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Origin, Prenatal Development and Structural Organization of Layer I of the Human Cerebral (Motor) Cortex

A Golgi Study *

Miguel Marin-Padilla and Teresa M. Marin-Padilla
Department of Pathology, Dartmouth Medical School Hanover, New Hampshire, U.S.A.

Summary. The composition and structural organization of layer I of the human motor cortex were studied throughout the course of prenatal cortical neurogenesis with the rapid Golgi method. The components of layer I are six. The specific afferents of layer I (primitive corticipetal fibers) and the Cajal-Retzius neurons are its essential intrinsic components, while the apical dendritic bouquets of all pyramidal neurons and the axonic terminations of all Martinotti neurons are its essential extrinsic elements. These four components are recognized throughout the entire course of prenatal cortical neurogenesis. The small neurons and terminals from afferent systems of lower cortical strata, which are incorporated into layer I late in cortical neurogenesis, represent its non-essential components. The specific afferents of layer I are the first corticipetal fibers to arrive at the developing telencephalic vesicle marking the beginning of cortical neurogenesis. These primitive fibers extend throughout the surface of the cerebral vesicle establishing an external white matter. They are considered to be the stimulus for the development and maturation of the Cajal-Retzius neurons. Together they form a primitive cortical organization, the primordial plexiform layer, which precedes the appearance of the cortical plate and is considered to be common to and shared by amphibians, reptiles and mammals including man. Layer I evolves from this primordial cortical lamination. The Cajal-Retzius neurons are all characterized by a single descending axonic process which becomes a long horizontal (tangential) fiber in the lower half of layer I. Although the body and main dendrites of these neurons are only found at strategic and old cortical regions (e.g. the motor, acoustic and visual areas) their long horizontal axons extend, anteroposteriorly, throughout the entire surface of the cerebral cortex and establish synaptic connections with the apical

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Offprint requests to: Dr. M. Marin-Padilla, Department of Pathology, Dartmouth Medical School, Hanover, N.H. 03755. U.S.A.

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dendrites of all pyramidal neurons regardless of location, cortical depth or functional role.

In the course of cortical development, all developing pyramidal neurons ascend through the cortical plate in order to establish primary synaptic contacts with layer I. Only then, do they become ready to be displaced downward by the arrival of the next set of migrating neuroblasts. All pyramidal neurons of the cerebral cortex are actually suspended from layer I anchored to it by their apical dendritic bouquets. The need for all pyramidal neurons to reach and establish original synaptic connections with layer I could explain the remarkable 'inside-out' formation of the cortical plate. This fact could also explain the characteristic shape of these neurons, as well as their abundance, structural uniformity and universal radial orientation to layer I. The functional role of layer I seems to be the spreading of the same kind of primitive information to all pyramidal neurons of the cerebral cortex whether they be motor, sensory, acoustic, visual or associational in nature, or whether they be large or small.

The observations presented in this study further corroborate the concept of the dual origin of the mammalian cerebral cortex. The study emphasizes the important role played by layer I in the overall organization of the cerebral cortex. It proposes that in the course of cortical neurogenesis all future pyramidal neurons are attracted to layer I where they establish original synaptic connections and all receive from it the same kind of primitive information needed for their maturation. There seems to be no obvious reason to believe that the original synaptic contacts established between all pyramidal neurons and layer I disappear in the course of cortical neurogenesis. On the contrary, the progressive growth of the apical dendritic bouquets within layer I seems to indicate that they actually expand.

Key words: Layer I – Motor cortex – Human – Prenatal neurogenesis – Golgi study

Introduction

The present study analyzes, with the aid of the rapid Golgi method, the structural organization of layer I of the human cerebral (motor) cortex throughout the entire course of prenatal ontogenesis. It is the first attempt to study a lamina of the human cerebral cortex through its entire prenatal development. The objective of this study is to establish the intrinsic and the extrinsic components of layer I, analyze their developmental history and structural relationships and distinguish between its essential and non-essential elements. Only the specific afferent fibers of layer I and the Cajal-Retzius neurons, which are recognized throughout the entire prenatal development of this lamina, are considered to be its essential intrinsic components. The knowledge of the origin, developmental history and structural relationships of these two essential components is considered to be *sine qua non* for an understanding of the nature and functional organization of layer I of the cerebral cortex. Such knowledge is also necessary to understand the functional relation between layer I and the remaining cortical layers. Layer I also receives extrinsic neuronal and fibrous elements in the course of cortical neurogenesis. During the maturation of the cortical plate the apical dendrites of all pyramidal neurons and the axons of Martinotti neurons are progressively incorporated into the basic organization of layer I, without causing any significant structural modifications in that organization. There are also late additions to layer I, namely, the small neurons and the terminal fibrils from extrinsic afferent systems of deeper cortical levels. These late additions to layer I are considered to play a secondary role within its basic organization.

A complete developmental investigation of layer I of the human cerebral cortex with the rapid Golgi method has not been carried out previously because this type of study requires intact and unaffected (fresh) autopsy material not readily available. The early human autopsy material used in this study has been collected over a period of more than eleven years, (about two cases per year). We would like to acknowledge that without the collaboration of members of the Department of Maternal and Child Health at Dartmouth Medical School and very specially that of Dr. William H. Edwards, the gathering of this material would have been impossible. The parental understanding and collaboration in giving us early autopsy permission is also acknowledged with thankfulness and appreciation.

Prior to the presentation of the data, a review of some of the prevailing ideas and controversies surrounding the structural organization of layer I of the mammalian cerebral cortex will be presented and briefly discussed.

Literature Survey

A review of the literature concerning layer I of the mammalian cerebral cortex (including man) is not as informative as one would like it to be. The information is fragmentary, incomplete, unclear, and often controversial. One fails to obtain from such a review a coherent picture about the nature of this superficial lamination or about its basic structural organization. To facilitate the analysis and presentation of the data, this review will be separated into four chapters dealing respectively with morphologic, developmental, histologic, and functional aspects of layer I.

I. Morphologic Aspects of Layer I

The superficial lamina (the marginal or molecular zone; the plexiform layer; or simple layer I) of the mammalian cerebral cortex is characterized by a simple structure which is poor in neurons and rich in fibers. These fibers spread horizontally or parallel to the pial surface and its individual elements can be followed for a long distance. The rich plexus formed by these fibers represents the most prominent feature (external plexiform layer of Cajal) of this superficial lamina. Some fibers of this plexus are known to acquire myelin sheaths very early in cortical ontogenesis, thus suggesting an early functional role (Cajal 1911; Zuzino 1909; Brodmann 1910; Szentagothai 1970, 1978). The origin, composition, and possible function of this axonic plexus has never been satisfactorily explained.

The plexiform structure of layer I contrasts sharply with that, rich in neurons, of the other cortical laminae. Layer I is recognized throughout the entire cerebral cortex. Its simple structure and fiber composition seem to be similar among many mammals including man. Layer I undergoes no apparent major changes in its basic fiber composition in the course of phylogenetic evolution (Sas and Sanides 1970; Marin-Padilla 1971, 1978; Kirsche 1974; Raedler and Raedler 1978). Similarly, this lamina is established early and undergoes no major changes in its basic organization in the course of cortical ontogenesis (Marin-Padilla 1971, 1972). No explanation has been proposed for the long structural stability of layer I of the mammalian cerebral cortex.

II. Developmental Aspects of Layer I

Although the early appearance and possible functional maturation of layer I in the course of cortical neurogenesis have been recognized for a long time (Koelliker 1896; Cajal 1911; Tello 1934, 1935; Godina 1951; Rabinowich 1964; Brun 1965; Åström 1967; Molliver et al. 1970, 1973; Marin-Padilla 1970) its actual origin has not been investigated until recently (Marin-Padilla 1971, 1972, 1978; König et al. 1975, 1977; Raedler et al. 1976, 1978, 1980; Rickmann et al. 1977; Shoukimas and Kinds 1978; Takashima et al. 1980). These studies have demonstrated that the original marginal zone of the developing cerebral vesicle is not lacking in cells as was formerly thought (His 1904; Boulder 1970; Derer 1974) but is composed of demonstrable corticipetal fibers and immature neurons with synaptic contacts between them. This superficial lamina has been renamed *the primordial plexiform layer* (Marin-Padilla 1971). The formation of this primordial plexiform layer precedes the appearance of the cortical plate and is transformed by its subsequent formation. The formation of the cortical plate takes place *within* the primordial plexiform layer dividing it into superficial and deep plexiform layers representing respectively the future layers I and VII (subplate or subcortical lamination) of the mammalian cerebral cortex (Marin-Padilla 1971, 1972, 1978; Raedler et al. 1976, 1978, 1980; König et al. 1975, 1977; Rickmann et al. 1977). These two fundamental early stages in the origin of layer I have been recently corroborated in the human cerebral cortex (Larroche 1981; Larroche et al. 1981).

These findings lead to the formulation of a new hypothesis which proposes a dual origin for the mammalian cerebral cortex (Marin-Padilla 1978). According to this hypothesis, the mammalian cerebral cortex would be constructed on the one hand, of two primitive plexiform layers (layers I and VII) reminiscent of premammalian cortical organization, and on the other hand, of an expanding cortical plate (a mammalian structure) located between them which gives rise progressively to layers VI, V, IV, III and II of the future cerebral cortex.

Another important developmental aspect of layer I is its early structural and possible functional relationships with layer VII (layer VIb, ental stratum of Sugita (1971) or subplate stratum). Structural relationships between layers I and VII first pointed out by Marin-Padilla (1971) have been subsequently demonstrated by many investigators (Marin-Padilla 1972, 1978; Moliver et al. 1973; Person 1973; Peters and Feldman 1973; König et al. 1975; Rickmann et al. 1977; Schlumpf et al. 1977, 1980; Raedler and Raedler 1978; Morrison et al. 1978; Larroche et al. 1981).

It has been suggested that the interrelationships between layers I and VII constitute the first functional system recognizable in the mammalian cerebral cortex during early embryonic life prior to the maturation of the cortical plate (Marin-Padilla 1971, 1972, 1978). Later, during the maturations of the cortical plate, some of the structural relationships between layers I and VII disappear. While layer I seems to retain its basic neuronal and fibrillar composition throughout the course of prenatal cortical ontogenesis, some neurons of layer VII progressively lose their connections with layer I (Marin-Padilla 1972). Further investigations about these transformations are needed in order to determine their possible significance.

III. Histologic Aspects of Layer I

Unquestionably, the major source of controversy surrounding layer I has derived from the many different and often contradictory opinions expressed about its neuronal and fibrillar composition. The mere existence of neurons in layer I has been much debated and the opinions expressed have ranged from the presence of specific neurons to no neurons at all, or to neurons that eventually will disappear or undergo degenerative changes.

Cajal (1890, 1891) described for the first time the presence of horizontal cells in layer I of the cerebral cortex of small mammals. The presence of these cells was confirmed by Retzius in the cerebral cortex of man and several other experimental mammals (Retzius 1891, 1893, 1894). Retzius (1893) acknowledged Cajal's discovery of these neurons and proposed that they should be called "Die Cajalszellen". Today, in spite of some controversy (Molliver and Van der Loos 1970) these cells are generally recognized as the Cajal-Retzius neurons. Some of the morphologic features of these neurons were described by Cajal (1896, 1897, 1900, 1911) who considered them to be specific to layer I. Cajal (1911) further suggested that the axons of these neurons may become the characteristic thick tangential fibers of layer I. This idea was corroborated by Retzius (1893) and later by Lorente de Nó (1949). Cajal described two developmental stages – the fetal and the adult – in these cells and never suggested that they will eventually disappear or undergo degenerative changes. The presence of Cajal-Retzius neurons has been subsequently demonstrated in the cerebral cortex of man and experimental animals by many investigators (Veratti 1897; Lorente de Nó 1922, 1949; Novack and Purpura 1961; Poliakow 1961; Marty 1962; Fox and Inman 1966; Sas and Sanides 1971; Baron and Gallego 1971; Shkol'nik-Yarros 1971; Gallego 1972; Sousa-Pinto et al. 1975; Baron 1976; Purpura 1975; Raedler and Sievers 1976; Rickman et al. 1977; König et al. 1977; Marin-Padilla 1970, 1971, 1972, 1974, 1978; Shoukimas and Hind 1978; Tömböl 1978; Wolf 1978; Takashima et al. 1980; Braak 1980; Larroche 1981; Larroche et al. 1981).

On the other hand, these neurons are either mentioned briefly or are not mentioned at all in many other studies, some of which even doubt their existence (His 1904; Godina 1951; Nañagas 1923; Rabinowicz 1964; Collonier 1968; Sholl 1956; Armstrong-Jones and Johnson 1970; Boulder 1970; Jones and Powell 1970a, b; Lund and Lund 1970; Adinolfi 1972). Other investigators have suggested that although these neurons might be common in the fetal cortex, they eventually disappear in the adult (Conel 1941, 1947, 1951; Purpura et al. 1960; Åström 1967; Duckett and Pearse 1968; Bradford et al. 1978). Apparently the only reason for suggesting the disappearance of these neurons, as far as one could gather from the literature, is the fact that they are difficult to find in the adult cerebral cortex. This phenomenon has been explained as the result of the considerable dilution of these primitive neurons during the progressive expansion of layer I as the cerebral cortex grows (Marin-Padilla 1972; Raedler and Siever 1976; Raedler and Raedler 1978; Rickmann et al. 1977). The number of Cajal-Retzius cells is established at the beginning of cortical neurogenesis and probably remains unchanged during the subsequent growth and expansion of the cerebral cortex. This fact could explain why these neurons seem to be more common in younger or small brains than in older or larger ones. It should be pointed out that although difficult to find, Cajal-Retzius neurons have been described in the adult cerebral cortex by some investigators (Fox and Inman 1966; Poliakov 1961 1974; Sas and Sanides 1970; Baron and Gallego 1971; Baron 1976; Rickmann et al. 1977). The possibility that these neurons may be present in some cortical regions but not in others has been suggested recently by Braak (1980), although no explanation for this particular behavior has been proposed.

There have been other opinions expressed about the nature of these neurons for which there seem to be no adequate or supportive data. The following opinions about the Cajal-Retzius neurons could belong in this category: That they could represent a special type of glia (Koelliker 1896); that they may be precursors of giant pyramidal neurons (Duckett and Pearse 1968); that they may lack axons (Gallego 1972; Baron and Gallego 1971; Baron 1976); that they undergo degenerative changes (Purpura et al. 1960, 1964; Åström 1967; Bradford et al. 1978); or that they may not be entirely related to the transmission of electric activity (Noback and Purpura 1961). Further information concerning the controversial origin and nature of Cajal-Retzius neurons, and of layer I as a whole, with a review of many of the early opinions can be found in the extensive work of Brun (1965). The need for a better understanding of the nature of Cajal-Retzius neurons, of their location within layer I, and of their possible persistence in the adult cerebral cortex seems to be obvious.

Layer I has, in addition to Cajal-Retzius neurons, a variety of smaller neurons throughout its territory. These small neurons were also first described by Cajal (1897, 1911) in the cerebral cortex of small mammals and young infants. Lorente de Nó (1922) confirmed their presence in the cerebral cortex of the mouse. Since these original descriptions very little has been added to our knowledge about the small neurons of layer I (Baron 1976). Only brief mention of their presence appears in some recent studies of the cerebral cortex (Meller et al. 1968a, b; Colonnier 1968; Lund and Lund 1970; Sousa-Pinto et al. 1975). The possibility that these small neurons may be inhibitory has been recently suggested (Hendry and Jones 1980).

The fibrillar (plexiform) composition is another prominent histologic feature of layer I. The abundance of fibers and the scarcity of recognizable neurons of this superficial lamina has always puzzled investigators (Jones and Powell 1970a; Szentágothai 1978). The origin of this plexus and how many different types of fibers enter in its composition are important questions for which we still do not have appropriate answers (Szentágothai 1970).

In some of his early works, Cajal (1900) described the presence of ascending fibers from the white matter that reach layer I and become horizontal within its territory. However, no special mention about these types of fibers is made in his later works (Cajal 1911). Lorente de Nó (1922, 1933) and Tello (1934, 1935) corroborated the presence of these ascending afferent fibers and more recently Marin-Padilla (1970, 1974) has described them in the motor cortex of premature and newborn infants.

Reference to similar types of ascending fibers can be found in the works of some Russian investigators (Poliakov 1971, 1974; Shkol'nik-Yarros 1971). Shkol'nik-Yarros (1971) pointed out that these ascending fibers become horizontal within layer I and could be followed for a long distance, Pinto-Lord and Caviness (1979) have also described a smilar type of ascending afferent fibers to layer I in both normal and abnormal (reeler) mice. A developmental relationship between these ascending afferent fibers to layer I and the development and maturation of Cajal-Retzius neurons has been suggested by Marin-Padilla (1970). He proposed the existence of a distinct pathway or system formed by these two elements within layer I.

