramón y Cajal described short-axon cells in all layers and in all areas, dividing them into forms with local axons, vertical axons, or horizontal axons. Most have been recognized in recent studies (e.g., Jones, 1975). The relatively large numbers of spines shown by Ramón y Cajal on many of them, however, has on the whole not been reproducible, possibly because he

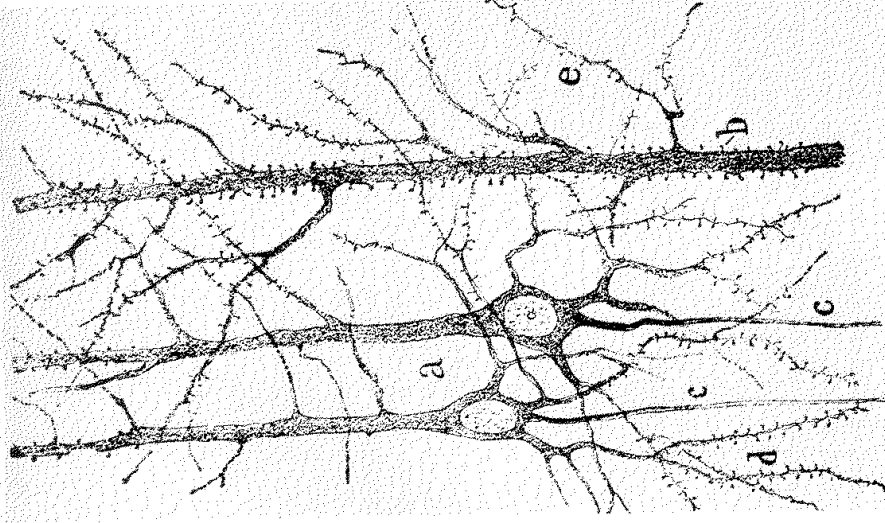


Figure 15. Drawings by Ramón y Cajal (1954) of methylene blue-stained pyramidal cells in the cerebral cortex of a cat, used by him to reinforce his belief in dendritic spines.

mostly used material from immature brains. Unique forms of neurons found in layer I particularly of infant animals were the Cajal–Retzius cells (Fig. 12; and see Chapter 14), and the short-axon and pyramidal cells of layer VI adopted a variety of forms different from those of other layers. Unique, he thought, to the auditory area was a special form of giant cell and unique to layer IVb of the visual cortex a type of large spiny nonpyramidal cell with an axon that, unlike those of other nonpyramidal cells, entered the white matter (Ramón y Cajal, 1922). Various forms of afferent fibers were also described and he was probably the first to clearly identify the terminal territories of thalamic afferents in layer IV. In his final work (1954) he concluded the section on the cerebral cortex thus: “One thing is certain: classification of the manner of connection between the innumerable centrifugal and centripetal, terminal and collateral branches emanating from thalamic, callosal and association fibers constitutes at present an overwhelming problem. In it many generations of future neurologists will put their sagacity and their patience to the test.”

4. Golgi Studies after Ramón y Cajal

The chief aficionado of the Golgi technique in the years that followed Ramón y Cajal's death in 1934 was undoubtedly Lorente de Nó, who had completed his first study of what he took to be the auditory cortex of the mouse under Ramón y Cajal's direction in 1922. The area he was studying was probably the first somatic sensory area. In it he was able to detect many of the cell forms described earlier by Ramón y Cajal and made pertinent observations on the relationships of certain short-axon cells and of the dendritic fields of certain pyramidal cells to the terminal ramifications of thalamocortical axons. Lorente de Nó's subsequent published work on the cortex was mostly devoted to the hippocampal formation and adjoining areas. However, for Fulton's *Physiology of the Nervous System*, the last edition of which was published in 1949, he provided a general account of neuronal organization in the neocortex that stands as a frequently quoted classic (Fig. 16). In it he proposed a model of cortical circuitry based on thalamocortical axons terminating in layer IV on the dendrites of both pyramidal

and short-axon cells. From these, activity was conducted upwards and downwards in the cortex by pyramidal cell axons and by short-axon cells with vertical axons. At all levels there were recurrent loops formed by the collateral axon branches of pyramidal cells and by short-axon cells with local axon plexuses. Hence, a vertically oriented, reverberating circuit of activity would be set up. In this scheme we can detect the first glimmerings of a concept of columnar organization in the cortex, a fact that was recognized by Mountcastle (1957) in his original paper on the cortical column.

