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An Ultrastructural Study of the Maturation of Neuronal Somata in the Visual Cortex of the Rat

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Summary. The postnatal development of neuronal perikarya in layers II–VI of the visual cortex of perfusion-fixed albino rats, 12 h to 180 days old, has been studied by electron microscopy. Particular attention was paid to cells in photographic montages of 75 μm wide strips extending through the full depth of the occipital cortex, cut from 100 μm Vibratome sections of the brain.

At birth, and during the first few postnatal days, most of the neurons present in the cortex are small, tightly packed 'indifferent' cells with scanty cytoplasm containing mitochondria and chiefly free ribosomes; a few presumptive pyramidal cells with a developing apical dendrite and more voluminous cytoplasm can be recognized in deep cortex. Non-pyramidal cells can be identified on postnatal day 6, when although scarce and with immature cytoplasmic features, they already display a more electron opaque chromatin pattern than developing pyramidal cells and receive axo-somatic contacts of Gray's type I.

During the second postnatal week there are conspicuous increases in the maturity of the cells, which acquire a rich complement of cytoplasmic organelles: in general cells situated in the deep cortical plate are larger and better differentiated than those in the superficial plate, and non-pyramidal cells are less well differentiated than the associated pyramidal cells. By the end of the second week, differences in cytoplasmic maturity between superficial and deep, and between pyramidal and non-pyramidal cells are less evident.

Maturation proceeds during the third postnatal week; both types of cells acquire an adult complement of axo-somatic synapses and their mature nuclear and cytoplasmic features, and by day 24 are indistinguishable from their adult counterparts. In keeping with previous Golgi studies of this same cortex, the non-pyramidal cells did not acquire mature ultrastructural

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features significantly later than the pyramidal cells. A possible correlate of particularly active synaptogenesis and plasticity in the population of non-pyramidal cells during the third postnatal week (immediately after eye-opening), was that at this time these cells contained very prominent accumulations of granular reticulum, ribosomes and Golgi apparatus, and appeared hypertrophic.

Key words: Visual cortex – Development – Pyramidal neurons – Non-pyramidal neurons – Rat.

Introduction

The morphological features of differentiating neurons impregnated by the Golgi techniques have been extensively studied and thoroughly described, nowhere more so than in the mammalian cerebral neocortex (e.g. Cajal, 1911; Aström, 1967; Noback and Purpura, 1961; Berry, 1974; Lund et al., 1977; Kristt, 1978; Parnavelas et al., 1978). However, although there have been a number of ultrastructural studies of developing mammalian neocortex, in which many features of immature neurons have been described (e.g. Caley and Maxwell, 1968; Butler and Caley, 1972; Raedler and Sievers, 1975), there have been no systematic studies, and the cytological features of developing neocortical neurons have been much less comprehensively documented than their morphological features.

We describe here systematic studies, by electron microscopy, of the postnatal development of the cell bodies of neurons in the visual cortex of albino rats. The observations cover the period from birth – at which stage the neurons present are all extremely immature and migration into the future grey matter from the periventricular proliferative zone is still in progress (Berry, 1974; Lund and Mustari, 1977) – to maturity. A specific concern in these studies was to compare the findings by electron microscopy with observations by light microscopy in our recent Golgi study of this same cortex (Parnavelas et al., 1978), which showed that, contrary to the prevalent view, non-pyramidal cells (with the exception of those in layer I) reach maturity uniformly throughout the depth of the cortex, and at the same time as the pyramidal cells with which they are associated.

Materials and Methods

The animals used were female albino rats of the following postnatal ages: 0 (12 h), 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 24, 28, 35, 40, 90 and 180 days. All were perfused with aldehyde mixtures according to Peters (1970). Fixative was delivered at room temperature, using a flow inducer via a cannula tied into the ascending aorta (animals 16 days and older) or inserted into the left ventricle (animals 12 hours to 14 days old). Strips of occipital cortex for analysis were selected from frontal 100 μm Vibratome slices of the brain after the slices had been osmicated and embedded flat in Araldite. The strips of cortex were cut from the frontal slices, remounted on Araldite stubs and thin-sectioned in the frontal plane. Full details of the preparation procedures are given elsewhere (Parnavelas et al., in preparation). Tissue from at least two animals of each age was examined and, to avoid sampling bias, an extensive survey was conducted on photographic montages,

each comprising a strip of cortex 75 μm wide and extending from pia to the subcortical white matter.

Six montages (final magnification × 7,500) were prepared from either two or three animals of each of the following ages: 12 hours, 4, 6, 8, 10, 12, 14, 16, 20, 24, 90 and 180 days.