Primitive afferent fibers, which arrive at the cerebral vesicle very early in development, have been described by Marin-Padilla (1971, 1972) and confirmed by several investigators (König et al. 1975; Rickmann et al. 1977; Raedler and Sievers 1976; Raedler and Raedler 1978). According to some investigators (Marin-Padilla 1971, 1972; Rickmann et al. 1977) these fibers do not disappear in the course of cortical ontogenesis, although they undergo a considerable dilution. The possibility that these primitive fibers could represent those described in older brains must be further investigated.

There is experimental evidence suggesting that these primitive afferent fibers might be monoaminergic in nature. Recent studies have demonstrated the existence of monoaminergic fibers in the early embryonic stages of mammalian cortical neurogenesis (Ungerstedt 1971; Olson et al. 1973; Nobin and Björklund 1973; Lapierre et al. 1973; O'Rahilly and Gardner 1977; Schlumpg et al. 1977, 1980; Morrison et al. 1978). Some of these monoaminergic fibers form distinct plexuses above (layer I) and below (layer VII) the developing cortical plate (Schlumpf et al. 1977, 1980; Morrison et al. 1978). This particular type of distribution of the monaminergic fibers is indistinguishable from that of the primitive corticipetal fibers described in Golgi and other silver preparations (Tello 1935; Marin-Padilla 1971, 1972, 1978; Pinto-Lord and Caviness 1979). The nature of the ascending afferent fibers to layer I, their origin and their possible persistence into the adult cortex must also be further investigated.

It should be clearly emphasized that, in addition to these primitive afferent fibers, layer I also receives terminals from other afferent systems in the course of cortical neurogenesis (Jones and Powell 1970a, b; Chow and Leirman 1970; Shkol'nik-Yarros 1971; Strick and Sterling 1974; Jones 1975; Rockland and Pandya 1979; Szentágothai 1970, 1971, 1978). These late-arriving terminals come from afferent systems whose main targets are lower cortical layers. Probably terminals from non-specific as well as specific thalamic fibers, from commissural or callosal fibers and from cortico-cortical fibers arrive progressively at layer I in the course of prenatal cortical neurogenesis. The main target of these afferent systems is not layer I, although some of their terminals could reach it. The number of these late arriving terminals increases progressively in the course of prenatal cortical neurogenesis. Some investigators believe that the plexus of fibers of layer I is primarily composed of terminals from those afferent systems (Jones and Powell 1970a, b; Szentágothai 1970, 1978; Eccles 1979). However, these late-arriving terminals must be clearly distinguished from the primitive afferent fibers to layer I described above. Further investigations about the nature of these two types of afferent fibers to layer I are obviously needed.

Another source of controversy concerning layer I has been the nature of the so-called 'tangential fibers'. The term is attributed to Retzius (Cajal 1891, 1911). Cajal (1911) pointed out that some of the so-called tangential fibers are thicker than others and that they acquire myelin sheathes very early in prenatal cortical ontogenesis. He also suggested that some of the thick myelinated tangential fibers of layer I are the axonic trunks of the horizontal (Cajal-Retzius neurons) neurons. Retzius (1891, 1893, 1894) and Lorente de Nó (1949) have also suggested that possibility. On the other hand, Marin-Padilla (1970, 1974) has recently pointed out that perhaps some of the so-called tangential fibers might derive from the ascending afferent fibers of layer I. These two different, apparently contradictory, opinions must be reconciled to avoid further confusion. Obviously part of the controversy has been caused by the term 'tangential' itself in view of the fact that all fibers within layer I are indeed tangential or horizontal. This term should be abandoned altogether or reserved to designate either the horizontal axons of Cajal-Retzius neurons or the horizontal branches of the ascending afferent fibers of layer I.

One final comment concerning the horizontal (tangential) fibers of layer I should be made. It seems that practically all fibers of layer I, as well as the plexus formed by them, are spatially oriented in a characteristic manner. Cajal (1911) first pointed out that the fibers in layer I are predominantly oriented in an anteroposterior direction throughout the cerebral cortex. This particular spatial orientation has also been pointed out by Marin-Padilla (1970) and Bradford et al. (1978). Recently it has been confirmed in a detailed experimental study by Fleischhauer and Laube (1977). These investigators have demonstrated that the majority of the 'tangential fibers' of layer I are predominantly oriented in an anteromedial to posterolateral direction. Also, Szentágothai (1965, 1978) utilizing degenerative studies, has demonstrated a similar orientation of the 'tangential fibers' of this lamination. The significance of this preferential anteroposterior orientation among the fibers of layer I is unknown and should also be further investigated.

The axonic terminals of Martinotti neurons (Martinotti 1890) represent an extrinsic fibrillar component of layer I. The ascending axons of these neurons terminate within layer I in a characteristic manner (Cajal 1911; Valverde 1971; Szentágothai 1970; Marin-Padilla 1970, 1972, 1974). Martinotti neurons are probably found in all cortical levels and in all cortical regions. The deep Martinotti neurons of layer VII (subcortical stratum) are among the first neurons to appear and to mature in cortical neurogenesis (Marin-Padilla 1971, 1972). Little is known about these neurons or about their specific axonic terminations in layer I. These neurons have received very little attention in the literature.

Finally, the most prominent extrinsic components of layer I are the apical dendritic bouquets of practically all pyramidal neurons of the cerebral cortex. Together they constitute an immense receptive surface. Why practically all pyramidal neurons of the cerebral cortex regardless of their cortical depth or region terminate in layer I has not been adequately explained either.

IV. Functional Aspects of Layer I

The functional role of layer I of the mammalian cerebral cortex remains poorly understood and enigmatic. Its functional importance is obvious since the apical dendrites of practically all pyramidal neurons, regardless of their cortical depth, terminate and branch profusely in it. The early myelination of some of its horizontal fibers also attests to its functional prominence. Axospinodendritic and axosomatic synapses have been described in layer I by several investigators, (Pappas and Purpura 1961; Meller et al. 1968a, b; Armstrong-Jones and Johnson 1970; Jones and Powell 1970b; Adinolfi 1972; Szentágothai 1971; Poliakov 1974; Sousa-Pinto et al. 1975). The presence of synaptic contacts early in cortical neurogenesis has also been demonstrated in layer I of embryos of man and experimental mammals (Molliver and Van der Loos 1970; Molliver et al. 1973; Marin-Padilla 1971, 1972, 1978; König et al. 1975; Raedler and Sievers 1976; Rickmann et al. 1977; Wolf 1978; Raedler and Raedler 1980; Larroche 1981; Larroche et al. 1981). A few electrophysiologic studies dealing indirectly with layer I have been carried out (Adrian 1936; Purpura et al. 1960, 1964, Persson 1973; Baron 1976). These studies have shown a predominant surface-negative potential. Molliver and Van der Loos 1970; Persson (1973) have shown developmental changes of the evoked surface potentials (from positive to negative) which could be related to the degree of maturation of the cortex. Further electrophysiologic studies of layer I are needed.

From this brief literature review of layer I of the mammalian cerebral cortex the following comments could be made. The nature and functional role of layer I remain unknown and enigmatic. Its primitive plexiform organization, rich in fibers and poor in neurons, remains inexplicable with the information presently available. Further studies are necessary to determine its essential intrinsic and extrinsic components and their structural organization. Its early embryonic origin should be established. Its progressive incorporation into the remaining cortical layers, or theirs into layer I, should be clarified and established. Further developmental neurophysiologic studies are also necessary to understand its functional maturation.

Material and Methods

The material utilized in this study has been collected throughout many years. Sections of the motor cortex of embryos, fetuses, premature infants, and newborns of various gestational ages (11, 15, 16, 18, 20, 22, 24, 26, 28, 29, 30, 32, 36, 38, and 40 weeks of gestation respectively) have been obtained at postmortem. The clinical cause of death in the majority of the youngest cases has been developmental immaturity incompatible with extrauterine life. The cause of death in the older group studied has included most frequently, cardiorespiratory failure, multiple congenital malformations, respiratory distress syndrome (hyaline membrane disease), congenital heart disease, renal agenesis, and necrotizing enterocolitis. Autopsy permission was obtained in all cases. The removal of the brain was carried out from 30 min to 2 $^1/_2$ h postmortem. Several blocks measuring 10 x 5 x 2.5 mm of the motor cortex, or its equivalent in younger brains, were dissected out from each brain. All blocks were cut perpendicular to the pial surface and perpendicular to the long axis of the precentral gyrus or equivalent region in younger brains. Each block represents therefore, a sagittal, roughly anteroposterior section of the motor cortex.

The blocks were immersed in an osmic-acid-potassium dichromate solution (1 g of osmium tetroxide; 12 g of potassium dichromate and 500 ml of distilled water) for a period ranging from a few hours (10–12) to a few days (2–3). Younger specimens were always fixed for shorter times than the older ones. After fixation, the blocks were transferred to a 0.75 silver nitrate solution for staining. The staining time ranged from 12 to 24 h. To avoid heavy silver precipitates at the pial surface of layer I, short staining time was preferred. The blocks were then serially cut freehand with a razor blade, cleared in oil of cloves, mounted consecutively on glass slides and covered with Damar resin. The large number of sections prepared and studied from this material (over 2,000 sections) compensates for the occasional incompleteness of the staining in some of them.

In addition, hematoxylin and eosin preparations of the developing cerebral cortex of a 7 week old human embryo were included in this study. The cerebral cortex of this embryo represents an example of the primordial plexiform layer stage of development of the human brain which precedes the appearance of the cortical plate. The cerebral cortex of the next human embryo of our series (11 week old embryo) has already a narrow newly formed cortical plate. The cerebral cortex of this embryo was stained according to the Golgi-Cox procedure because it was received already fixed in formalin.

Observations

The prenatal neurogenesis of layer I of the human cerebral cortex could be divided into three developmental periods, namely, embryonic, fetal and neonatal. The embryonic period extends from about the 7th to the 11th week of gestation; the fetal from the 11th to the 28th; and the neonatal from the 28th to the 40th. Although this division is not without some developmental and morphologic foundations, the timing used to separate each particular period may be somewhat arbitrary.

The embryonic period begins with the appearance in the developing telencephalic (cerebral) vesicle of the first recognizable cortical lamina, namely, the primordial plexiform layer (Marin-Padilla 1971, 1978) or marginal zone of the old classification (Boulder 1970). In man, this superficial lamina first becomes recognizable by the 7th week of gestation and persists until the appearance of the cortical plate around the 8th to 10th week of gestation (O'Rahilly et al. 1971, 1977; Hamilton et al. 1972; Larroche et al. 1981). The fetal period is characterized by the progressive inside-out growth and maturation of the cortical plate. During this time, the cortical plate grows from a narrow zone of few undifferentiated bipolar neurons to a stratified structure more than 1,000 μm thick. The neonatal period is characterized by the considerable neuronal and fibrillar maturation of the cortical plate. Measurements of the various cortical strata during the course of prenatal human cortical ontogenesis are reproduced in Table 1. The length of each specimen is also included in Table 1. All cortical measurements are taken from the motor region or its equivalent in younger specimens.

Table 1. Thickness of various strata of the human cerebral (motor) cortex in the course of prenatal ontogenesis

Age	Length	Layer I	Cortical plate (CP)	Development cortical plate	Layer VII
7 w.g.	22 mm C-R	PPL	No CP	–	–
11 w.g.	40 mm C-R	25–35 μm	100–120 μm	Undifferentiated CP	30–50 μm
15–16 w.g.	80–100 mm C-H	50–60 μm	300–500 μm	Layers VI, V, Undiff. CP	250–300 μm
18–20 w.g.	140–160 mm C-H	90–100 μm	700–800 μm	Layers VI, V, IV Undiff. CP	Undetermined*
24–26 w.g.	200–250 mm C-H	125–135 μm	900–1,100 μm	Layers VI, V, IV IIIC, Undiff. CP	Undetermined*
28–30 w.g.	280–320 mm C-H	150–170 μm	1,300–1,500 μm	Layers VI, V, IV, IIIC, IIIB, Undiff. CP	Undetermined*
38–40 w.g.	420–460 mm C-H	250–300 μm	1,800–2,100 μm	Layers VI, V, IV, IIIC, IIIB, IIIA IIB, Undiff. CP	Undetermined*

* As layer VII become progressively intermingled and incorporated into the growing internal white matter, its dimension and limits are no longer recognizable. Key: the age of the specimen is recorded in weeks of gestation (w.g.); PPL = Primordial Plexiform Layer; C-R and C-H = crown-rump and crown-heel respectively; mm = milimeters; μm = micrometers

The neonatal period of the development of layer I will be described first, followed by the descriptions of the fetal and embryonic periods. This approach has been selected because the various components of layer I are better defined in older than in younger specimens. Once the morphologic characteristics of the various components of layer I are established in the older specimens, it should be easier to recognize and analyze them in the fetal and embryonic periods. It should be pointed out that in a developmental study of this type some repetition may be unavoidable.

Neonatal Period

The cases studied at this developmental period include several prematurely born infants of various gestational ages (28, 29, 30, 32 and 36 weeks respectively) and six newborn infants ranging in ages from 38 to 40 weeks gestation. Only the older (38–40 weeks gestation) and the younger (28–30 weeks gestation) specimens of this developmental period will be described in detail.

38–40 Weeks of Gestation

The motor cortex at this age is almost fully developed except for a narrow superficial zone of the cortical plate which still is undifferentiated (Table 1). The cortical gray is 1,800–2,100 μm thick and has well developed pyramidal neurons in layers VI, V, lower and upper III, and lower II. Three horizontal

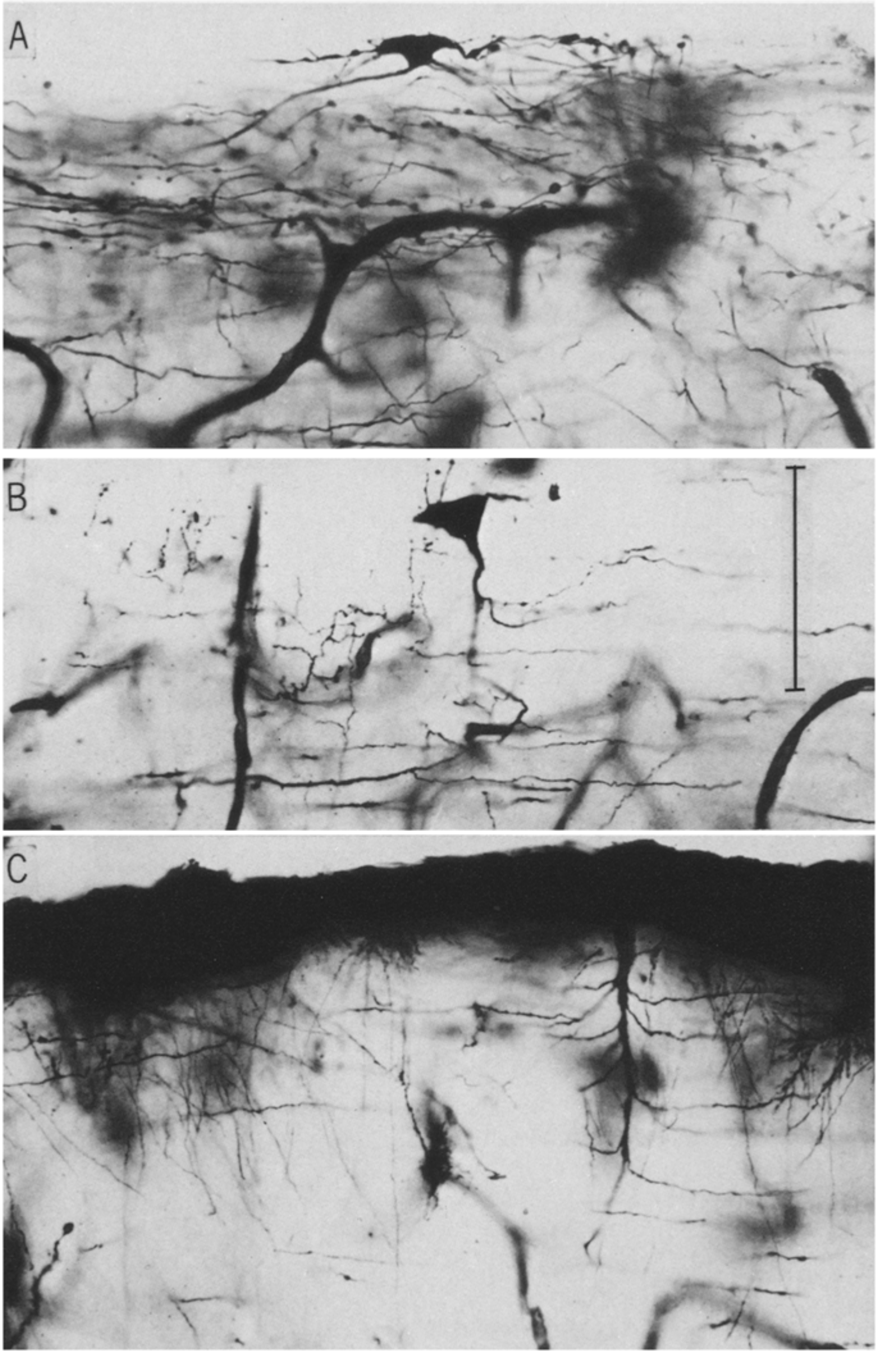

Fig. 1 A–C. Rapid Golgi preparations of the motor cortex of a two-month old infant (**A**) and two newborns (**B**, **C**) illustrating three different shapes found among the Cajal-Retzius neurons of layer I. The main horizontal dendrites of these neurons are not entirely visible either because they are out of focus (**A**), out of the preparation (**B**) or covered by silver precipitates (**C**). Their distinct descending axonic process is, however, clearly visible in all of them. Camera lucida drawings of the neurons illustrated in B and C are reproduced in Fig. 2A. Scale: 100 μm