Lorente de Nó is often taken to task for describing too many cortical cell types. He mentioned some 40 in his first paper, though he later reduced the number to about 5. It is doubtful, however, that he meant these to be more than but variants of a much more fundamental plan of organization in which some short-axon cells operated over relatively long intracortical distances, commonly in the vertical dimension, while others exerted extremely local effects.

There were a number of descriptive Golgi studies subsequent to Lorente de Nó's account but those published between 1940 and about 1970 seem remarkably superficial and it is doubtful that any truly lasting data emerged from them. A possible exception is the work of Sholl (1956) who made rather more use of the mercury-based Golgi-Cox method (Cox, 1891) than had previous investigators and directed his major efforts at the quantification of dendritic field architecture. His methods for graphic representation of the lengths of dendritic branches (Fig. 17) and for measuring dendritic field complexity in terms of numbers of dendritic profiles that intersect a series of circles of increasing radius centered on the cell soma (Fig. 17), are still widely used.

Sholl is now coming to be criticized for his classification of cortical neurons simply into pyramidal and stellate forms and for making little attempt to define different classes of stellate cells. One reason for this was undoubtedly that the Golgi-Cox method as used by him did not reliably stain the axons which are the major distinguishing feature of the different classes of nonpyramidal cells (Jones, 1975). Within his frame of experimental reference, however, this was unnecessary for Sholl.

The advent of electron microscopic studies of the central nervous system resulted in a new phase of descriptive morphology using Golgi preparations, since there was a need to correlate the profiles identified electron microscopically with components of particular cell classes of light microscopy (see Chapter 4 on neuronal classification). The first return to the cortex was in the work of Szentágothai (1969) and of Valverde (1971) who noted again some of the forms of short-axon cells described by Ramón y Cajal (Figs. 18, 19). A second significant contribution was that of Lund (1973) who defined two classes of nonpyramidal cells, spiny and nonspiny. In 1975 the author made a concerted effort to define nonpyramidal cells in terms of their axonal arborizations (Jones, 1975). From this emerged eight or nine distinctive cell classes, all of which seem to have stood the test of time and subsequent studies (e.g., Peters and Regidor, 1981; and other chapters of this book). In many respects the new Golgi studies have led to a rediscovery of the cortical cell types of Ramón y Cajal. However, the work has generally been carried out in a more systematic manner than in the past, and in the light of knowledge of cortical connectivity derived from experimental studies. There has also been an emphasis on classifying nonpyramidal cells ac-