Results

Adult Rats

The ultrastructural features of neurons in the 90 day and 180 day animals were very similar and the two groups are considered together here. Pyramidal cells and non-pyramidal cells were identified by the nuclear, cytoplasmic and synaptic features that have been described in detail in previous studies of cerebral neocortex of rats (e.g. Peters and Kaiserman-Abramof, 1970; Peters, 1971; Parnavelas et al., 1977; Peters and Fairen, 1978), and other mammals (e.g. Colonnier, 1968, cat; Garey, 1971, cat and monkey; Sloper, 1973, monkey).

Pyramidal cells (Fig. 1) were characterized by a relatively large, electron lucent nucleus in which the chromatin was evenly dispersed, with only slight marginal concentrations. The cytoplasm of the larger pyramids was moderately organelle-rich, with prominent concentrations of granular endoplasmic reticulum (GER). The smaller pyramids had a rather sparse GER consisting of irregularly oriented and usually individual cisterns. Dendrites, when present in the plane of section, were usually broad and organelle-rich at their origin from the perikaryon, particularly apical dendrites, and elements of the Golgi apparatus were commonly concentrated in this region (e.g. D_1 in Fig. 1). Axo-somatic synaptic contacts were relatively sparse and were all of Gray's type II (arrow, Fig. 1). Axo-dendritic synapses were a mixture of type I and type II (with type II predominating), and synaptic contacts on dendritic spines were all of type I.

Non-pyramidal cells (Fig. 2) differed from pyramidal cells in a number of ways, the most important of which, for diagnostic purposes in electron micrographs, were the following:

1. Their nuclei were, overall, more electron dense than the nuclei of pyramidal cells. This difference is attributable to a more densely packed granular chromatin and more prominent clumps of heterochromatin at the margin of the nucleus. In addition, the nuclei of non-pyramidal cells were commonly irregular in outline. This was particularly obvious in cells with eccentric nuclei: the nuclei of such cells very commonly displayed deep invaginations of the aspect facing into the main body of cytoplasm.

2. The larger non-pyramidal cells, and many of the smaller ones, were characterized by large concentrations of GER consisting of orderly arrays of unbranched, often very long cisterns, arranged parallel to one another and to the nuclear and cell contour. Stacks of GER in pyramidal cells, even in large pyramidal cells with abundant GER, were seldom as large or as orderly. The greater electron density of the cytoplasm of non-pyramidal cells (due to the presence therein of large numbers of free ribosomes and polysomes), a diagnostic feature stressed by Peters (1971), was not observed consistently in our material.

3. Axo-somatic synapses were more frequently encountered than on pyrami-

dal cells. The axo-somatic synapses of non-pyramidal cells fell into three categories, in accordance with the observations of Peters (1971): typical Gray type II synapses (arrow 2, Fig. 3a) identical to those on the cell bodies of pyramidal cells; typical Gray type I synapses with an extremely prominent postsynaptic density (arrow, Fig. 2 and inset; Fig. 3b); synaptic contacts with a widened cleft but with a postsynaptic density that is narrower than that of typical Gray type I contacts (arrow 1, Fig. 3a). Type II synapses constituted a minority of the axo-somatic synapses.

Non-pyramidal cells displayed some additional ultrastructural characteristics which distinguished them from pyramidal cells, but which were less useful than the above for purposes of identification. One of these was the very wide spectrum of cell body size, another was that their outline, usually circular or oval (but occasionally pear-shaped) tended to be smooth, with dendrites being narrow at their origins and emerging rather abruptly from the perikaryal profile. A third was their tendency to associate in clusters (particularly in layer IV) in which extensive areas of intimate, but apparently unspecialized, apposotion occurred between contiguous somal membranes.

Finally, the dendrites of spine-free non-pyramidal cells were found to receive both type I and type II synaptic contacts, with type I predominating, and the dendrites of spinous non-pyramidal cells also displayed type I synaptic contacts on their spines.