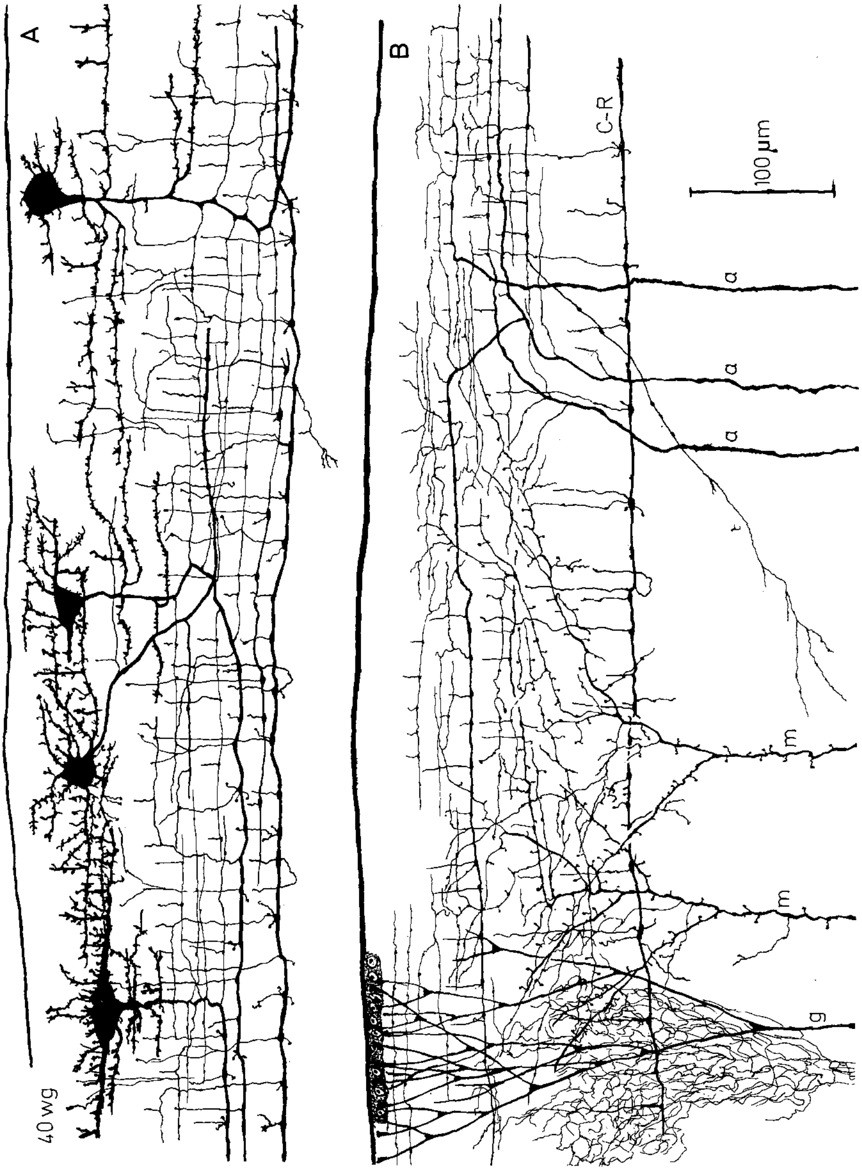

Fig. 2A, B. Composite figure of camera lucida drawings made from rapid Golgi preparations of the motor cortex of newborn infants illustrating the structural features and preferential distribution of both Cajal-Retzius neurons (**A**) and specific afferent (*a*) fibers (**B**) of layer I. Also illustrated are the structural features and distribution of the axonic terminals of Martinotti neurons (*M*), the terminations of the radiating glial fibers (*g*), and a complex axonic plexus formed by some small neurons of layer I (left **B**). The axons of Cajal-Retzius neurons form a prominent plexus of horizontal (tangential) fibers in the lower half of layer I while the specific afferent fibers form another in its upper half (Compare **A** and **B**). The horizontal fibers of both plexuses give off numerous ascending and few descending terminals throughout their entire length imparting to layer I its characteristic appearance. Scale: 100 µm systems of afferent fibers are recognized in the motor cortex at this age. They are roughly located at the level of layers VI–V; layer IV and lower III; and upper layer III, respectively. Fine terminals from these three systems of afferent fibers ascend and terminate in layer I.

At this age layer I is a prominent plexiform lamination 250–300 μm in thickness (Figs 1–5). The following components are recognized in this lamina: a) Cajal-Retzius neurons; b) small or short circuit neurons; c) specific afferents or primitive corticipetal fibers; d) axonic terminals of Martinotti neurons; e) terminals from extrinsic afferent systems; and f) apical dendritic bouquets of pyramidal neurons. The morphologic feature of each one of these elements will be analyzed separately.

Cajal-Retzius Neurons are large and distinct neurons which are unique to layer I. Although not very abundant at the time of birth, they are always present in some cortical regions such as the motor cortex. The analysis of these neurons has demonstrated that in spite of some morphologic differences they are, in essence, variations of the same basic type of neuron (Figs. 1–4). Although the shape of the body and its location within layer I varies from one cell to another, their single axonic process always behaves in a distinct manner which is common to all of them.

The most common variety of Cajal-Retzius neuron encountered in the human motor cortex is the so-called pyriform, triangular, or monopolar type of Cajal and Retzius (Figs. 1B, 2A, 3A). The body of these neurons is large and often triangular or pyriform. It is invariably located beneath the pial surface. This superficial location makes the recognition of this type of neuron very difficult and often impossible in Golgi preparations (Figs. 1C, 2A; 3A). The heavy silver deposits which cover the pial surface and often penetrate into the upper region of layer I, obliterate the body and main dendrites of this type of neuron but not its characteristic descending axonic process (Figs. 1C, 2A, 3A). To study these neurons with the Golgi method, and hence the structure of layer I, it is absolutely necessary to reduce the silver impregnation time to only a few hours in order to avoid heavy silver deposits.

The second most common variety of Cajal-Retzius neuron is the so-called horizontal or bipolar type of Cajal and Retzius. The body of this neuron is located in the upper half of layer I, but some distance away from the pial surface (Figs. 2A, 3B, C; 4A, B). The body of this neuron is elongated with two prominent horizontal dendritic trunks extending from its opposite poles Figs. 2A, 3C, 4B). The lower location of this type of neuron in layer I confined within the plexus of horizontal fibers could explain its prominent horizontal morphology.

A less common variety of Cajal-Retzius neuron is the so-called irregular or stellate type of Cajal (Figs. 3D, 4C). Its body is usually located deeper within layer I and further away from the pial surface than the other two varieties. The body of this neuron is usually stellate with various processes extending from it (Figs. 3D, 4C). Nonetheless, the stellate branches of this type of neuron also become horizontally oriented.

All Cajal-Retzius neurons studied regardless of the shape or location of their body have two types of processes including: several main horizontal den-

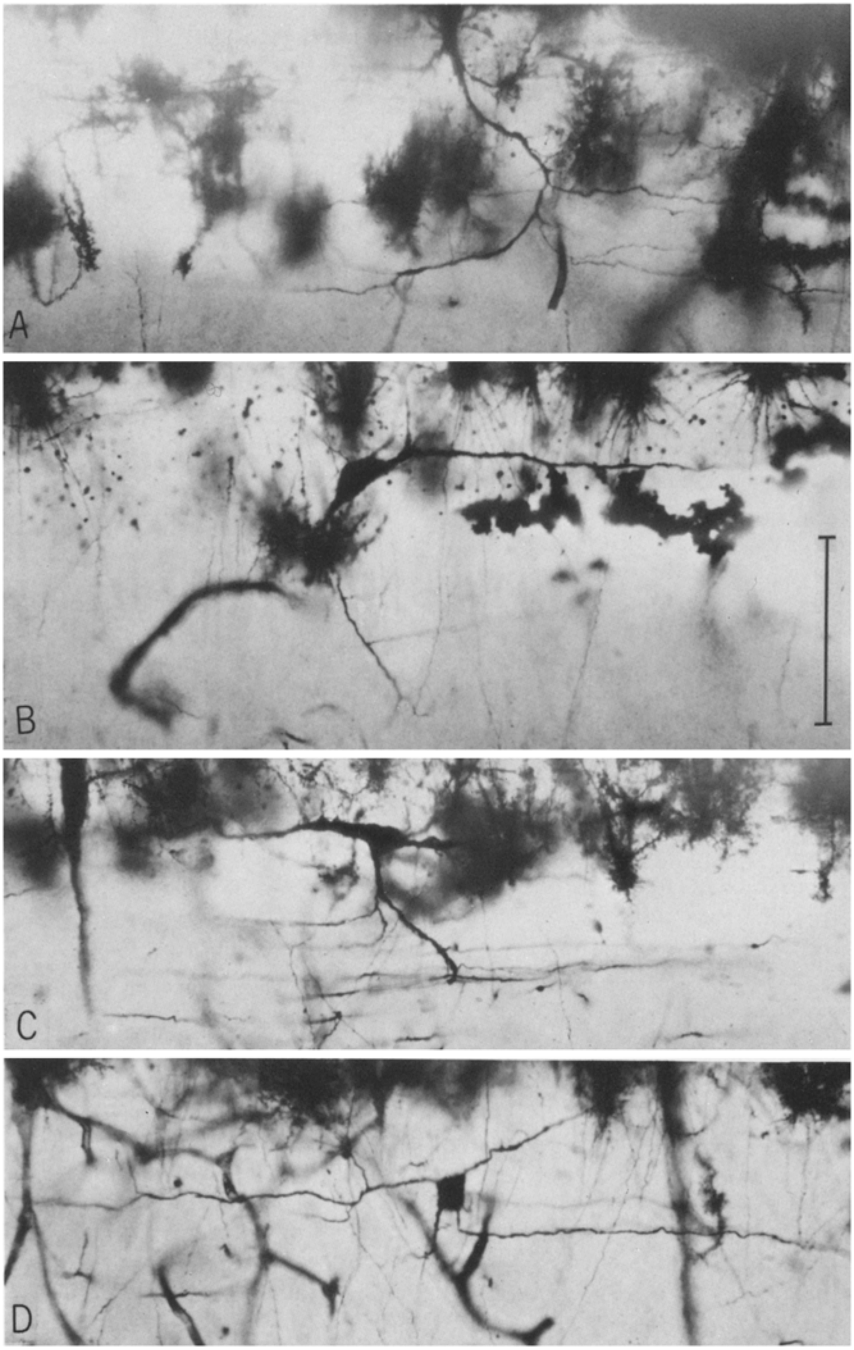

Fig. 3A–D. Rapid Golgi preparations of the motor cortex of the premature infant, 38 week gestation, illustrating four different forms assumed by Cajal-Retzius neurons of layer I in the same case. They inlcude: monopolar (**A**), horizontal (**B, C**), and stellate (**D**) shapes. The superficial (**A**), intermediate (**B, C**) or lower (**D**) position of these neurons within layer I could be related to their particular shape. Regardless of the shape assumed by these neurons all are characterized by a single descending axonic process which become a horizontal fiber in the lower half of layer I. Camera lucida drawings of the neurons illustrated in B, C and D are reproduced in Fig. 4A, B, and C respectively. Scale: 100 μm drites extending from the body, and a single, distinct descending process (Figs. 1–4). The main dendrites which originate from the neuronal body are predominantly horizontal and parallel to the pial surface. The majority of these horizontal dendrites are oriented in an anteroposterior direction, perpendicular to the long axis of the precentral gyrus, and therefore clearly visible in our preparations. Some dendrites have more transverse orientation as pointed out by Cajal (1909) with the Ehrlich's method. The main horizontal dendrites are irregular, very long and have many ascending and few descending dendritic collaterals. A few irregular and long spines can be recognized on these horizontal dendrites and their collaterals (Figs. 1–4).

The descending process of the Cajal-Retzius neuron is undoubtedly its most distinctive feature. It usually originates from the neuronal body although it could originate from one of the main horizontal dendrites. The descending process is thick and prominent (Figs. 1–4). It gives off first, several thin, long, horizontal dendritic branches and lower down, it also gives off several thin, long horizontal axonic collaterals (Figs. 1 B, C, 2 A, 3 A, C, 4). Then the descending process penetrates into the lower half of layer I where it becomes transformed into a thick, long horizontal (tangential) axonic fiber. All Cajal-Retzius neurons of the human motor cortex analyzed share these characteristics.

The descending axons of Cajal-Retzius neurons form a prominent plexus of thick horizontal (tangential) fibers in the lower half of layer I (Figs. 2, 4). This plexus of horizontal fibers extends throughout the entire surface of the cerebral cortex even through cortical regions in which the original neuronal type might be absent. Cajal-Retzius neurons are primitive cells which undergo a progressive horizontal lengthening (horizontalization) of their process as the cerebral cortex expands. The bodies of Cajal-Retzius neurons are located only at specific or strategic, probably old, regions of the cerebral cortex, such as the primary motor cortex, but their axons extend throughout the entire surface of the cerebral cortex. The horizontal axons of Cajal-Retzius neurons, as well as the entire plexus formed by them, are oriented predominantly in an anteroposterior direction through the cerebral cortex. On the basis of our observations, it can be stated that the majority of the so-called tangential (horizontal) fibers of the lower region of layer I are the axons of Cajal-Retzius neurons (Figs. 2, 4).

Both the thin horizontal axonic collaterals and the thick axonic trunks of Cajal-Retzius neurons give off numerous long and short ascending and very few descending collaterals throughout their entire length (Figs. 1–5). These numerous ascending and descending axonic branches are found everywhere within layer I and constitute one of its most distinctive structural features.

The long and short ascending axonic collaterals often terminate in a small dilatation which could represent growth terminal cones. Some of the long ascending collaterals terminate under the pial surface but without making direct contacts with it. Others bifurcate or become slightly oblique. Some of these ascending collaterals become themselves after a short ascending course, long horizontal fibers which could be followed for long distances. These secondary horizontal axonic collaterals are always distributed in the upper half of layer I and they also give off numerous short and long ascending and descending terminal

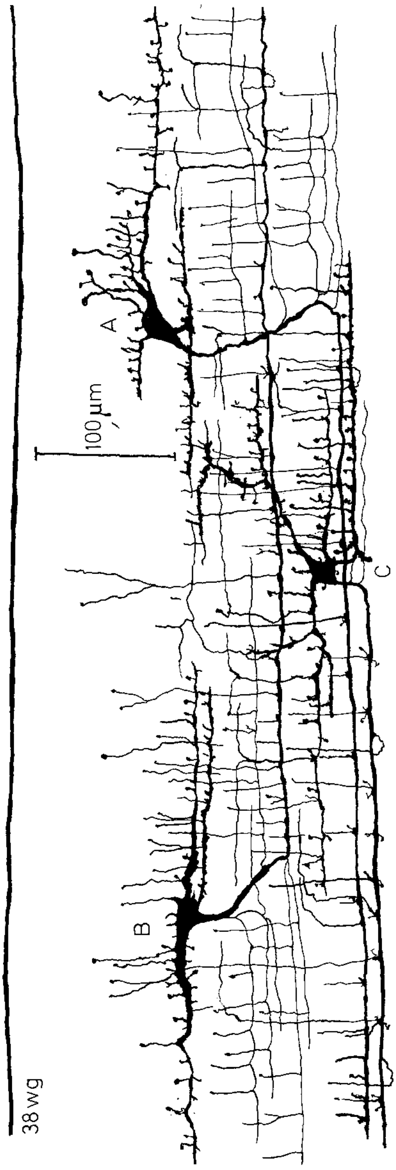

Fig. 4A–C. Composite figure of camera lucida drawings made from rapid Golgi preparations of the motor cortex of the premature infant, 38 week gestation, illustrating the complete structure and location of roughly triangular (**A**), horizontal (**B**) and stellate (**C**) Cajal-Retzius neurons of layer I of the same case. Scale: 100 µm

branches (Figs. 1, 2A, 3, 4). All of these ascending and descending collaterals are believed to be the terminal axonic rami of Cajal-Retzius neurons and to participate directly in the establishment of the terminal neuropile of layer I. In Golgi preparations they are seen making direct contacts with the spines of the apical dendrites of pyramidal neurons (Fig. 5A). A single Cajal-Retzius neuron with its long horizontal axon and through its numerous ascending and descending terminals is able to make contacts with the apical dendrites of many near and distant pyramidal neurons. It seems that all pyramidal cells contacted by a single Cajal-Retzius neuron are located within a distinct sagittal or anteroposterior plane within the cerebral cortex.