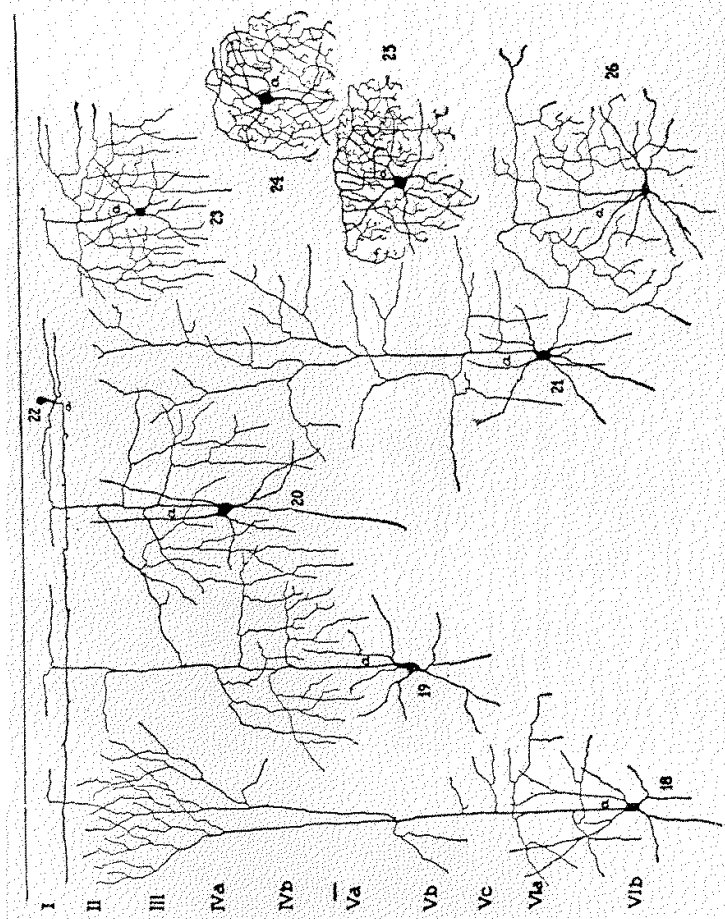


Figure 16. Drawings by Lorente de Nó (1949) showing his three types of neurons with intracortical axons. 18–21: cells with ascending axons; 22: cell with horizontal axon; 23–26: cells with short axons.

cording to their axonal ramifications which can be remarkably stereotyped and more useful than classification in terms of dendritic field shapes (Jones, 1975; see Chapter 13). From these types of studies a number of hypothetical schemes have been put forward, particularly by Szentágothai (1969, 1970, 1973, 1975, 1978) in an effort to provide a circuit diagram that underlies the functional columnarity of the cortex (Fig. 19).

Two major contributions have been technical. The first was that of Colonnier (1964a) who showed that by slightly modifying a variant of the Golgi stain originally introduced by Kopsch (1896), tissue from the same animal fixed by

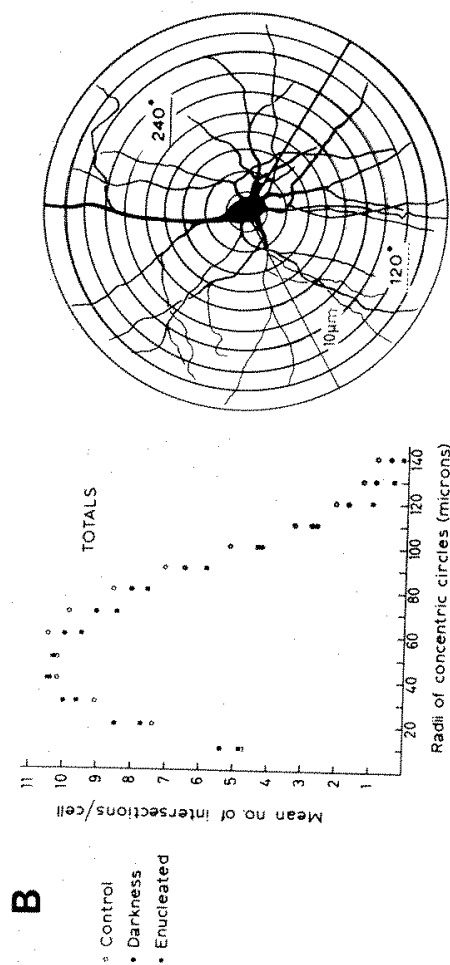
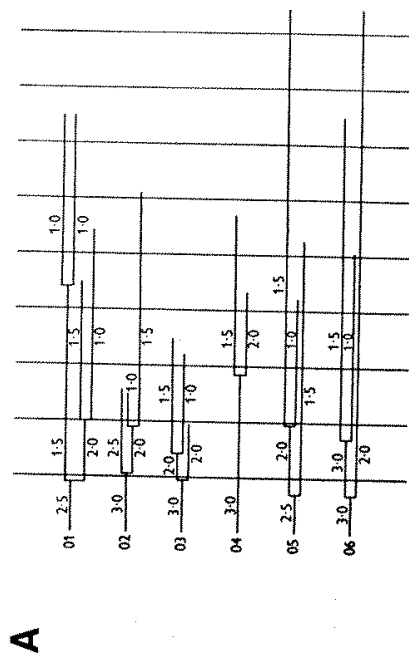


Figure 17. (A) Sholl's (1956) method of "graphical representation of the lengths of dendritic branches for a single neuron." (B) Sholl-type analysis for complexity of dendritic branching based on number of intersections made by dendrites with circles of increasing radii centered on soma. For basal dendrites of layer III pyramids in the visual cortex of normal mice (control), mice reared in darkness, and mice enucleated at birth. From Valverde (1971).