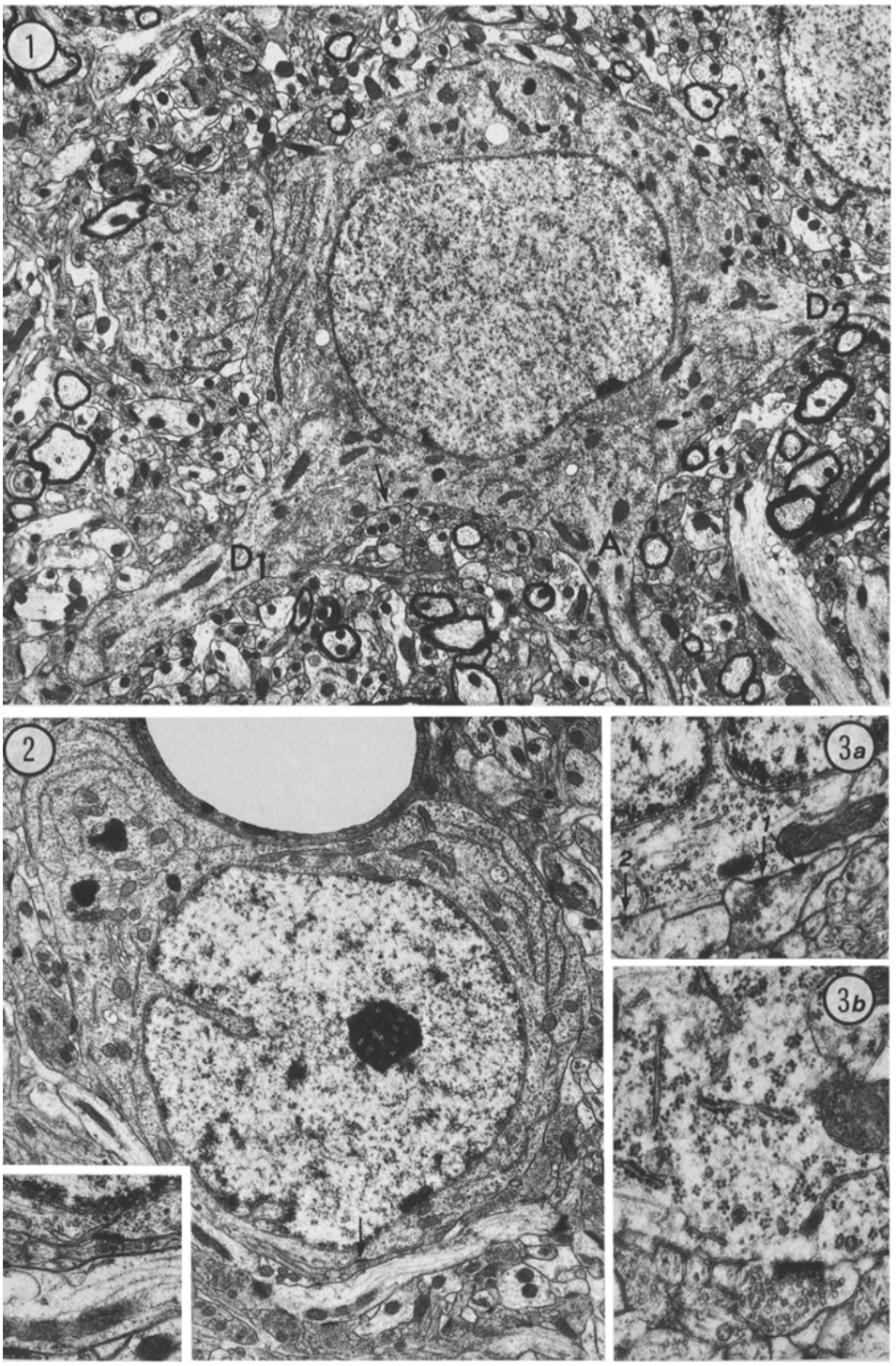
First Postnatal Week

At birth, and for the first few days thereafter, the cortex is extremely immature and consists of the cell bodies and processes of migrating and postmigratory neurons, glioblasts and immature glial cells. The neurons could be distinguished from cells of the glial lineages by their relatively paler nuclei: the neuronal nuclei displayed fine granular chromatin which was fairly homogeneous in texture except at the periphery where clumps of chromatin were concentrated. The neurons spanned a considerable spectrum of maturity. At one extreme were cells with relatively large nuclei, lacking, or containing only small nucleoli. Such cells had a thin rim of perinuclear cytoplasm containing free ribosomes and polysomes, small mitochondria, sometimes a few individual, small cisterns

Fig. 1. Adult; pyramidal cell of layer V. The axon hillock (*A*) and initial segment of the axon, and two basal dendrites (D_1, D_2) are in continuity with the cell body. ×7,000. All illustrations are electron micrographs of thin sections, cut in the frontal plane, of the visual cortex in albino rats

Fig. 2. Adult; non-pyramidal cell of layer II. Note the indented nucleus and compare the chromatin pattern with that of the pyramidal cell nucleus in Fig. 1. The *arrow* indicates an axo-somatic synaptic contact of Gray's type I, enlarged in the inset. ×8,300 (inset ×17,500)

Fig. 3a. Adult; axo-somatic synaptic contacts on a non-pyramidal cell of layer II. The synaptic contacts at *arrow 1* are of the wide-cleft, narrow postsynaptic density variety and that indicated by *arrow 2* is a typical Gray type II contact. ×16,000. **b** Adult; typical Gray type I axo-somatic synaptic contact on a non-pyramidal cell of layer IV. ×25,200


1
D2
D1
A
2
3a
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2
3b

of GER, but few other organelles. These cells resembled the indifferent cells of Caley and Maxwell (1968) and were most commonly encountered in the superficial portion of the cortical plate, in which they were tightly packed (Fig. 4). Other cells displayed nuclei with more prominent nucleoli, a more voluminous and better differentiated cytoplasm containing ribosomes, GER, mitochondria, microtubules, and Golgi elements (Fig. 5). With the exception of the Retzius-Cajal cells – a distinctive class of non-pyramidal cell in layer I, generated very early and achieving a differentiated state before any other cortical cell type (Raedler and Sievers, 1976; Bradford et al., 1977; König et al., 1977) – the more highly differentiated cells at any specific age during the first week were situated in the deeper part of the cortical plate.