Small Neurons of layer I are recognized throughout the human motor cortex by the time of birth (Fig. 5B). The body of these neurons is small and their dendritic arborizations are poor and short. The dendrites have few collaterals and some have dendritic spines. There are no significant distinguishing features among the small neurons of layer I as far as their body or dendritic arborizations are concerned. However, obvious differences can be recognized in their axonic arborizations. At least three different axonic arborizations can be recognized among these small neurons. The most characteristic consists of a rather complex axonic nest with innumerable collaterals (Figs. 2B, 5B, a). This complex axonic plexus, already described by Cajal, originates in small neurons which are located near or at the border between layers I and II. This plexus has a roughly triangular shape and often extends into the upper region of layer II (Fig. 2B). A second pattern of axonic distribution of small neurons of layer I consists of a very poor plexus with few collaterals (Fig. 5B, b). It is associated with small neurons found at the levels of layer I. This poor axonic plexus contrasts sharply with the rich one described above. Finally, there are small neurons in layer I in which it is difficult to distinguish between their axonic and dendritic branches (Fig. 5B, c). This type of small neuron might correspond to the so-called neurogliform type described by Cajal. None of these small neurons, however, can be confused with the very abundant glial elements of layer I (Fig. 5B).

Specific Afferent Fibers of layer I have been previously described in the motor cortex of newborn infants (Marin-Padilla 1970). They are frequently found by the time of birth. They are a distinct type of fiber which arrives from the white matter, ascends more or less vertically and penetrates into layer I, branching at its upper half in a characteristic manner (Fig. 2B).

The ascending portion of these fibers is thick and free of collaterals except for a few branches which it gives off to layer VII (subcortical or subplate region). These fibers penetrate into layer I, cross the plexus of horizontal (tangential) fibers in its lower half and branch into several long horizontal collaterals within its upper half (Fig. 2B). One of these horizontal collaterals is usually thicker than the others, representing the main trunk of the afferent fiber. These afferent fibers together with their many horizontal collaterals also form a distinct plexus within layer I above that formed by the axons of Cajal-Retzius neurons (Fig. 2, compare A and B). The upper plexus of layer I is composed of thinner, more abundant and more compact fibers than its lower plexus, which is composed of fewer and thicker elements. Some specific afferent fibers as they arrive in layer I become horizontal at its lower half, accompanying the axons of Cajal-Retzius neurons for some distance. These apparently misplaced specific afferent fibers are considered to be 'in transit' through the lower part of layer I since they eventually reach and branch in its upper half. Similarly, some axons of Cajal-Retzius neurons pass through the upper half of layer I for some distance before they finally reach its lower region.

The main trunk of the specific afferent fibers as well as all its horizontal collaterals also give off short and long ascending and fewer descending terminals through their entire length. These ascending collaterals are structurally not unlike those derived from the axons of Cajal-Retzius neurons. The numerous short and long ascending branches of these two systems impart to layer I a characteristic appearance which is recognizable throughout the entire cerebral cortex (Fig. 2A, B). The ascending and descending branches of the specific afferent fibers are also considered to be terminal branches and therefore basic functional elements of the neuropile of layer I. They are believed to establish synaptic contacts with the dendrites of Cajal-Retzius neurons and possibly also with the apical dendrites of some pyramidal neurons.

Axonic Terminals of Martinotti Neurons are easily recognized by their distinctive arborizations within layer I (Fig. 2B). Martinotti neurons are probably found at all levels of the cerebral cortex from the deepest to the most superficial. They range in size from small to large depending on their cortical level. They have ascending and descending dendrites with few short transverse ones. There dendrites are beaded with few scattered long dendritic spines. The ascending axon gives off short spine-like processes throughout its entire length. These short axonic processes, although not very abundant, are quite characteristic of these neurons (Fig. 2B). The terminal portion of the ascending axon as it approaches layer I fans out into several oblique collaterals (Fig. 2B). These terminal arborizations have also short spine-like processes (Fig. 2B).

The "fanlike" branching of the terminal axonic tree of Martinotti neurons is quite characteristic. They mimic quite closely the branching of the apical dendrites of pyramidal neurons. The morphologic resemblance suggests structural as well as possible functional interrelationships between the axonic terminals of Martinotti neurons and the apical dendrites of the pyramidal neurons. A single Martinotti neuron can only make contact with a small group of pyramidal cells in its own cortical region because its axonic terminals do not extend horizontally for a long distance within layer I. The horizontal spread of these axonic terminals within layer I is also comparable to that of the apical dendrites (Compare Figs. 2B, 5A). Martinotti neurons are considered to be important extrinsic components of layer I and their peculiar axonic terminations are suggestive of a limited inhibitory role upon the apical dendrites of pyramidal neuron.

Terminal Fibers from the Extrinsic Afferent System arrive progressively in layer I during the course of cortical neurogenesis. At birth, fine fibrils are seen approaching more or less obliquely and penetrating into layer I (Fig. 5A). They branch poorly in it and their termination appears to be non-specific (Fig. 5A). In good Golgi preparations the origin of some of these terminals can be traced back to thicker horizontal fibers of deeper cortical strata. We have been able to trace some of them back to superficial (Layers III–II), intermediate (Lower Layer III) and deep (Layers VI–V) horizontal afferent systems. Obviously, the main target of these afferent systems must be the neuronal elements of deeper cortical strata rather than layer I, although some of their terminals could reach it. These fibers seem to have a limited spread in layer I and do not become long horizontal fibers within it. These terminals are considered to be extrinsic elements of layer I and nonessential components of its basic structural organiza-

Fig. 5A–B. Composite figure of camera lucida drawings made from rapid Golgi preparations of the motor cortex of newborn infants, 40 week gestation, illustrating the structure and distribution of the apical dendritic bouquets of the pyramidal neurons (**A**) and a variety of small neurons (**a, b, c**) and glial cells (*g*) of layer I (**B**). Notice the distinct structural and functional (axo-spinodendritic synapses) relationships between the ascending and descending terminal branches from the axons of Cajal-Retzius neurons, the specific afferent fibers, and the apical dendrites of pyramidal neurons (**A**). Complex (*a*) and poor (*b*) axonic plexuses formed by the small neurons of layer I as well as neurogliform (*c*) neurons, clearly distinguishible from the glial cells, are also illustrated (**B**). Scale: 100 µm

tion. Some of them arrive very late in cortical development when the basic structural organization of layer I is already well established. Therefore, their arrival could not modify the basic organization of layer I. The arrival of these fibers in layer I depends on the time of arrival of the main afferent systems from which they derive. The time of arrival of these extrinsic afferent systems varies significantly. Those reaching the deeper cortical layers occurs much earlier in development than those reaching the most superficial strata.

Apical Dendritic Bouquets or practically all pyramidal neurons of the cerebral cortex, regardless of their cortical depth, are found in layer I (Fig. 5A). This is true for the pyramidal neurons of all regions of the cerebral cortex. The apical dendrites fan out into several terminal branches forming characteristic bouquets within layer I (Fig. 5A). They are covered by numerous short spines with distinct terminal heads.

In rapid Golgi preparations axo-spinodendritic synaptic contacts are often recognized in the apical dendrites of pyramidal neurons. These contacts are established between the numerous ascending and descending terminal axons of layer I and the spines of the apical dendrites (Fig. 5A). Multiple contacts are often seen between a single ascending axon and several spines of the same dendrite (Fig. 5A). The ascending axons making these synaptic contacts originate from the horizontal fibers of layer I which extend through the entire cerebral cortex. The major source of these axo-spinodendritic synapses of the apical dendrites of pyramidal neurons are the terminal axons of Cajal-Retzius neurons. In addition, some of these synaptic contacts might also be formed by the terminals of the specific afferent fibers and late in development by the terminals of other afferent systems. The apical dendritic bouquets of the pyramidal neurons represent the most important extrinsic component of layer I. They constitute an enormous receptive surface which represents undoubtedly the principal, if not the only, functional outlet of layer I.

28–30 Weeks of Gestation

At this developmental age the motor cortex is characterized by the marked development of pyramidal neurons of layers V and lower III and by two prominent horizontal plexuses of afferent fibers located roughly above and below the level of the giant pyramidal neuron of layer V. The cortical plate measures between 1,300 and 1,500 µm in thickness and has a superficial zone, 10–15 cells thick, of undifferentiated bipolar neurons. The cortical plate still is actively growing by the addition of new migrating neurons at its surface. Layer I is 150–170 µm thick, and is well developed and all its basic components are recognizable.

Cajal-Retzius Neurons are large cells and are particularly prominent at this age (Figs.6, 7A, B). Their bodies can assume a variety of morphologic appearances including: horizontal (Figs. 6A, D, 7B), monopolar (Fig. 6B), triangular (Fig. 6C) or stellate (Fig. 7A). Their main horizontal dendrites are also particularly prominent at this age. They are thick and irregular and have numerous ascending dendritic collaterals (Figs. 6, 7). These collaterals appear to be more numerous at this age because they are closer to one another than they are in the older specimens described above.

Because of their numerous ascending dendritic collaterals, the Cajal-Retzius neurons resemble the so-called 'fetal type' described by Cajal (Figs. 6, 7). The separation or distance between these ascending dendritic collaterals increases with age as the neurons undergo a progressive horizontal lengthening of their processes with the expansion of the cerebral cortex. Therefore, in younger speci-

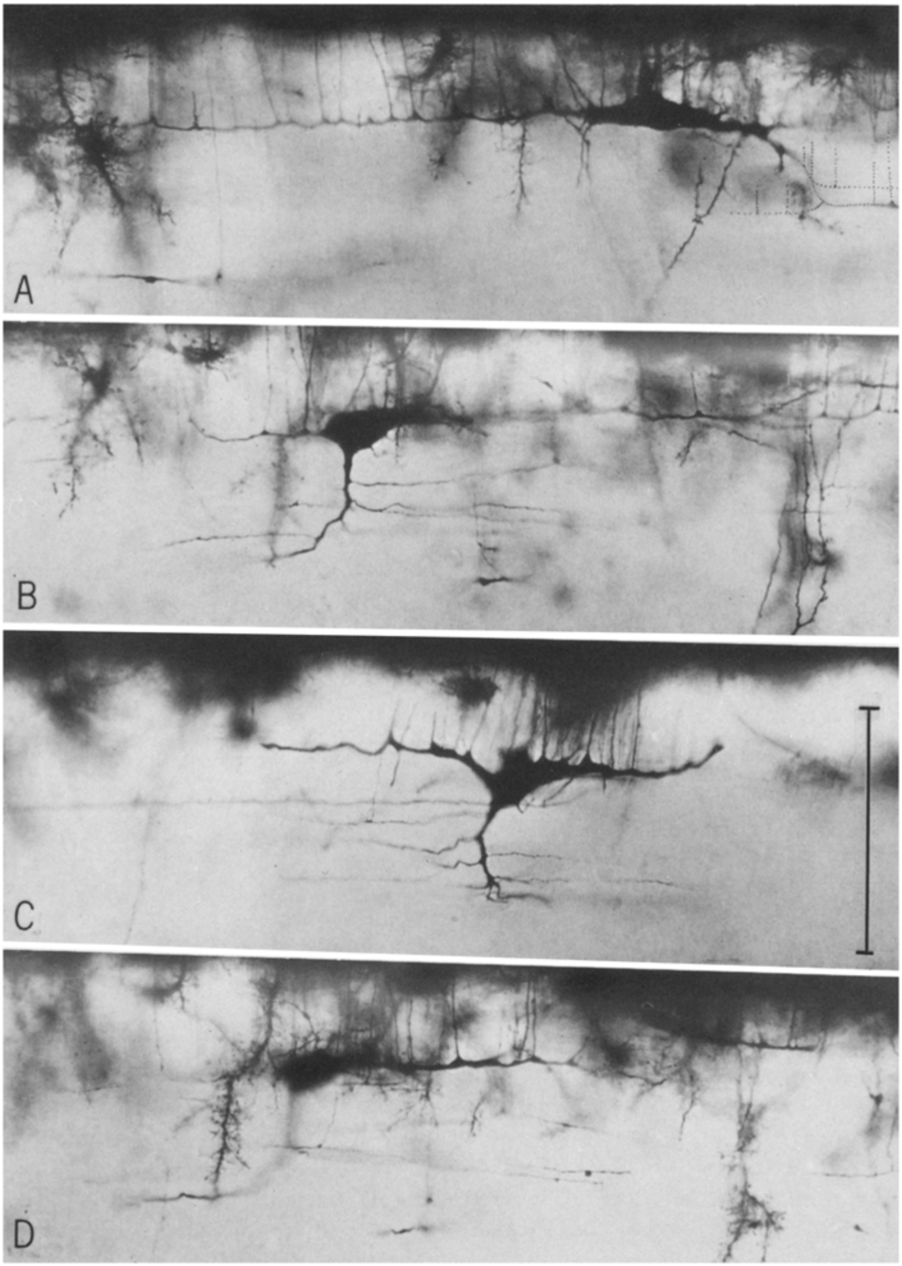

Fig. 6A–D. Rapid Golgi preparations of the motor cortex of a premature infant, 30 week gestation, illustrating the structure of four differently shaped Cajal-Retzius neurons of layer I including: horizontal (**A, D**), monopolar (**B**) and triangular (**C**) shapes. The numerous ascending dendritic branches which characterize these neurons are clearly visible in all of them as well as their distinctive single descending axonic process. Scale: 100 μm

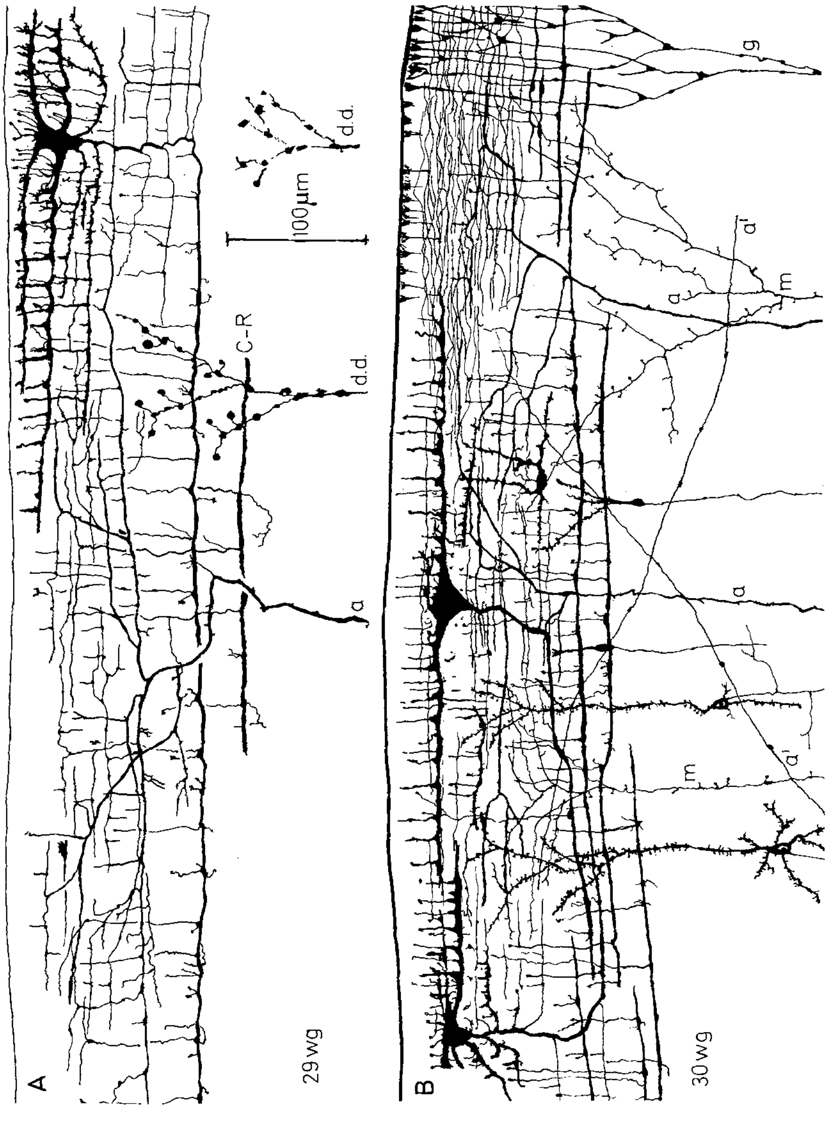

Fig. 7A, B. Composite figure of camera lucida drawings made from rapid Golgi preparations of the motor cortex of premature infants, 29 (**A**) and 30 (30) week gestation respectively, illustrating the basic structural organization of layer I and the structure and distribution of its essential component. The structural relationships and their preferential distribution within layer I between a single stellate Cajal-Retzius neuron and a single specific afferent fiber are clearly illustrated (**A**). Also illustrated are degenerating dendrites (*d. d.*), the axonic terminals of Martinotti neurons (*M*), specific afferent fibers (*a*), terminals of extrinsic afferent systems (*a'*) from deeper cortical strata, and the terminations of glial fibers (*g*). The basic structural organization of layer I is already well established at this developmental age (**B**). Scale: 100 µm mens the separation is smaller than in older specimens. This peculiar developmental phenomenon is also applicable to the distance between the ascending and descending branches of the horizontal axonic fibers of Cajal-Retzius neurons.