perfusion with mixed aldehydes could be used both for Golgi impregnation and for electron microscopy. This method has become one of the most widely used of all the Golgi methods. Derivative of it is the method of perfusing with the initial Golgi reagent, potassium dichromate, mixed in with the aldehydes (Reithely, 1972). A second major innovation was that of Fairén *et al.* (1977) who showed that the silver chromate precipitate filling a well-impregnated neuron could be replaced with finer gold particles that were not only more amenable to electron microscopic study but left the ultrastructure remarkably well preserved (see Chapters 9–13). In this way a cell identified light microscopically can be examined electron microscopically, often in conjunction with another marker (e.g., axon terminal degeneration) and the afferent and efferent connectivity of the cell defined. In the future it seems inevitable that the Golgi method will also be made compatible with other techniques, particularly those involving immunocytochemistry, autoradiography, and labeling by axoplasmic transport.

Scheibel and Scheibel posed the question in 1971: "The rapid Golgi method: Indian summer or renaissance?" There can be no question that there has been a definite renaissance in this time-honored method and despite advances in other forms of cell labeling it seems likely that it will hold its place as a major method on which we base our classifications of cortical cells for many years.

5. Recent Innovations

Most of the methods that have been introduced for the study of cortical neurons in recent years are outlined in Chapter 4. The first of these was undoubtedly electron microscopy. Probably the first significant contributions with the new technique were made by Gray (1959) whose method of fixation involved dripping osmium tetroxide onto the cortex or dicing it into small pieces prior to immersion in osmium. Gray was also one of the first to embed neural tissue in Araldite prior to sectioning. Among his fundamental observations were the identification of asymmetrical and symmetrical synapses (which he called types I and II) and the clear delineation of dendritic spines as biological entities rather than, as some had supposed, artifacts of the Golgi stain or impregnated synaptic terminals. He showed that most synapses were on spines rather than on the dendritic shafts of pyramidal cells. Soon after the introduction of perfusion with mixed aldehydes as the primary fixative of choice in electron microscopy of the nervous system (Karnovsky, 1965; Vaughn and Peters, 1966), two further observations of fundamental significance were made by Colonnier (1968). He showed (in a classic plate illustrating 100 synapses with parallel sectioned membranes) that axon terminals making Gray's asymmetrical synapses invariably contained synaptic vesicles that were spherical in shape, while those making symmetrical synapses invariably contained vesicles that were flattened or pleomorphic when fixed in aldehyde mixtures of relatively high osmolarity. An association of symmetric, flattened vesicle-containing synapses with inhibitory synapses had already been made in the cerebellar cortex by Uchizono (1965). Colonnier also pointed out that pyramidal and nonpyramidal cells could be distinguished by differences

cells only emerged with the application of the Golgi and methylene blue stains. Golgi discovered the silver stain that bears his name in 1873 and by 1874 had applied it to the cerebellar cortex. When he first used it to examine the cerebral cortex is difficult to ascertain but by 1883, he had described both pyramidal cells and large star-shaped cells in some detail (see Chapter 5). According to Ramón