During the first few postnatal days (0, 2, 4) the neuronal population could not be subdivided into pyramidal and non-pyramidal cells, although some of the more mature cells in the deep portion of the cortical plate, with large perikarya and a thick apical process rich in organelles, were considered to be presumptive pyramidal cells (Fig. 6). Towards the end of the first postnatal week, however, the number of cells with the features of pyramidal cells increased (Fig. 7, 6 days) and, for the first time, cells with cytoplasmic, nuclear and synaptic features marking them as probable non-pyramidal cells could be identified in the deep cortical plate (Figs. 7, 9), although in the superficial cortical plate there remained numerous closely packed, small and immature indifferent cells (Fig. 8). In Figure 7, for example, the presumptive non-pyramidal cell (NP) displays a nucleus (with an invagination), that is slightly 'darker' than the nucleus of the adjacent pyramidal cell (P) with a prominent apical dendrite, and receives an axosomatic synapse of type I (arrow, and Fig. 9a). More mature non-pyramidal cells were also present at postnatal day 6 and one with an eccentric nucleus, organelle-rich cytoplasm and a type I axo-somatic synapse is illustrated in Fig. 9. On the basis of cytoplasmic characteristics, the non-pyramidal cells at this stage were less mature than most of the pyramidal cells and the larger pyramidal cells of the deep cortical plate (e.g. Fig. 10, a layer V pyramid) appeared to be better differentiated than the smaller pyramidal cells. Within 2 days, however, small pyramidal cells with mature cytoplasmic features were also present in superficial cortical laminae (e.g. Fig. 10a, a layer III pyramid at 8 days).

Second Postnatal Week

Major changes in the size and maturity of the cortical neurons occurred over this period, during which apical dendrites of pyramidal cells expanded and basal dendrites arising from their somata became progressively more frequently observed. At the beginning of the second week, cells that could be identified with confidence as non-pyramidal cells were still comparatively infrequent and situated chiefly in the deeper layers (Figs. 11, 12). Many of these, including some cells with immature cytoplasmic characteristics, received numerous axo-somatic synaptic contacts (Fig. 11). By the end of this period (day 14) most neurons could be identified as either pyramidal or non-pyramidal, even in the superficial cortex (e.g. Fig. 13, layer II), and cells of both types had acquired a rich complement of cytoplasmic organelles.