The single descending axonic process of all Cajal-Retzius neurons, regardless of their morphologic appearance, behaves in the same manner. (Figs. 6, 7). They give off, first, thin horizontal dendritic and axonic collaterals and then they descend to the lower half of layer I where they become transformed into a long horizontal axon. The terminal axons of Cajal-Retzius neurons could be followed for long distances with in layer I. They all form a prominent plexus of horizontal (tangential) fibers in the lower half of layer I. Both the horizontal axonic trunks and the thin horizontal axonic collaterals give off numerous short and long ascending terminal branches throughout their entire length (Fig. 8F).

Small Neurons (Fig. 7B) are found at all levels of layer I at this age. Their dendritic and axonic arborizations are poorly developed probably because they are still growing. There are no distinguishing features among these small neurons to warrant their subclassification. The rich axonic plexus formed by some of them, observed at the time of birth, are not found at this deverlopmental age (Fig. 5B).

Specific Afferent Fibers of layer I are also particularly prominent and easily recognizable at this developmental age (Figs. 7A, B, 8A–D). They seem to be more numerous than they are at the time of birth perhaps because the distance between them is smaller at this age (Fig. 8). These ascending fibers arrive in layer I more or less vertically, cross the lower plexus of the horizontal axons of Cajal-Retzius neurons, and branch into several long horizontal collaterals in its upper half (Figs. 7A, B, 8A–D), where they can be followed for long distances, giving off numerous short and long ascending branches throughout their entire length (Figs. 7, 8).

Terminal Axons of Martinotti Neurons are also found at this developmental age and are easily recognized by their short spine-like processes (Figs. 7B, 8E). They approach vertically layer I and branch (fan-out) into several terminal collaterals. These terminal collaterals also have spine-like processes. Their branching and territory of distribution within layer I mimics that of the apical dendrites of pyramidal neurons with which they probably establish synaptic contacts.

Terminal Axons from Extrinsic Afferent Systems are seen arriving in layer I at this age (Fig. 7B). Some of them can be traced back to horizontal afferent systems distributed at lower cortical levels. Structurally they are quite different from either the specific afferent fibers or the axonic terminals of Martinotti neurons. Their distribution within layer I is limited and non-specific.

Apical Dendrite Bouquets from all developing pyramidal neurons of the motor cortex are found in layer I (Fig. 7B). Some degenerating apical dendrites are

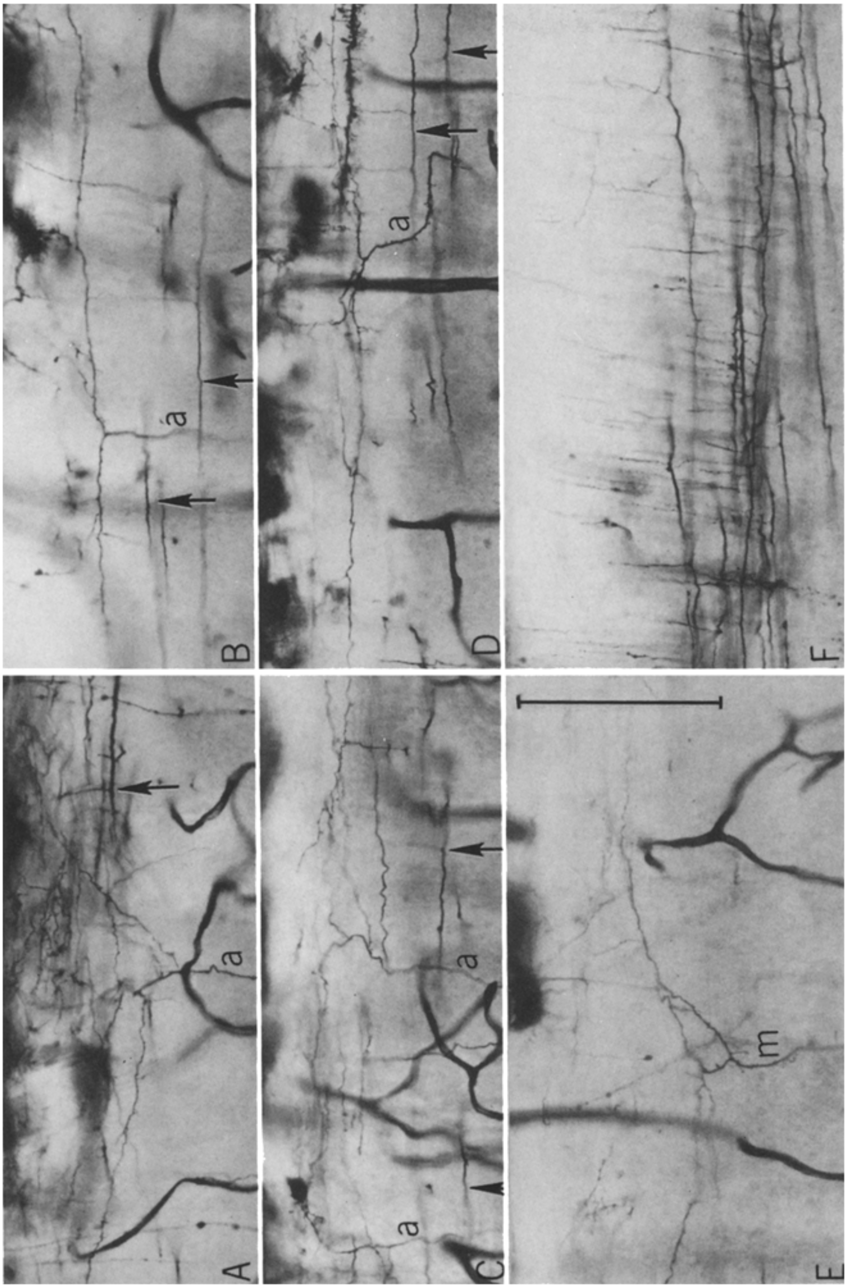

Fig. 8A–D. Composite figure of rapid Golgi preparations of the motor cortex of a premature infant, 29 week gestation, illustrating several specific afferent fibers (*a*) arriving and branching into long horizontal collaterals in the upper half of layer I (**A, B, C, D**); the typical axonic termination of a Martinotti neuron (**E**); and the prominent plexus of horizontal (tangential) fibers with numerous ascending terminals (*F*) formed by the axons of Cajal-Retzius neurons (lower half of layer I). All *arrows* (**A, B, C, D**) indicate horizontal axonic fibers of Cajal-Retzius neurons crossing clearly below the branching of the specific afferent fibers (*a*) within layer I. A camera lucida drawing of the specific afferent fiber illustrated in (**D**) is reproduced in Fig. 7A. Scale: 100 μm

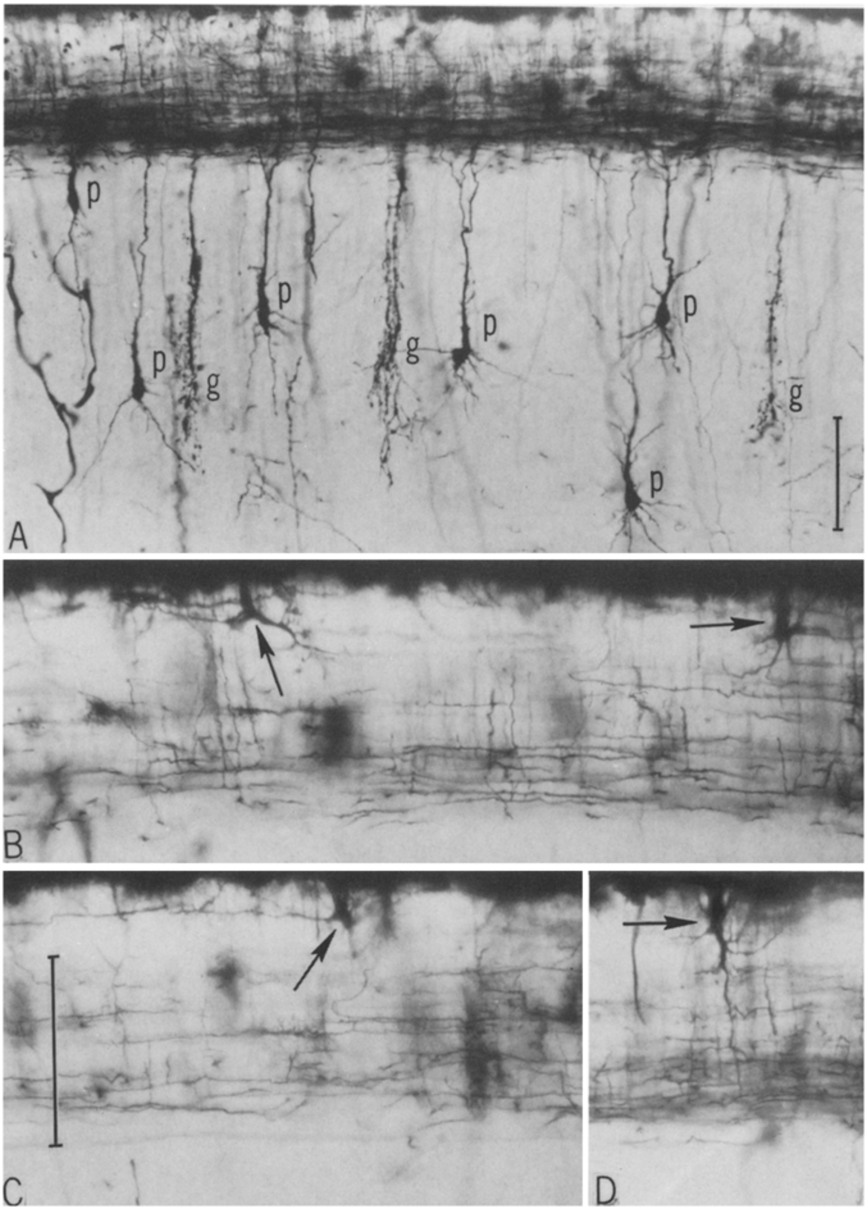

Fig. 9A–D. Composite figure of rapid Golgi preparations of the motor cortex of a premature infant, 26 week gestation, illustrating a general view of the upper half of the motor cortex and several closer views of layer I showing four differently shaped Cajal-Retzius neurons including: horizontal (**B** left, **C**), stellate (**B** right), and monopolar (**D**). Also clearly illustrated in all figures is the prominent plexus of horizontal (tangential) fibers formed by the axons of Cajal-Retzius neurons in the lower half of layer I. Notice that all pyramidal neurons (*p*) including the smaller and immature ones of the upper cortical plate have already contacted layer I by their developing apical dendrites (**A**). Few glial cells (*g*) are also illustrated (**A**). Scale: 100 μm

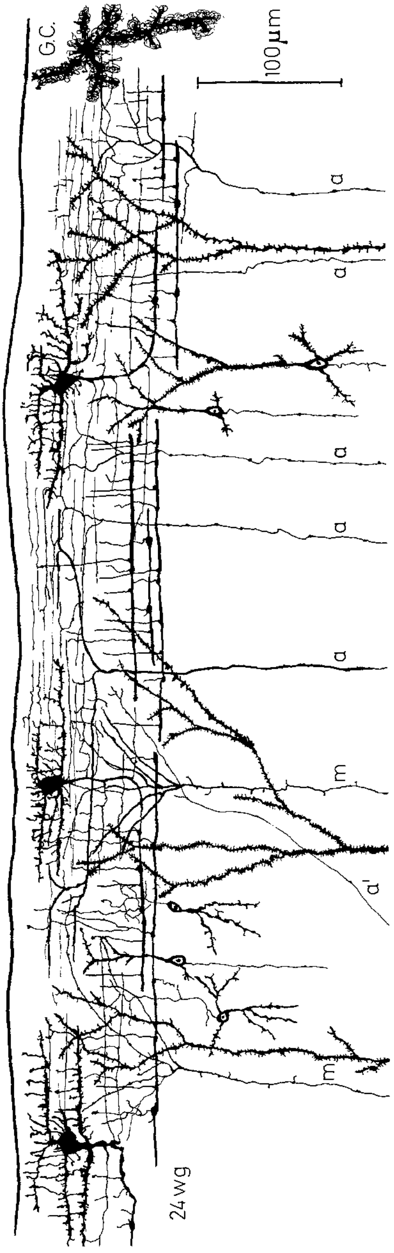

Fig. 10. Composite figure of camera lucida drawings made from rapid Golgi preparations of the motor cortex of a premature infant, 24 week gestation, illustrating the overall organization of layer I and the structure and relationships among its essential components including: Cajal-Retzius neurons, specific afferent fibers (*a*), axonic terminals of Martinotti neurons (*M*), terminals of extrinsic afferent systems (*a'*) from lower cortical strata and glial cells (*g.c*) Scale: 100 µm

also occasionally found at this age (Fig. 7A). These degenerating dendrites appear fragmented, beaded, and without recognizable dendritic spines. They belong to deep pyramidal neurons of layers VI and VII. Some of the deep pyramidal neurons seem to be losing their original contacts with layer I at this age. The progressive disappearance of original contacts with layer I among pyramid-like neurons of layer VII (VIb) has been previously described in the prenatal development of the cerebral cortex of the cat (Marin-Padilla 1972).

Fetal Period

From this developmental period, the structural organization of layer I of the older (24–26 weeks gestation), the intermediate (18–20 weeks gestation), and the younger (15–16 weeks gestation) specimens will be analyzed in detail.

24–26 Weeks Gestation

The primary motor cortex at this age is actively growing. The cortical plate measures 900–1,100 μm in thickness and is still growing. It is characterized by a large superficial zone (15–20 cells thick) of undifferentiated bipolar neurons. On the other hand, layer I appears well developed with all its essential components present and its basic structural organization already well established (Figs. 9, 10). At this age layer I measures 125–135 μm in thickness.

Cajal-Retzius Neurons appear to be abundant at this developmental age (Figs. 9B, D, 10). These neurons may have a horizontal (Fig. 9B, C) stellate (Fig. 9B), or monopolar (Fig. 9D) appearance. Their main dendrites are shorter than in older specimens and have numerous fine ascending collaterals, which are very close to each other, giving the whole neuron a rather compact appearance.

Regardless of their morphologic appearance, the descending axonic processes in all Cajal-Retzius neurons studied penetrate the lower half of layer I and become thick and long horizontal axonic fibers, which form a prominent plexus (Figs. 9, 10). These horizontal axons give off inumerable fine short and long ascending branches throughout their entire length. Specific afferent fibers of layer I are also seen at this time (Fig. 10). They ascend from the white matter and branch into long horizontal collaterals in the upper half of layer I giving off numerous short and long ascending terminal branches throughout their entire length (Figs. 9, 10). Axonic arborizations of Martinotti neurons (Fig. 10) terminate in layer I in their characteristic manner. A few small neurons are also found occasionally at this age. Terminals from extrinsic afferent systems are rarely found at this age. They approach layer I obliquely and terminate in it without any specific pattern of distribution. Apical dendritic bouquets from all pyramidal neurons, even from the smaller ones, are also found in layer I (Fig. 10).