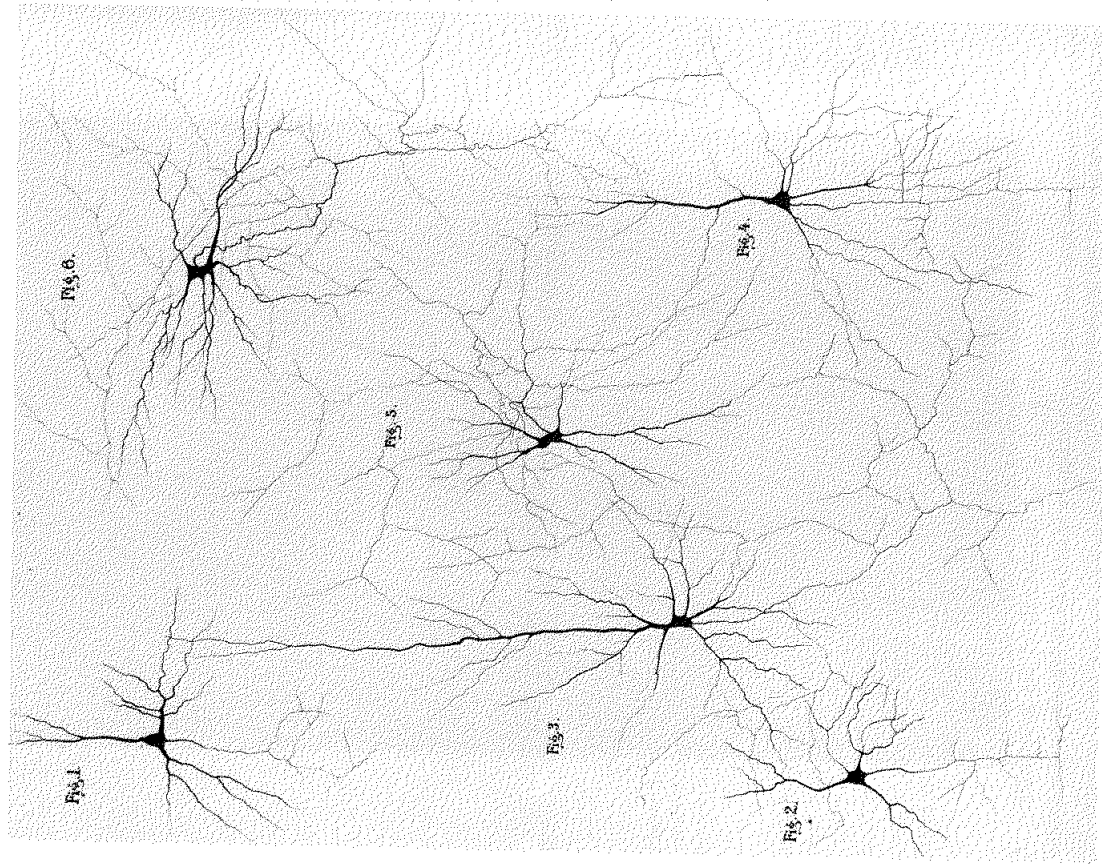


Figure 10. Drawings by Golgi of pyramidal and nonpyramidal cells from the human cerebral cortex. The original drawing showed axons in red. From Golgi (1883b).

y Cajal (1954), one of Golgi's chief contributions at this stage was to indicate that the dendrites ended freely, not by anastomosing with one another. Probably Golgi should also be credited with the first clear distinctions between axons and dendrites in the cortex, though Deiters had indicated this much earlier in other regions. Golgi was able to stain the axons of many of the cortical cells and observed collateral branches, probably for the first time (Fig. 10). He did not draw spines on the dendrites of any cells though Ramón y Cajal, who first described them on pyramidal cells in 1891, stated (1954) that Golgi must have seen them.

Between 1883 and publication of Volume 2, Part 2 of the original Spanish version of Ramón y Cajal's *Histologie du Système Nerveux*, in 1904, there were several excellent studies of the cerebral cortex made by using the Golgi method particularly by Golgi himself (1884, 1885, 1886, 1894), by Ramón y Cajal (1891, 1894, and other references in his books of 1904, 1911, and 1954), and by Retzius (1893, 1896). Many others dabbled with the staining of cortical cells (Fig. 11), but by far the most comprehensive surveys of cortical cell types are those of Ramón y Cajal and of Retzius (Fig. 12), who in general concurred with most of Ramón y Cajal's descriptions. A further readable and well-illustrated account, also in line with that of Ramón y Cajal, is the one published by von Kölliker