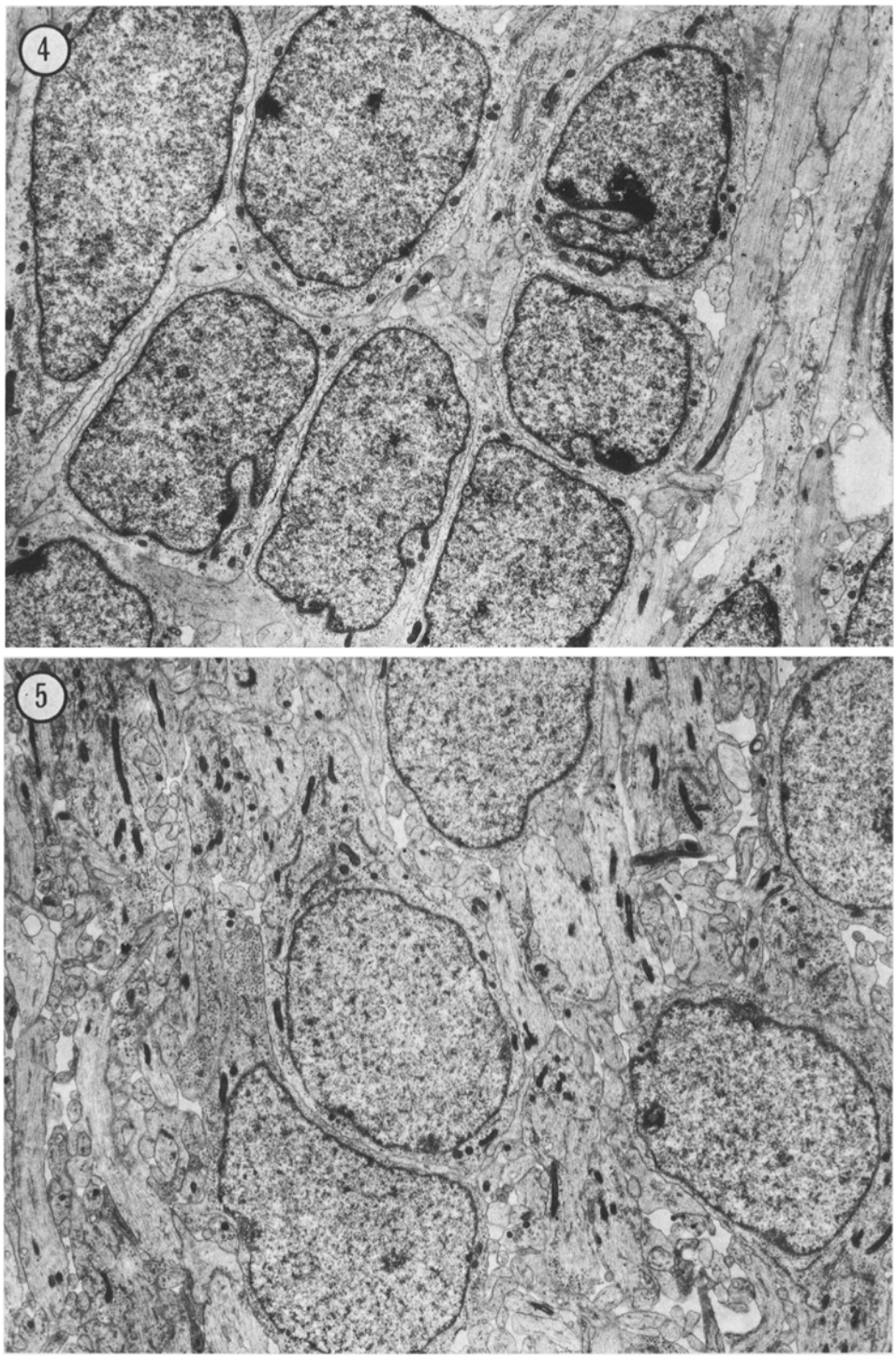


Fig. 4. 12 h postnatal. Tightly-packed, immature neurons of the superficial cortical plate are illustrated. The cells are small and their cytoplasm poorly differentiated. Groups of cells tend to be separated by clusters of radially oriented processes (to right of figure). ×3,800

Fig. 5. Postnatal day 4; superficial cortical plate. The individual neurons, though still immature, display a more voluminous cytoplasm and are spaced further apart by developing neuropil than at birth. ×4,200

By day 14, differences in the state of cytoplasmic maturity between pyramidal and non-pyramidal cells, were less evident than at earlier stages, and both types of neuron displayed an extensive GER, numerous mitochondria, filaments and microtubules, and an extensive Golgi apparatus. By day 14, also, the neurons of the superficial laminae no longer appeared immature by comparison with those of the infragranular layers. It appeared, in general, as though small cells, whatever their laminar position in the cortex, were less well differentiated than larger cells.

Third Postnatal Week

During this period (16, 18, 20 days) both pyramidal cells and non-pyramidal cells achieved maturity – as judged by perikaryal size and cytology – in all cortical layers (Figs. 14 and 15; 16 days; Figs. 16–19; 20 days). Non-pyramidal cells of all sizes displayed a strikingly organelle-rich cytoplasm, and the larger cells, in which nuclei were very commonly eccentrically situated, contained elaborate arrays of GER and a prominent Golgi apparatus (Fig. 17). The smaller cells usually had less and less elaborate GER, but contained a high density of free ribosomes (Figs. 18, 19).

By postnatal day 16 the frequency of axo-somatic contacts (arrows, Figs. 14–19) was high, close to that found in adults. The neuropil too, by the end of the third week, appeared qualitatively indistinguishable from the neuropil of the adult animals. There was, however, one significant difference: the density of synaptic contacts in the neuropil was lower than at 90 and 180 days (Parnavelas et al., in preparation) and this suggests that synaptogenesis proceeds beyond the end of the third postnatal week, a finding that differs from those of Caley and Maxwell (1968) for the developing parietal and visual cortices of the rat.