18–20 Weeks of Gestation

At this age the cerebral (motor) cortex has a primitive appearance with prominent pyramidal neurons in only lavers V and VII (Fig. 11). The cortical plate measures 700–800 μm in thickness and is still growing. Almost its entire upper half is still undifferentiated. It should be noticed that even the small, immature and bipolar neurons of its upper half have already established contacts with

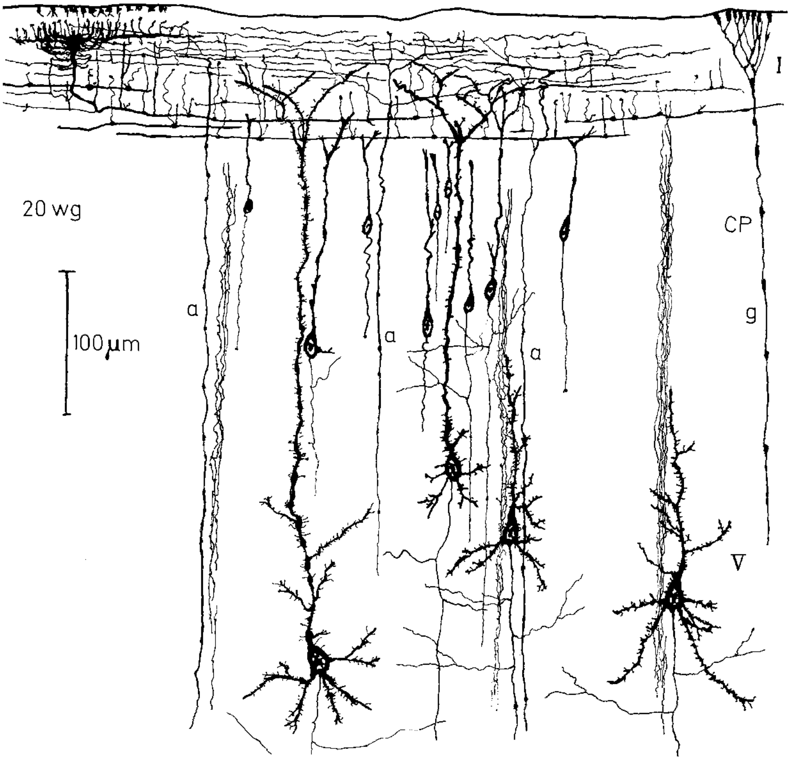

Fig. 11. Composite figure of camera lucida drawings made from rapid Golgi preparations of the motor cortex of a premature infant, 20 week gestation, illustrating the overall basic organization of layer I and the structure and relationships among its essential components at this developmental age. Specifically illustrated are the Cajal-Retzius neurons, the specific afferent fibers (*a*), the developing pyramidal neurons of the cortical plate already connected to layer I by the apical dendrites, the termination of glial fibers (*g*), and the maturing pyramidal neurons of layer V. Scale: 100 µm

layer I (Fig. 11). Layer I measures 90–100 µm in thickness and has all its essential components except for small neurons which have not yet appeared (Fig. 11).

The only pertinent observation to be made of this developmental age is that Cajal-Retzius neurons are abundant and have a primitive or immature appearance (Figs. 11, 12). Their form can be monopolar (Fig. 12A, B), horizontal (Fig. 12C), or irregular (Fig. 12D). All of them are rather compact with short dendritic branches with many ascending collaterals, which are very close to one another, reflecting the immaturity or the lack of expansion of these neurons at this age (Fig. 12). The axons of all Cajal-Retzius neurons invariably descend to the lower half of layer I, becoming long horizontal fibers (Figs. 11, 12). Specific afferent fibers are also numerous at this age. They penetrate into layer I and branch into horizontal fibers in its upper half.

15–16 Weeks of Gestation

The cerebral hemispheres at this age are vesicular structures with large ventricular cavities. The entire cerebral cortex of the frontal lobe at the level of the

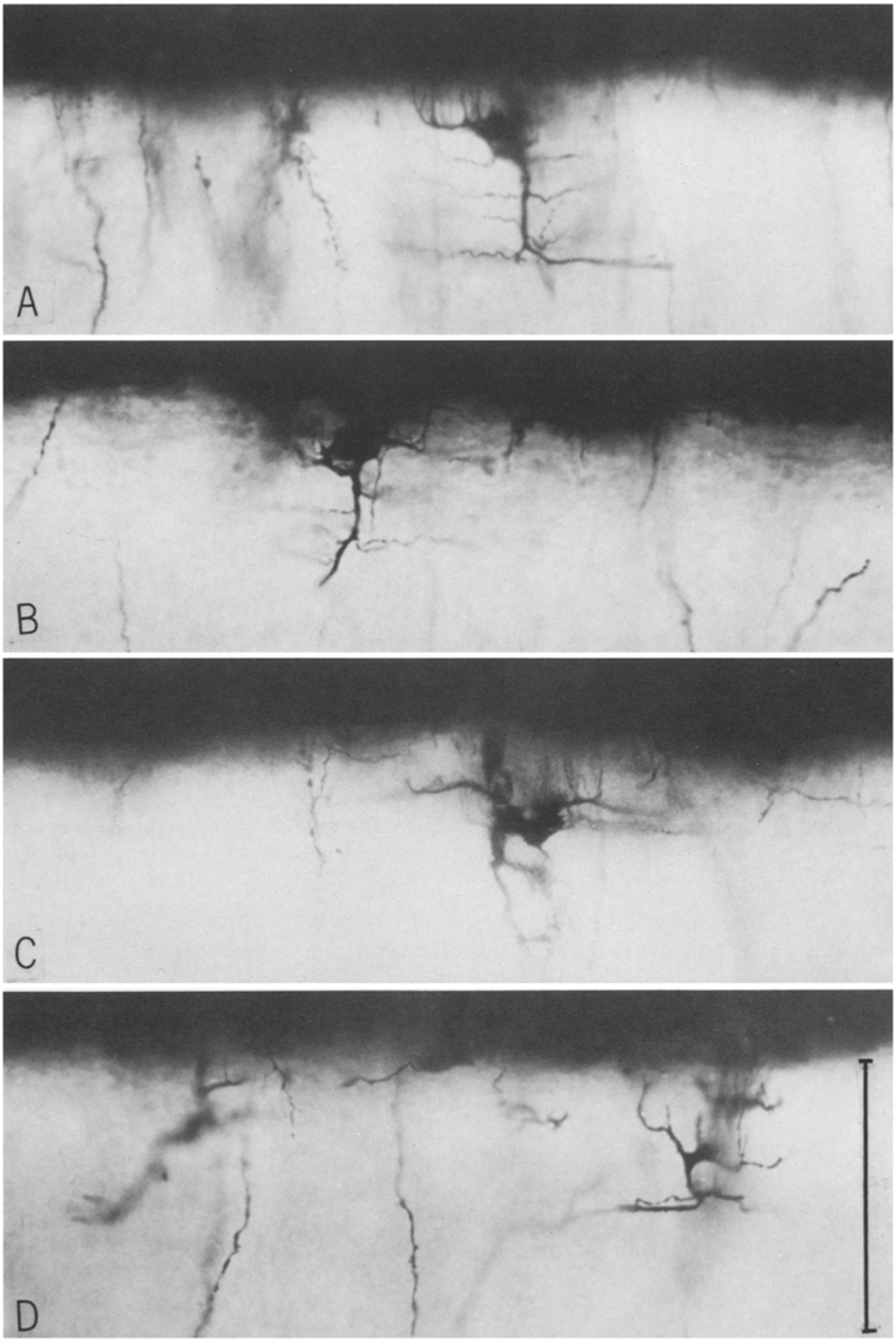

Fig. 12A–C. Composite figure of rapid Golgi preparations of Cajal-Retzius neurons of the motor cortex of a premature infant, 22 week gestation, illustrating the different morphology assumed by these neurons including: triangular (**A**), monopolar (**B**), horizontal (**C**) and irregular (**D**) shapes. The single descending axonic process is clearly visible in all. Scale: 100 µm

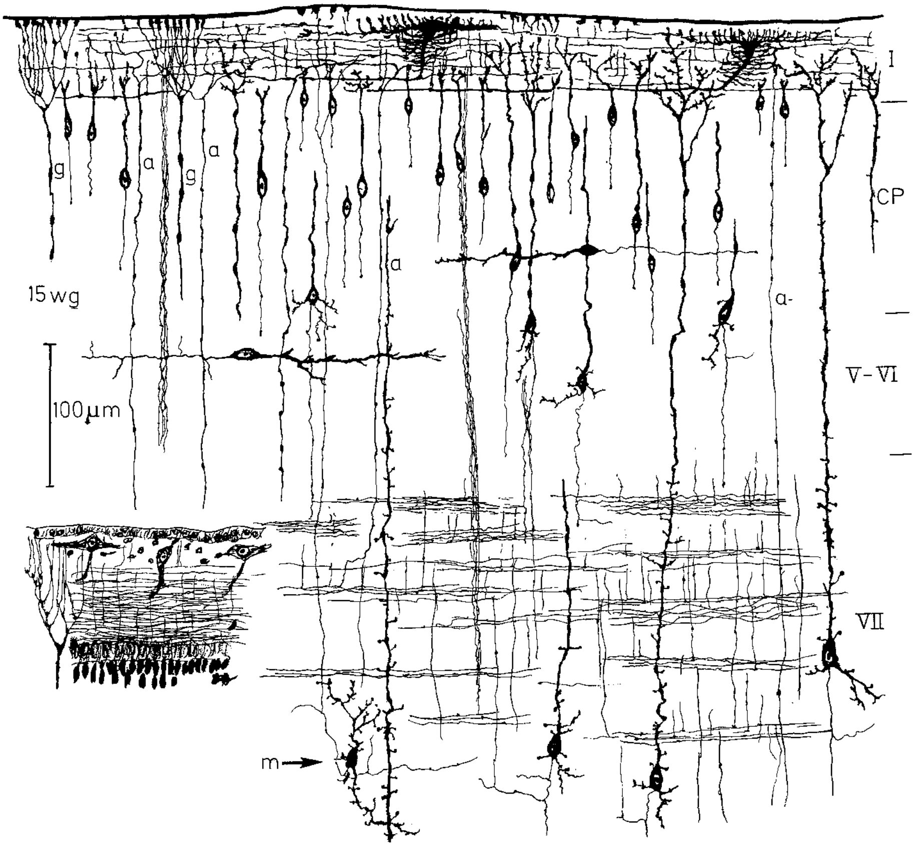

Fig. 13. Composite figure of camera lucida drawings made from rapid Golgi preparations of the motor cortex of a premature infant, 15 week gestation, illustrating its overall structural organization and relationships and distribution of its various components. At this age the motor cortex has the following laminae. A layer I with its basic organization already established and all its essential components present (Cajal-Retzius neurons, specific afferent fibers (*a*), axonic terminal of Martinotti neurons (*M*), and the apical dendritic bouquets of all pyramidal neurons). A cortical plate composed mainly of immature and still bipolar neurons with an ill-defined lamina at its lower edge representing the developing layers VI and V. A prominent deep plexiform layer or layer VII with large pyramid-like neurons anchored to layer I by their apical dendrites and Martinotti neurons (*m*). *Insert:* a close view of layer I, demonstrating the apparent abundance of Cajal-Retzius neurons at this age. Scale: 100 µm

presumptive motor region measures between 2 and 2.2 mm in thickness. The cortical plate measures 300–500 µm and layer I 50–60 µm in thickness respectively. The following laminae are recognized in this primitive motor cortex: a) layer I; b) the cortical plate with its upper two thirds still undifferentiated; c) a narrow zone at the lower region of the cortical plate representing the maturing layers VI and V; d) a prominent subplate region representing the deep plexiform lamina or layer VII; e) a thick layer of white matter; and, f) the matrix zone (Fig. 13). Within the matrix zone there is a narrow band composed of horizontal fibers near the ventricular surface. A plexus of horizontal fibers crossing the lower region of the matrix zone has been previously described in the human cerebral cortex (Marin-Padilla 1970). Although the origin of this deep plexus remains unknown, it is considered to represent the developing internal limiting glial membrane. In spite of the immaturity of the cerebral (motor) cortex at this developmental age, layer I is well developed. Its basic structural organization is already well established and all its essential components are recognized. However, the small neurons have not yet appeared and no terminals from extrinsic afferent systems have been found arriving at layer I at this developmental age (Fig. 13).

Cajal-Retzius Neurons are numerous and very close to each other at this time (Fig. 13). Their bodies are located in the upper region of layer I under the pial surface and all have a very primitive and immature appearance (Fig. 13). They have numerous fine branches extending from the body and a descending process (Fig. 13). These fine branches give to these Cajal-Retzius neurons a rather compact, or better, an unexpanded appearance. It seems that these fine branches will undergo a progressive horizontal lengthening (horizontalization) as the cerebral cortex expands. The descending axonic process of these neurons invariably reaches the lower half of layer I and becomes in it a long horizontal fiber (Fig. 13). These horizontal axonic fibers give-off numerous ascending terminal branches (Fig. 13).

Specific afferent fibers are also numerous and quite prominent at this age (Figs. 13, 14B, C). They originate from the white matter, ascend vertically through the undifferentiated cortical plate and branch into several long horizontal collaterals within layer I (Figs. 13, 14B, C). Axonic terminals of Martinotti neurons are also recognized at this age. Some of them belong to the deep neurons of layer VII (Fig. 13). Apical dendritic bouquets from all pyramidal neurons of this developing cerebral cortex are present in layer I (Fig. 13). It should be emphasized that *all* pyramidal neurons of the cerebral cortex from the large ones of layer VII to the very small, immature and still bipolar of the developing cortical plate have already established contacts with layer I (Fig. 13). Furthermore, it appears that these original connections between the pyramidal neurons and layer I are retained during the course of cortical neurogenesis. Therefore, the pyramidal neurons undergo a progressive elongation of their apical dendrites in the course of cortical neurogenesis, retaining their original connections with layer I.

Embryonic Period

Only two human embryos have been studied from this period. The brain of the oldest specimen is an example of the human cerebral cortex with a newly-formed cortical plate (Figs. 14A, 15) and that of the youngest represents the primordial plexiform layer stage of cortical neurogenesis (Fig. 16).

11 Weeks of Gestation

At this age the human forebrain is represented by two cerebral vesicles with a large common ventricular cavity with narrow developing cerebral cortices.