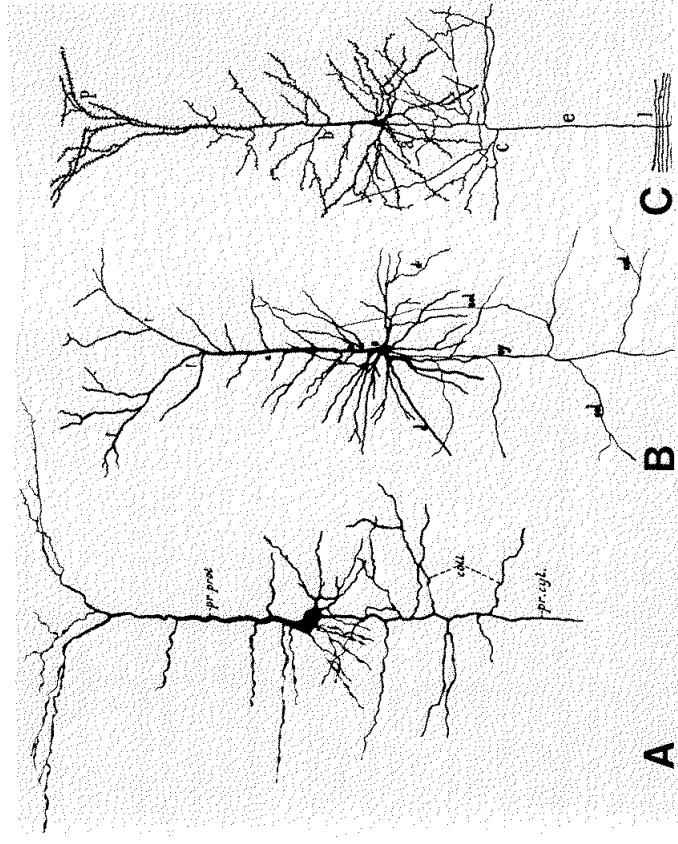


Figure 11. Drawings of Golgi-impregnated pyramidal cells from the cortex of a 9-day-old mouse (A), adult man (B), and a mouse of unspecified age (C). By Van Gehuchten (1897, A), by Ramón y Cajal's translator, Azoulay (from Dejerine, 1895, B) and by Ramón y Cajal himself (1909–1911, C). All indicate the axon and its collaterals. (B) and (C) show dendritic spines.