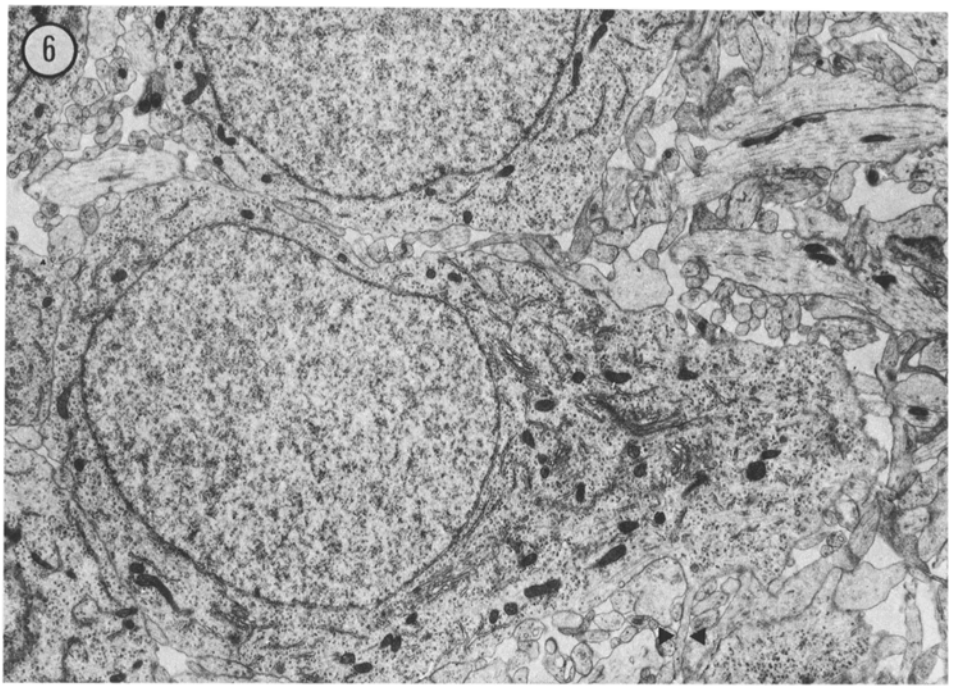
Fourth Postnatal Week

The perikaryal size, ultrastructure and complement of axo-somatic synapses of both pyramidal and non-pyramidal cells (Fig. 20) in all cortical layers were indistinguishable from those of their adult counterparts.

Fig. 6. Postnatal day 4; mid-cortical plate. At this level (presumptive layer IV) neurons are more highly differentiated than in the superficial plate and one of these neurons, with a pale nucleus containing evenly distributed chromatin, and with a broad, organelle-rich apical dendrite (the pial surface is to the right of the figure) can be identified as a developing pyramidal cell. The *arrowheads* indicate a fine lateral branch emerging from the base of the apical dendrite. ×6,030

Fig. 7. Postnatal day 6; layer IV. A pyramidal cell (*P*), small, but with well-differentiated cytoplasm and a pale nucleus, gives rise to an organelle-rich apical dendrite extending towards the pial surface. The small cell lying close by can be identified as a non-pyramidal cell (*NP*). It has an indented nucleus which is more elctron opaque than that of the pyramidal cell, a poorly differentiated, scanty cytoplasm, and receives an axo-somatic synaptic contact of type I (*arrow*). ×6,000

Fig. 8. Postnatal day 6. At this stage in the superficial cortical plate (layer II), there are still closely packed, small immature neurons. A small process extends from one of these cells. ×9,900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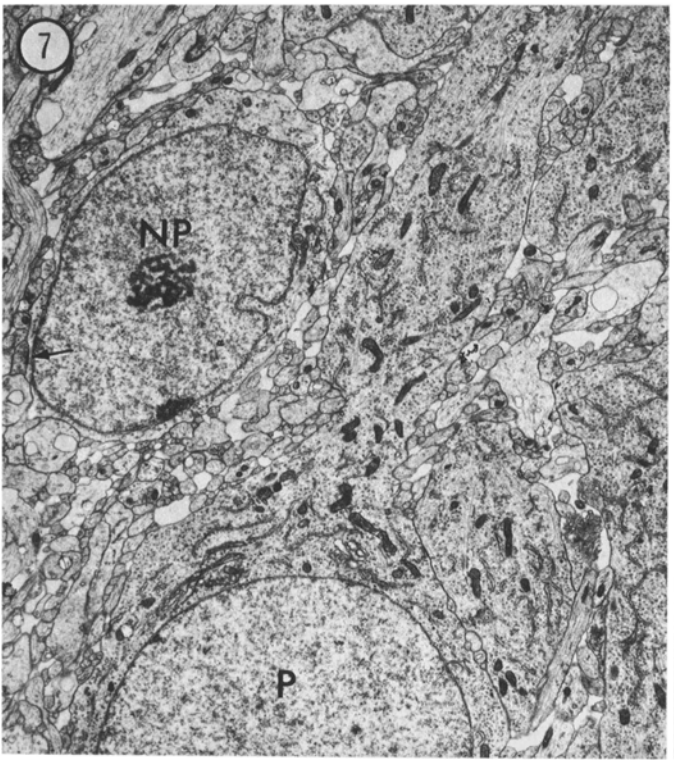
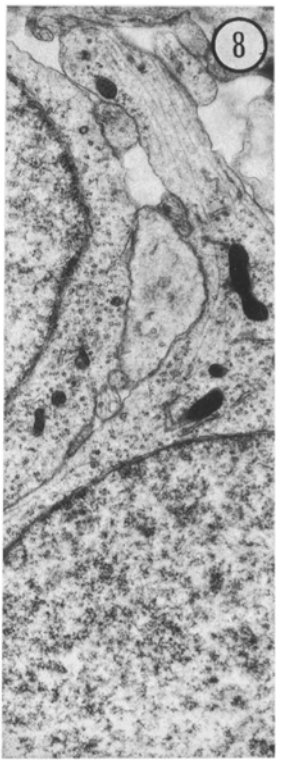