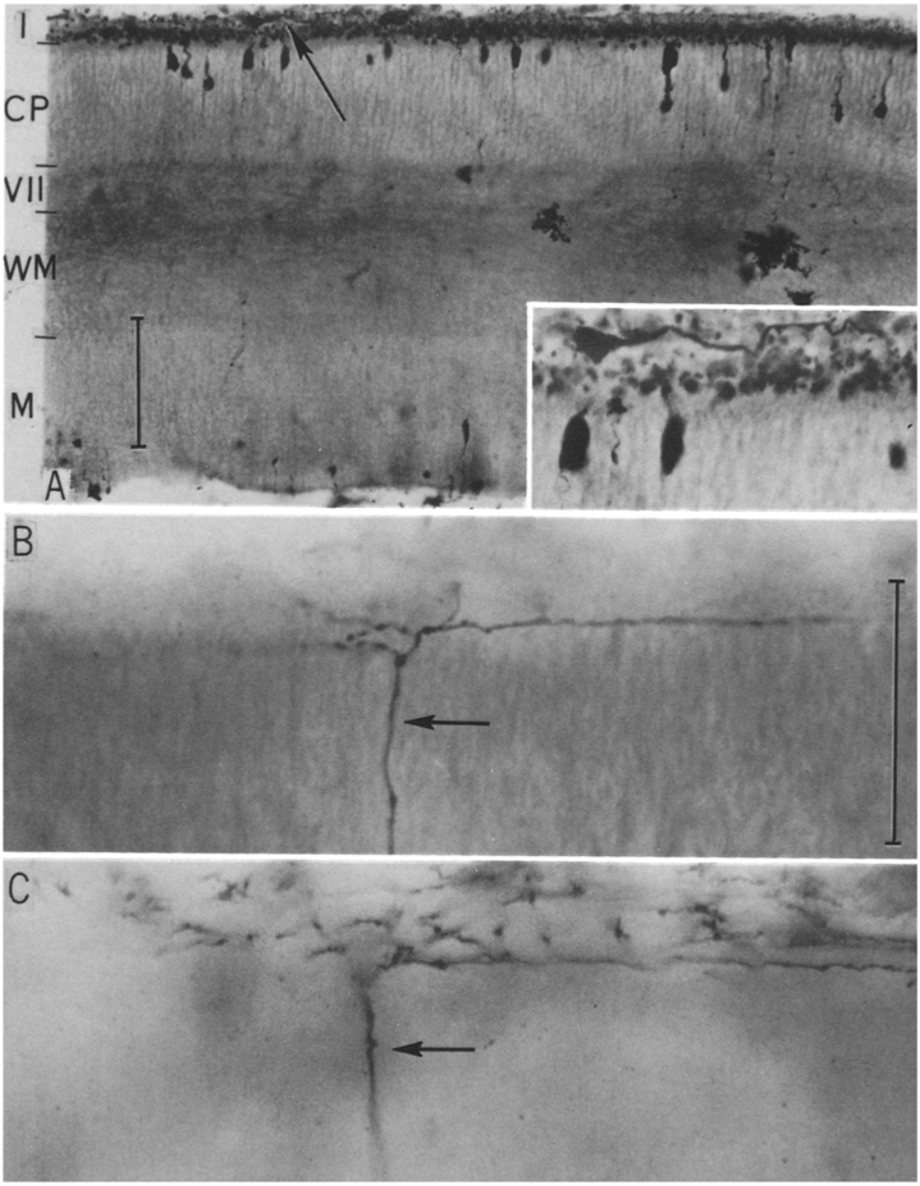

Fig. 14. A Golgi-Cox preparation of the cerebral (motor) cortex of a premature infant, 11 week gestation, illustrating its overall structure and the various laminae recognized at this development age. The following laminae are recognized: layer I with primitive horizontal neurons (*arrow*) representing immature Cajal-Retzius neurons (*insert*), a newly formed cortical plate composed of bipolar immature neurons (5 to 8 cells thick) already connected to layer I by their apical dendrite, a deep plexiform layer or layer VII, the internal white matter, and the matrix. Camera lucida drawings made from the cerebral cortex of this infant are reproduced in Fig. 15. **B** and **C** reproduce the arrival and horizontal branching within layer I of two specific afferent fibers from rapid Golgi preparations of the motor cortices of premature infants 16 (**B**) and 15 (**C**) week gestation respectively. Scale: 100 μm

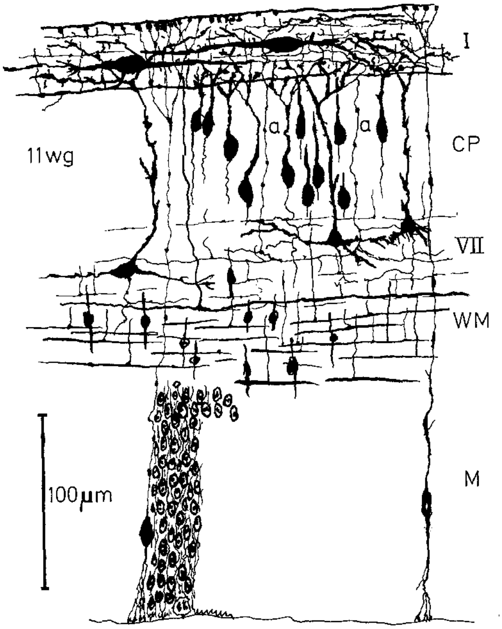

Fig. 15. Composite figure of camera lucida drawings made from Golgi-Cox preparations of the entire cerebral (motor) cortex of a premature infant, 11 week gestation, illustrating its overall structural organization, its various components and the laminations recognized at this developmental age. Layer I is already established with horizontal cells representing immature Cajal-Retzius neurons and many horizontal fibers. The cortical plate (5 to 8 cells thick) is composed of immature bipolar neurons connected to layer I by their developing apical dendrites. These original connections with layer I will be retained during the entire course of cortical neurogenesis. Layer VII or the deep plexiform lamination is also recognizable at this age. It is composed of pyramid-like neurons anchored to layer I by their apical dendrites. The internal white matter is also recognizable as well as the matrix zone. Scale: 100 μm

The entire cerebral cortex at the dorsolateral region of the telencephalic vesicle only measures 300–400 μm in thickness (Figs. 14A, 15). The cortical plate measures 100–120 and layer I 25–35 μm in thickness respectively. In this primitive cerebral cortex the following laminae are recognized: layer I; an undifferentiated cortical plate; a narrow deep plexiform lamination or layer VII; the white matter; and, the matrix zone (Figs. 14A, 15).

At this early age, layer I already has its basic plexiform organization (Fig. 15). It has large horizontal cells, identified as immature Cajal-Retzius neurons, and numerous horizontal fibers. These immature Cajal-Retzius neurons are found throughout the layer I without specific location in it and most of them have horizontal branches (Figs. 14A, 15). The horizontal axons of these neurons also run through the territory of layer I without any preferential distribution within it. Ascending specific afferent fibers are also seen coming from the white matter, crossing the undifferentiated cortical plate and terminating in layer I. They branch into several horizontal collaterals without demonstrating any preferential distribution within layer I (Fig. 15).

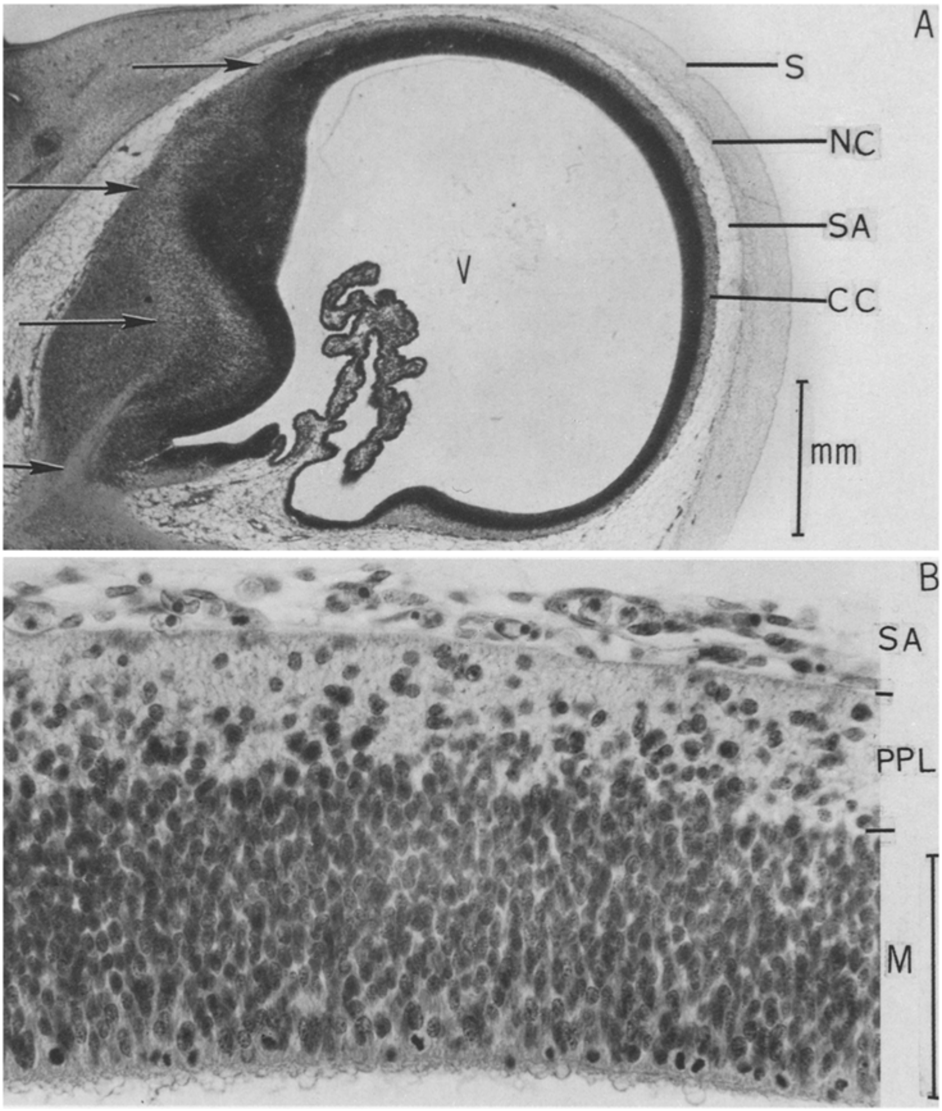

Fig. 16A, B. A general view of the entire cerebral hemisphere of a premature infant, 7 weeks gestation (obtained from a hysterectomy specimen) illustrating the primordial plexiform layer throughout the entire surface of the developing cerebral cortex. Also illustrated are the skin (*S*), the membranous neurocranium (*NC*), the subarachnoidal space (*SA*), the cerebral cortex (*CC*), the ventricle (*V*), the choroid plexus, and the immature and developing striatum. The *arrows* mark a bundle of fibers approaching from below with some of its fibers penetrating into the developing striatum, while others are seen approaching externally the developing cerebral cortex. These latter fibers are believed to enter externally into the developing cerebral cortex, to extend throughout its entire surfaces establishing an external white matter and to be the stimulus for the development and maturation of Cajal-Retzius neurons. Together they establish the primordial plexiform layer. H and E scale: 1 mm. **B** Closer view of the developing cerebral cortex at this age illustrating the superficial plexiform layer (*PPL*) and the matrix zone (*M*). The presence of neurons (embryonic Cajal-Retzius neurons), fibers (primitive corticipetal fibers), and primitive type of synaptic contacts has been demonstrated recently in the primordial plexiform layer of another seven week old human embryo (Larroche 1981). Scale: 100 μm

At this age, the newly-formed cortical plate is a narrow band (5 to 8 cells thick) of undifferentiated neurons (Fig. 15). However, many of these immature neurons have already established contacts with layer I. They perhaps represent future pyramidal neurons. Below the cortical plate, the plexiform lamina or layer VII (Figs. 14A, 15) is composed of immature pyramid-like neurons and numerous fibers. The apical dendrites of these neurons form ill-defined dendritic bouquets in layer I. It should be pointed out that these apical dendrites have elongated by the appearance of the cortical plate between them and layer I. We believed that the original connections of these dendrites with layer I (primordial plexiform layer) precedes the appearance of the cortical plate. Therefore, these dendrites will be progressively elongated by the subsequent growth of the cortical plate. In other words, the apical dendrite of these neurons do not reach layer I by growing toward it, but rather the neurons are suspended by their dendrites with the original connections with layer I. A recent electron microscopic study of the cerebral cortex of a human embryo of a comparable age to the one here described demonstrated the presence of neurons, fibers and synaptic contacts (between them) only above (layer I) and below (layer VII) the newly formed cortical plate (Larroche et al. 1981).

7 Weeks of Gestation

Only hematoxlyn and eosin preparations of the cerebral cortex of a fifty day old embryo, measuring 22 mm in crown-rump length, have been studied. The cerebral hemispheres of this embryo are large vesicular structures with very narrow cerebral cortices, prominent striatum and a large common ventricular cavity with prominent choroid plexus (Fig. 16A). The striatum is still primitive and developing. A large bundle of fibers is recognized entering the striatum and running externally to it, toward the external surface of the developing cerebral cortex (Fig. 16A). Fibers from this bundle (internal capsule) seem to penetrate and extend throughout the surface of the developing cerebral cortex, establishing an external white matter. As neurons develop this external lamina is transformed into the primordial plexiform layer. At this age the narrow cerebral cortex therefore has only two distinct laminae: a superficial one representing the primordial plexiform layer, and a deep one representing the matrix zone (Fig. 16B). The entire cerebral cortex is only 100–150 µm thick. The primordial plexiform layer has a distinct plexiform appearance with primitive neurons scattered between the fibers (Fig. 16B). Unfortunately, there are no Golgi preparations available of the human cerebral cortex at this early embryonic age. However, a recent electron microscopic study of the cerebral cortex of a human embryo of the same gestational age has demonstrated the presence of neurons (embryonic Cajal-Retzius neurons), fibers (specific afferents) and synaptic contacts within this primordial plexiform layer (Larroche 1981). Thus corroborating that the primordial plexiform layer is the first lamina to develop in cortical neurogenesis and that it precedes the appearance of the cortical plate.

Discussion

The structural organization of layer I of the human motor cortex has been studied throughout the course of prenatal neurogenesis utilizing the rapid Golgi method. This study represents the first complete developmental investigation of a lamina of the human cerebral cortex. It extends from the establishment of the first lamination recognized in cortical neurogenesis through the progressive formation of the multilayered cerebral cortex of the newborn infant.

Braitenberg (1978) once said: "We have no explanation why the histology of the cerebral cortex is what it is." This statement is particularly applicable to the structural organization of layer I. Its unique plexiform structure with numerous fibers and only a few neurons has always, and still does puzzle many investigators. Only a complete developmental study could furnish the necessary information about the essential components and basic structural organization of this enigmatic cortical lamina. In addition, a developmental study of layer I of the mammalian cerebral cortex could establish its early origin in embryonic life which precedes the formation of the cortical plate (mammalian neocortex). It could demonstrate that all pyramidal neurons establish primary connections with it. It could further demonstrate the structural stability of its basic organization during the course of prenatal cortical neurogenesis. It could perhaps indicate that layer I is part of a primitive cortical organization – the primordial plexiform layer – that might be common to and shared by amphibia, reptiles and mammals. From such a developmental study one should be able to provide a more accurate picture about the structural organization of layer I and perhaps one might be able also to answer some questions about its origin, composition, functional organization and possible nature.

Origin of Layer I

In early mammalian cortical ontogenesis two essential transformations take place in the undifferentiated telencephalic vesicle which result in the establishment of layer I (and of layer VII) of the cerebral cortex. The first transformation, according to the original idea (Marin-Padilla 1971, 1978) consists of the arrival of afferent fibers at the telencephalic vesicle followed by the appearance and maturation of primitive neurons among the fibers. These early corticipetal fibers penetrate into the telencephalic vesicle externally, extend under the pial surface throughout its entire surface, and establish an external white matter with few developing neurons. This first transformation has been corroborated by experimental studies (Raedler et al. 1975, 1976, 1978, 1980; König et al. 1975, 1977; Rickmann et al. 1977) and recently in the human cerebral cortex (Larroche 1981).

This first external lamina of the developing cerebral cortex, which has been previously considered to be wanting in neurons (the marginal or molecular zone of the old classification), has been renamed *the primordial plexiform layer*. In man, it is established around the seventh week of gestation preceding, therefore, the appearance of the cortical plate by 1 to 3 weeks (Hines 1922; Bartelmez and Dekaban 1962; Hamilton et al. 1972; O'Rahilly et al. 1977; Larroche et al. 1981). This primordial plexiform layer of the mammalian cerebral cortex is considered to be a primitive cortical organization which is functionally active during early embryonic life prior to the appearance of the cortical plate.

The primordial plexiform layer has also been considered by Marin-Padilla (1971, 1978) to be a premammalian cortical organization and not a component of the so-called mammalian neocortex. The mammalian neocortex will evolve only from the cortical plate (pyramidal cell layer of the old nomenclature) which represents the new or recent addition to cortical neurogenesis. The structural organization of the primordial plexiform layer of the mammalian cerebral cortex resembles the more primitive cortical organizations found in amphibians and reptiles. The possible existence of a primitive cortical organization, characterized by an external white matter (corticipetal fibers) with neurons interspersed among the fibers, common to and shared by amphibians, reptiles and mammals supported by this and previous studies (Marin-Padilla 1971, 1978) should be further investigated.

The second transformation in mammalian cortical neurogenesis, according to the original idea (Marin-Padilla 1971, 1978), is the appearance of the cortical plate within the primordial plexiform layer. Its appearance therefore, divides the primordial plexiform layer into a superficial plexiform or layer I and a deep plexiform or layer VII. This second transformation has also been corroborated by both experimental and recently by human studies (Laroche et al. 1981). Layer I (and layer VII) which evolves directly from the primordial plexiform layer represents, therefore, part of that primitive cortical organization. Furthermore, some of the structural and functional interrelationships among the elements of the primordial plexiform layer are retained, following the appearance of the cortical plate, between the elements of the newly established layers I and VII. These interrelationships between layers I and VII constitute the first and the only functional organization of the mammalian cerebral cortex prior to the maturation of the cortical plate. The subsequent maturation of the cortical plate will result in some transformations involving primarily the neurons of layer VII. These neurons lose progressively their original connections with layer I as they are replaced by similar types of neurons evolving from the cortical plate (Marin-Padilla 1972). On the other hand, layer I seems to be unaffected by the maturation of the cortical plate, retaining its basic plexiform organization as well as all its original components throughout the course of prenatal (and possibly of postnatal) cortical development.

These observations lead to the proposition of a new concept concerning the origin of the mammalian cerebral cortex. This new concept proposes that the mammalian cerebral cortex, including that of man, has a dual origin as well as a possible dual nature (Marin-Padilla 1978). According to this hypothesis, the mammalian cerebral cortex will be constructed on the one hand, from two primitive plexiform laminae (layers I and VII) derived from the primordial (premammalian) cortical organization; and, on the other hand, by an expanding cortical plate between them which represents the actual mammalian neocortex and gives rise progressively to layers VI, V, IV, III and II respectively. This hypothesis further proposes that the number of laminae derived from the cortical plate increases in the course of phylogenetic evolution (Marin-Padilla 1978).