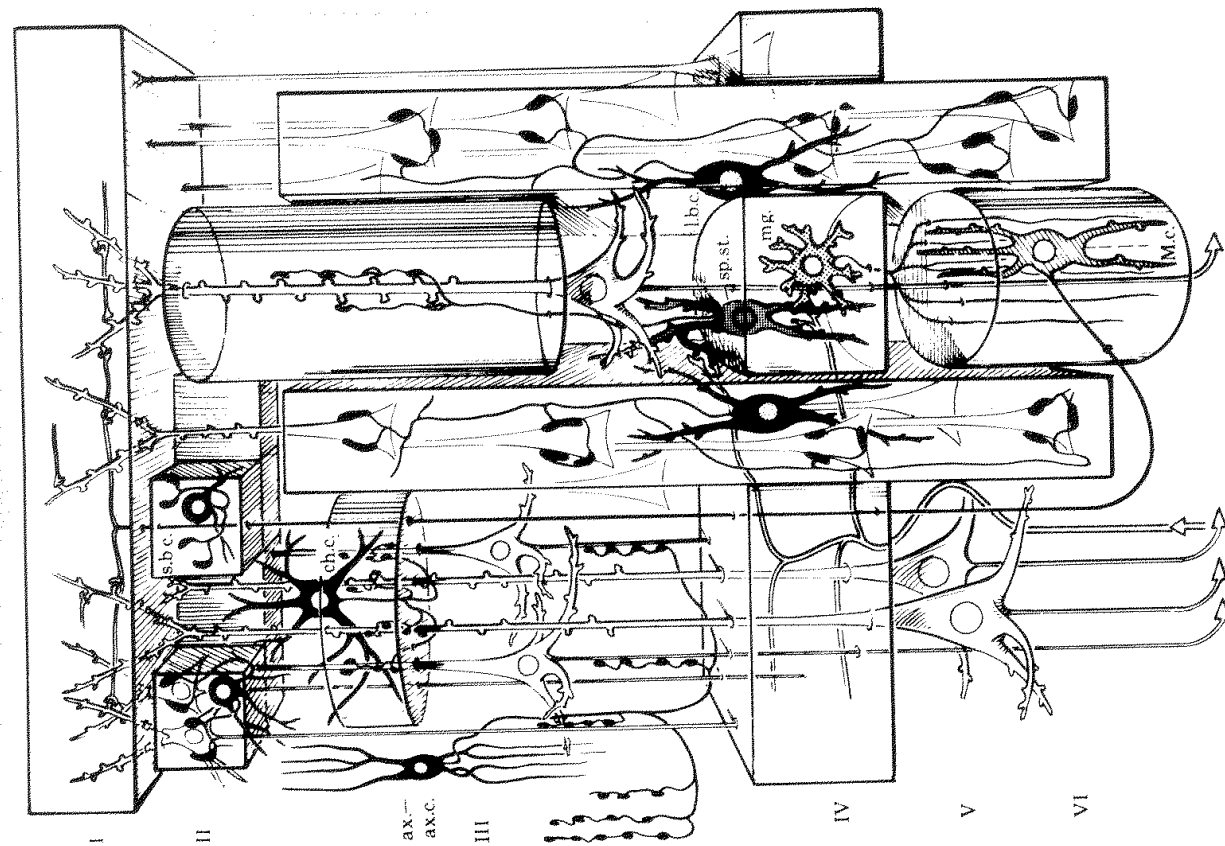


Figure 19. Another modern master, Szentágothai's (1978) "synthetic stereoscopic view of the modular arrangement of local neuronal connections" in the cortex, based on Golgi and experimental studies. Here, he attempts to relate the different classes of intrinsic neurons (inhibitory in black, excitatory shaded), to the chain of synaptic events that should ensue following the arrival of an afferent volley and which must underlie the functional columnarity of the cortex.

in their complements of organelles and in the numbers and proportions of different types of synapse that they received. For example, pyramidal cell somata received relatively few synapses, all of the symmetric type, while most nonpyramidal cells received many synapses of both types on their somata and dendrites. Colonnier's two observations have formed the basis for many subsequent fine structural studies of the cerebral cortex. He was also able to demonstrate the morphological characteristics of axon terminal degeneration that ensued in the cortex following undercutting (Colonnier, 1964b). The use of Wallerian degeneration to promote identifiable labeling of the terminals of specific afferent pathways entering the cortex was first applied by Jones (1968; Jones and Powell, 1970).

More recent technical innovations include the labeling of cortical cells by retrograde axoplasmic tracers, which between 1974 and 1977 enabled us to say conclusively not only that pyramidal cells are the major output cells of the cortex, and nonpyramidal cells intrinsic (Chapter 16), but also that the layers of the cortex have different output connections (see list of all early references in Wise and Jones, 1977). Their input connections have, similarly, been more thoroughly characterized than ever before by studies using anterograde axoplasmically transported markers (see Jones and Hartman, 1978).

Through the use of both techniques, coupled with [³H]thymidine autoradiography, the developmental history of the cortex has been elucidated (Angewine and Sidman, 1961; Rakic, 1974, 1976; Jones, 1981). Labeling of individual cell classes by immunocytochemistry or by autoradiography following uptake of their radiolabeled transmitter has given us the information that a large population and several varieties of the intrinsic neurons are GABAergic and that GABA is associated with symmetric synapses (Ribak, 1978; Hendry and Jones, 1981; Hendry *et al.*, 1983; Houser *et al.*, 1983; Peters *et al.*, 1982; see also chapter by Houser *et al.* in Volume 2). A number of forms of intrinsic neurons also contain various brain-gut peptides (Emson and Hunt, 1981). Receptor localization (Palacios *et al.*, 1981; Wise and Herkenham, 1982; see also chapter by Wamsley in Volume 2) is only just beginning in the cortex, one of the methods being used representing a return to that of Lewis (1878b).

The definition of individual cell classes in terms of their receptive field properties by intracellular recording followed by intracellular injection was commenced by Kelly and Van Essen in 1974 when they injected a small population of pyramidal and nonpyramidal cells in the cat visual cortex with procion yellow. This exhausting but rewarding work has been continued using horseradish peroxidase as the intracellular marker in the hands of Deschênes *et al.* (1979). Gilbert and Wiesel (1979), and Lin *et al.* (1979). The yield of cells to date is rather too small to make any generalizing statements about the relationship of cell type to receptive field type but already better information has been derived about the distribution of collateral branches of different types of pyramidal cells than had ever appeared in any previous Golgi studies.

Other types of study that are just commencing on the cortex include those on regional blood flow and metabolism (Sokoloff *et al.*, 1977) and the histochemical detection of oxidative enzymes (Wong-Riley, 1979). All of these methods, though not yet having reached the level of resolution of the single cell, lend themselves to experimental manipulation. It seems inevitable that further advances, perhaps using these in combination with other methods, will eventuate.

With so many new techniques appearing, the future of cortical studies is likely to be an active one. Among new technical innovations that may be envisaged are the recording of the activities of groupings of neurons working as functional units by the use of multiple, closely spaced microelectrodes and the specification of individual cell classes through a knowledge of their individual antigenic characteristics and, ultimately, through a knowledge of their genome. Perhaps in the not too distant future we shall understand not only why cortical cells express certain transmitters but also why they adopt individual morphologies and connectivities.

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