Composition and Structure of Layer I

The components of layer I are few and their structural organization is primitive and simple. The basic structural organization of layer I is established very early in embryonic life and remains essentially unchanged in the course of prenatal cortical neurogenesis.

The six main components of layer I can be separated into essential and non-essential, intrinsic and extrinsic elements. The essential intrinsic components are the specific afferent fibers of layer I (primitive corticipetal fibers) and the Cajal-Retzius neurons, and the essential extrinsic components are the axonic terminals of Martinotti neurons and the apical dendritic bouquets of pyramidal neurons, the later representing the principal, possibly the only, functional outlet of this superficial lamina. In addition, two non-essential components are also added to the organization of layer I. They are: Intrinsic small neurons which begin to appear around the 24th week of gestation and the terminals of various extrinsic afferent systems from deeper cortical strata, which become progressively incorporated into this lamina late in the course of prenatal cortical neurogenesis.

The specific afferent fibers of layer I (primitive corticipetal fibers) are the first elements to appear in cortical neurogenesis. They are considered to be essential components of this lamina. Their origin remains unknown. They arrive at the telencephalic vesicle externally and extend throughout its entire surface establishing an external white matter in which Cajal-Retzius neurons soon appear and start to mature. These fibers form a plexus of horizontal collaterals with numerous ascending axonic terminals in the upper half of layer I. It should be pointed out, that ascending specific afferent fibers which terminate by branching into long horizontal collaterals in the upper half of layer I, which give off few or no collaterals to other cortical layers, have been demonstrated in all prenatal developmental stages of the human cerebral cortex investigated in this study. They are considered to be the original primitive corticipetal fibers and are believed to be afferent and specific to layer I. Together with the Cajal-Retzius neurons they establish the basic structural organization of layer I. These specific afferent fibers must be clearly distinguished from the numerous terminals from other afferent systems which also arrive in layer I later in the course of cortical neurogenesis. These late-arriving terminals are known to originate from non-specific and specific thalamic nuclei (thalamic fibers), from the opposite cerebral hemisphere (callosal fibers), and from near and distanct cortical areas (cortico-cortical fibers). The arrival time of each one of these afferent systems is specific. For example, the callosal fibers cannot reach the opposite cerebral hemisphere until after the 12th or 13th week of gestation because the corpus callosum does not start to form until that time (Hamilton et al. 1972). The arrival in layer I of terminals from cortico-cortical fibers occurs even later in cortical neurogenesis. Furthermore, the primary target of all of these afferent systems is not layer I but lower cortical strata of the cerebral cortex. Also, these late-arriving terminals have a very limited spread within layer I and their distribution in it appears to be non-specific. In addition, some of these late-arriving terminals appear to be specific and limited to only certain cortical regions rather than to all areas. All of these features should be sufficient to differentiate between the specific afferent fibers of layer I and the late-arriving terminals of other afferent systems.

These original ascending specific afferent fibers of layer I may not be recognized in all cortical regions. They should be found only at strategic probably old, cortical regions such as the auditory (Cajal 1900) and the motor cortex (Marin-Padilla 1970). However, they could reach distant cortical regions by way of their long horizontal collaterals. These primitive fibers undergo a considerable dilution as the cerebral cortex expands and there are no indications to suggest that they disappear from it. The actual number of these fibers, established very early in embryonic development, probably remains unchanged during the course of cortical neurogenesis, a constancy which explains their progressive dilution in the growing brain. The main target of these specific afferent fibers is considered to be the Cajal-Retzius neurons. Probably they could also establish secondary synaptic contacts with the apical dendrites of near and distant pyramidal neurons through their long horizontal collaterals.

The Cajal-Retzius neurons are the essential neuronal elements of layer I. They are the first neurons to appear in cortical neurogenesis. Their long axons form a plexus of horizontal (tangential) fibers in the lower half of layer I. Their long horizontal axons give off innumerable ascending and descending terminal branches throughout their entire length. The body and main dendrites of Cajal-Retzius neurons are not found in all regions of the cerebral cortex. They are only found at strategic, possibly old, cortical regions such as the motor (Marin-Padilla 1970) and visual cortex (Takashima et al. 1980). On the other hand, their axons extend in an anteroposterior direction throughout the entire surface of the cerebral cortex. Probably there are no regions in the cerebral cortex without the horizontal axons of Cajal-Retzius neurons. All thick horizontal (tangential) fibers found in the lower half of layer I throughout the entire surface of the human cerebral cortex are considered to be the axonic trunks of Cajal-Retzius neurons. Although these neurons undergo a considerable dilution as the cerebral cortex expands, there are no indications to support the idea that they disappear or undergo degenerative changes during the course of postnatal development. Concerning the so-called 'disappearance' of Cajal-Retzius neurons, the following comments should be made. First of all, it should be pointed out that the surface of the human cerebral cortex increases from the seventh week of gestation to the neonatal period by approximately 150 fold and to the adult period by 250 fold (Blinkov and Glezer 1968). Therefore, it should be at least as difficult to locate a Cajal-Retzius neuron in the cerebral cortex of the neonate or the adult since the number of these neurons is established early in development and remains probably unchanged in the course of cortical neurogenesis. Secondly, those regions of the cerebral cortex which develop late in prenatal cortical neurogenesis, such as the associative areas, should be lacking in Cajal-Retzius neurons. Probably the association areas of the cerebral cortex are also free of specific afferent fibers to layer I. Although these association areas might lack the body and main dendrites of Cajal-Retzius neurons, they are not wanting in their horizontal axons. The pyramidal neurons developing in these associative areas must also receive the basic information transmitted by the Cajal-Retzius neurons throughout the entire cerebral cortex.

The main target of Cajal-Retzius neurons are the apical dendrites of practically all pyramidal neurons of the cerebral cortex regardless of their location or cortical depth. The numerous ascending and descending terminal collaterals of the horizontal axons of Cajal-Retzius neurons establish synaptic contacts with the spines of the apical dendrites of near and distant pyramidal neurons. In cortical neurogenesis, the first apical dendrites to establish synaptic contacts with layer I are those of pyramidal neurons of layer VII, and then progressively those of the future pyramidal neurons of layers VI, V, IV, II, and II respectively.

Therefore, all pyramidal neurons of the cerebral cortex receive progressively, as they mature, the same kind of information from layer I. The terminal apical dendrites of all pyramidal neurons become in the course of cortical neurogenesis an enormous receptive surface within layer I representing its principal and possibly its only functional outlet.

In this context, it should be pointed out, that the generally held idea that the apical dendrites of pyramidal neurons grow toward and terminate in layer I is erroneous. Based on the observations made in this study it seems that: a) the first dendrite of a developing pyramidal neuron to develop and to mature is the one connected with layer I; and b) once these original connections are established, they are retained (and expanded) during the course of cortical neurogenesis. Therefore, in a real sense, the pyramidal neurons of the cerebral cortex are suspended from layer I, anchored to it by their original apical dendritic connections. For example, a layer V pyramidal neuron of the human motor cortex at fifteen weeks of gestation is merely 100 μm long and is already anchored to layer I by its developing apical dendrite. The same neuron by the time of birth has reached the enormous length of 1,500 μm and is still anchored to layer I by its now well developed apical dendrite.

The classic analogy which compares neurons with trees, attributed to Golgi and so frequently used by Cajal, is inseparable from a variety of concepts such as: growing up, branching up and reaching up, which could be misleading. Even the Greek root for dendrite ($\delta\varepsilon\nu\delta\rho\sigma\nu$ = dendron) means tree. According to this analogy, the apical dendrite of pyramidal neurons are envisioned as growing up, branching up and reaching up to layer I with their terminal branches. Following the same analogy, the axon of a pyramidal neuron-tree will be its root while the dendrites will represent its arborizations. In view of the observations presented in this study, that analogy should be reconstructed as follows: The main root of a pyramidal neuron-tree will be its original apical dendrite, which established contacts with layer I, while its axon with its collaterals will represent its real arborizations or branches. It seems, therefore, that the old and colorful analogy, so frequently used, which compares neurons with trees, should be abandoned or used more adequately. With this new concept it may be possible now to explain (for the first time) the remarkable inside-out formation of the cortical plate (neocortex) of the mammalian cerebral cortex. It seems that in the developing mammalian cerebral cortex any set of migrating neurons must pass through all the preceding ones in order to establish contacts with layer I. Therefore, the newly-arrived migrating neurons must always occupy the most superficial zone (beneath layer I) of the developing cortical plate. Once these newly arrived migrating neurons have established synaptic contacts with layer I, they are ready to be displaced – without losing their original connections with it – by the arrival of the next set of migrating neurons. Therefore, all pyramidal neurons of the neocortex became anchored to layer I by their original connections and grow by elongating their apical dendrites until their somata reach their destination or cortical level. The final destination of each group of pyramidal neurons or cortical depth of their bodies is not an arbitrary event but one which is directly dependent upon the arrival of the different afferent systems to the cerebral cortex (Marin-Padilla et al. 1969). A pyramidal neuron destined to become motor, visual, sensory, acoustic or associational is maintained by the impulses of layer I during its growth and until it reaches its cortical depth, establishes connections with a specific afferent system (non-specific or specific thalamic, callosal or cortico-cortical), and assumes its particular functional role. This new concept emphasizes the primordial importance of layer I in the overall organization of mammalian cerebral cortex, thus suggesting the existence of a general architectural plan common to all mammals including man. It also explains why the majority of neurons of the cerebral cortex anchored to layer I by their apical dendrite must necessarily assume a pyramidal shape regardless of its size or functional role. It offers an explanation for the abundance of pyramidal neurons, of various sizes, throughout the cerebral cortex, a fact which has never been either understood or adequately explained.

The Martinotti neurons, on the other hand, have a limited axonic distribution within layer I. They could only establish synaptic contacts with the apical dendrites of a small group of pyramidal neurons. The few pyramidal cells contacted by a single Martinotti neuron are necessarily those of its own cortical region. Furthermore, since Martinotti neurons are probably found at all cortical levels, each one of them would establish contacts only with the pyramidal neurons of its own cortical level or depth. The morphologic features of Martinotti neurons and their limited but distinct axonic distribution are suggestive of an inhibitory functional role. The small neurons of layer I appear late in cortical neurogenesis. Their axonic and dendritic distribution are also quite limited within layer I. Although their function remains unknown, an inhibitory role has also been recently suggested for these small neurons (Hendry and Jones 1981).

Undoubtedly, the structural interrelationships among the various components of layer I, in the course of prenatal cortical neurogenesis, their location, their territory of distribution, their dimensions and their progressive growth, will be better illustrated and appreciated by the camera lucida drawings which accompany this communication than by trying to describe them verbally. All camera lucida drawings are reproduced at the same magnification in order to convey a sense of growth and to facilitate their comparative analysis. These camera lucida drawings illustrate, at the same magnification, the entire prenatal development of layer I of the human cerebral (motor) cortex.

Function and Nature of Layer I

According to the observations made in this developmental study, the basic functional role of layer I seems to be the spreading of a primitive kind of information to all pyramidal neurons of the cerebral cortex regardless of their location or cortical depth. In the course of cortical neurogenesis, this primitive information eventually reaches all pyramidal neurons from the primitive ones of layer VII to the most recent ones of layer II. This primitive information seems to have a vital importance for the functional maturation of all pyramidal neurons whether they be sensory, motor, visual, acoustic or associational in nature. It must be basic and non-specific since it spreads equally to all pyramidal neurons of the cerebral cortex. Perhaps it transmits to all pyramidal neurons either a basic modulatory effect or an activating one, or it could simply impart to them a basal tone necessary for their subsequent maturation and function.

The overall functional role of layer I is envisioned as follows. A primitive kind of information reaches layer I by a specific type of afferent fiber, is received by the Cajal-Retzius neurons and spread throughout the entire cerebral cortex by their long horizontal axons. This primitive information is transmitted from the horizontal axons to the apical dendrites of all pyramidal neurons by axo-spinodendritic synapses. These synaptic contacts are established between the numerous ascending and descending terminal branches of the horizontal axons of Cajal-Retzius neurons and the spines of the apical dendrites of all pyramidal neurons whether they be sensory, motor, visual, acoustic or associational in nature. The relationships among these three essential components – specific afferent fibers, Cajal-Retzius neurons and apical dendrites of pyramidal neurons – constitute the basic structural and functional organization of layer I. Within this basic organization of layer I the Martinotti neurons are believed to play specific and limited inhibitory roles upon a small group of pyramidal neurons by establishing synaptic (axodendritic) contacts with their apical dendrites. Similarly, the small neurons of layer I probably also play a very localized inhibitory role.

The functional role played by the late-arriving terminals of the thalamic, callosal or cortico-cortical afferent systems within the basic organization of layer I, is considered to be of secondary importance. Although the functional role of any of these afferent systems is undoubtedly of considerable importance within the overall functional organization of the cerebral cortex, their role within the functional organization of layer I is considered to be limited and specific. The functional role of these late-arriving terminals is limited to a given cortical region because they do not extend within layer I for a long distance and also specific to a given cortical region (such as the visual, the motor, the acoustic etc.) rather than universal to the entire cerebral cortex. The arrival time of these afferent systems to the cerebral cortex is also specific for each one and seems to be related to the maturation of a distinct cortical lamina (or region) other than layer I.

The origin of the primitive specific afferent fibers to layer I remains unknown. Perhaps it would be possible by establishing their basic features to delineate the kind of nucleus from which they originate. These primitive afferent fibers arrive in the cerebral cortex very early in embryonic development and, although progressively diluted, they persist in it during the course of cortical neurogenesis. They are already recognized by the seventh week of gestation in man (Larroche 1981) and by 20 days of gestation in the cat (Marin-Padilla 1971, 1978). At this early embryonic age the diencephalic centers and particularly the thalamic nuclei are either quite immature or are still undifferentiated, making them an unlikely source for these fibers. Although the striatum is mostly undifferentiated at this age, a band of fibers – the internal capsule – is already recognized entering into it and approaching the cerebral vesicle externally (Fig. 16). The majority of the fibers forming this primitive internal capsule must arrive from lower centers of the neuraxis. In addition, as far as it is known, the primitive afferent fibers of layer I might be monoaminergic in nature (Morrison et al.

1978; Schlumpf et al. 1977, 1980). In view of these features it may be possible to limit the origin of these fibers to primitive nuclei, perhaps composed of monoaminergic neurons, and located at mesencephalic or even lower levels of the neuraxis.

A nucleus that shares some of the above characteristics is the *locus ceruleus*. Phylogenetically, this nucleus is old, poorly delineated in amphibians and recognized as a distinct nucleus in birds reptiles, and mammals. Ontogenetically, it is also an old structure which acquires its adult neuronal differentiation and characteristic fluorescence very early in embryonic development (Amaraz et al. 1977). Furthermore, this nucleus is composed of nonadrenergic neurons and it is known to project to the forebrain including the cerebral cortex and layer I (Amaraz et al. 1977). The functional role of the locus ceruleus seems to be modulatory (Amaraz et al. 1977). Its projections may serve to maintain levels of excitability optimal for information processing. In view of these facts, the locus ceruleus should be explored as a possible source of the primitive afferent fibers to layer I.

But perhaps a most interesting idea, worthy of serious consideration, will be the possibility that layer I of the mammalian cerebral cortex could represent a distant component of the reticular activating system (reticular formation). This possibility is at least indirectly implicated and supported by the observations and ideas presented in this study. As a part of the reticular activating system, layer I could transmit to all pyramidal neurons of the cerebral cortex regardless of their location, cortical depth and function, a common basal tone necessary for their functional maturation. A common basal tone may be necessary to all pyramidal neurons whether they will eventually become specialized in sensory, motor, visual, acoustic or associational functions. The early origin of layer I, the fact that it is part of a primitive cortical organization (the primordial plexiform layer) possibly common to and shared by amphibians, reptiles and mammals, the fact that its primitive plexiform organization and basic composition remains unchanged in the course of both phylogenetic evolution and ontogenesis, the fact that it extends equally and throughout the entire cerebral cortex, and the fact that it makes similar types of contacts with all pyramidal neurons of the cerebral cortex are all features which give support to this idea.

Finally, it should be pointed out that the observations made in this study further corroborate the new concept concerning the dual origin and possible dual nature of the mammalian cerebral cortex, including that of man. It is hoped that the observations and ideas presented in this communication will stimulate much needed basic research into the nature and structural organization of the cerebral cortex and will encourage the development of new avenues of inquiry.

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