7
NP
P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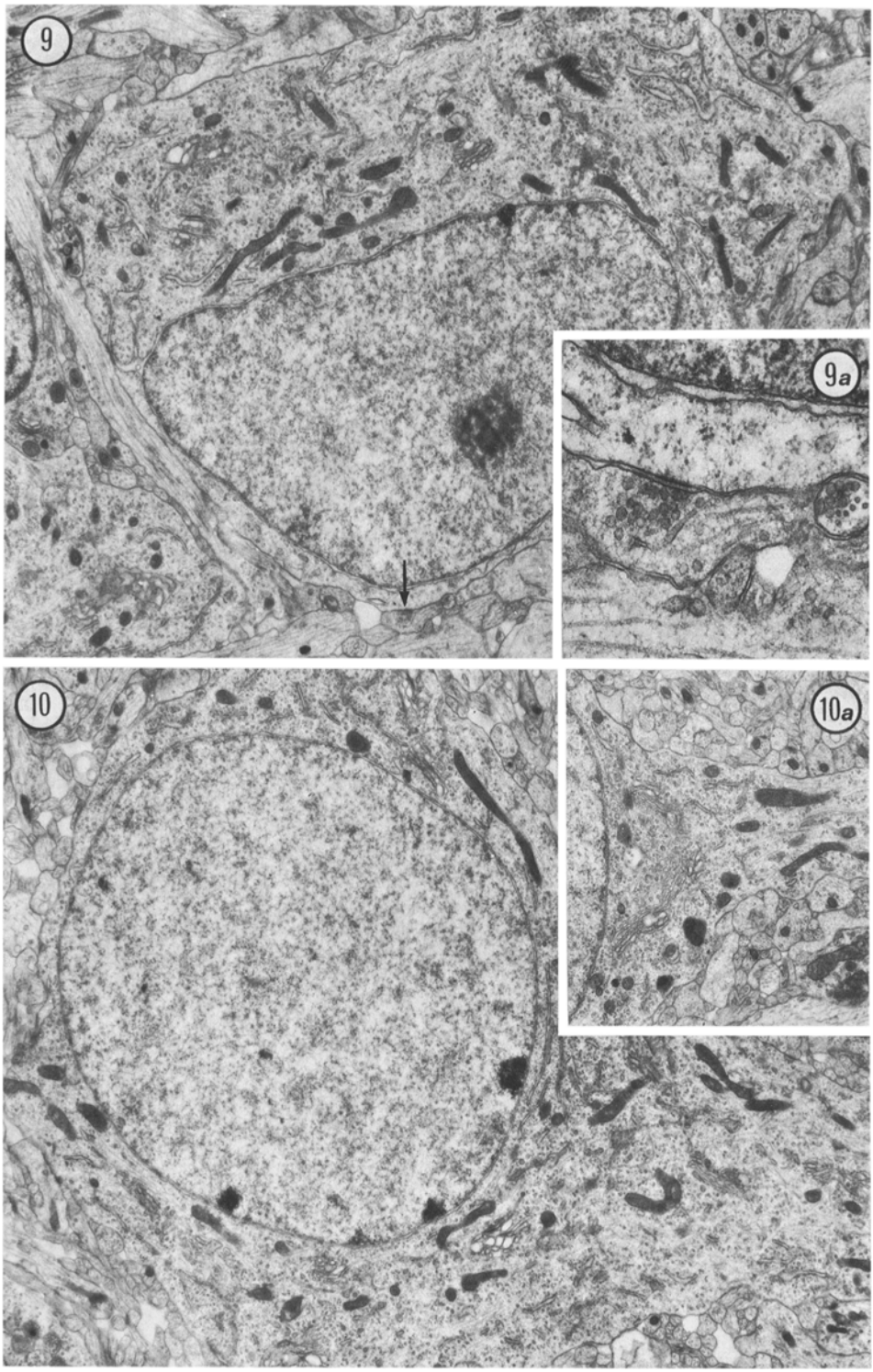
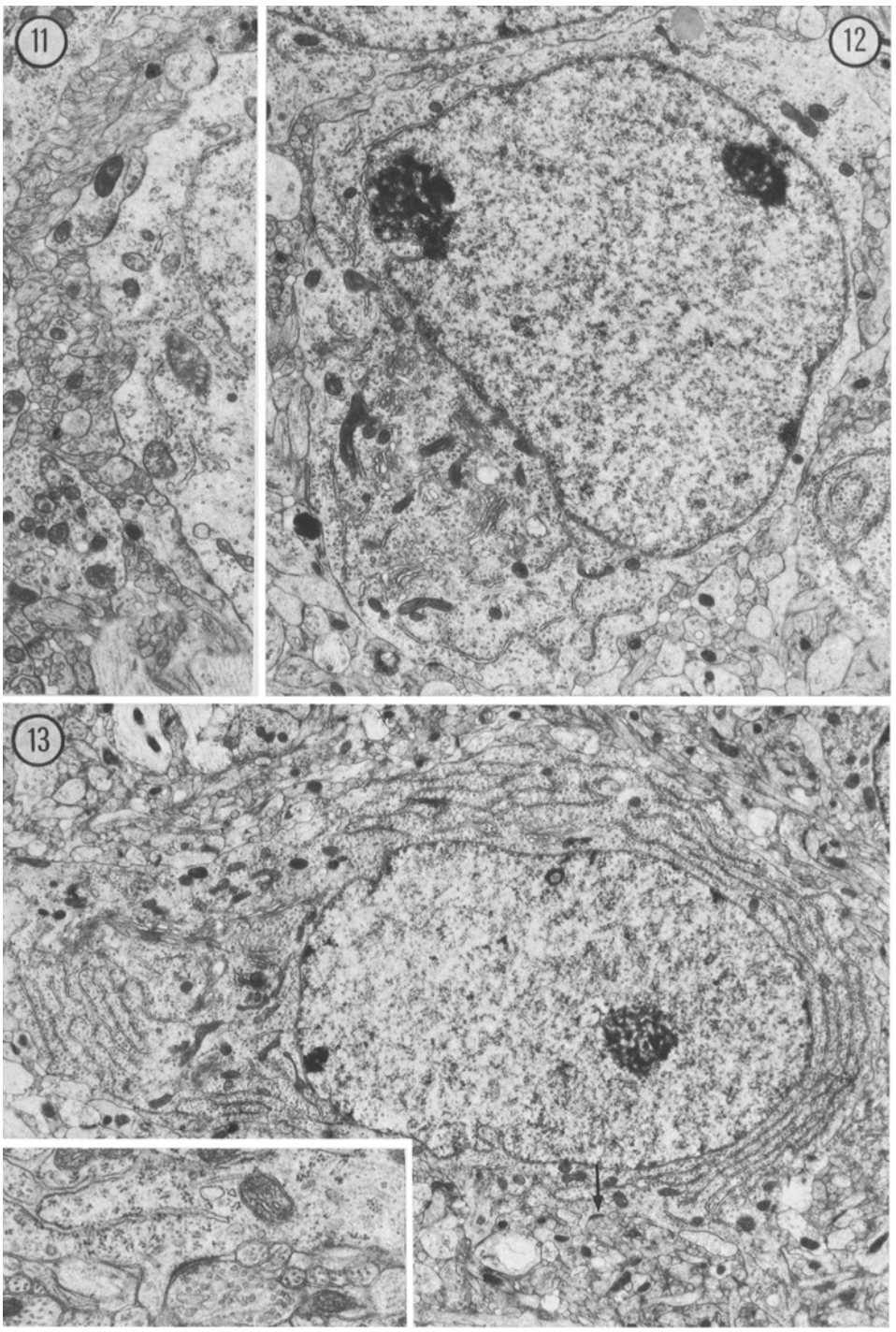


Fig. 9. Postnatal day 6; well-differentiated non-pyramidal cell of layer IV. The *arrow* indicates an axo-somatic synaptic contact of Gray's type 1, enlarged in Fig. 9a. ×8,000, Fig. 9a ×34,000

Fig. 10. Postnatal day 6; large, well-differentiated pyramidal cell in layer V, with its apical dendrite directed towards the cortical surface (to right of figure). ×7,500

Fig. 10a. Postnatal day 8; small pyramidal cell in layer III, with its apical dendrite extending towards the cortical surface (to right of figure). ×10,000



Figs. 11 and 12. Postnatal day 8; non-pyramidal cells in layer IV. Note the concentration of axosomatic synaptic contacts in Fig. 11 and the prominent Golgi zone in Fig. 12. Fig. 11 ×10,300. Fig. 12 ×9,000

Fig. 13. Postnatal day 14; a large non-pyramidal cell in layer II. The long axis of the cell is parallel to the pial surface. Note the prominent nucleolus and the extensive GER. An axosomatic synapse of Gray's type I is arrowed and enlarged in the inset. ×6,300; inset ×22,500

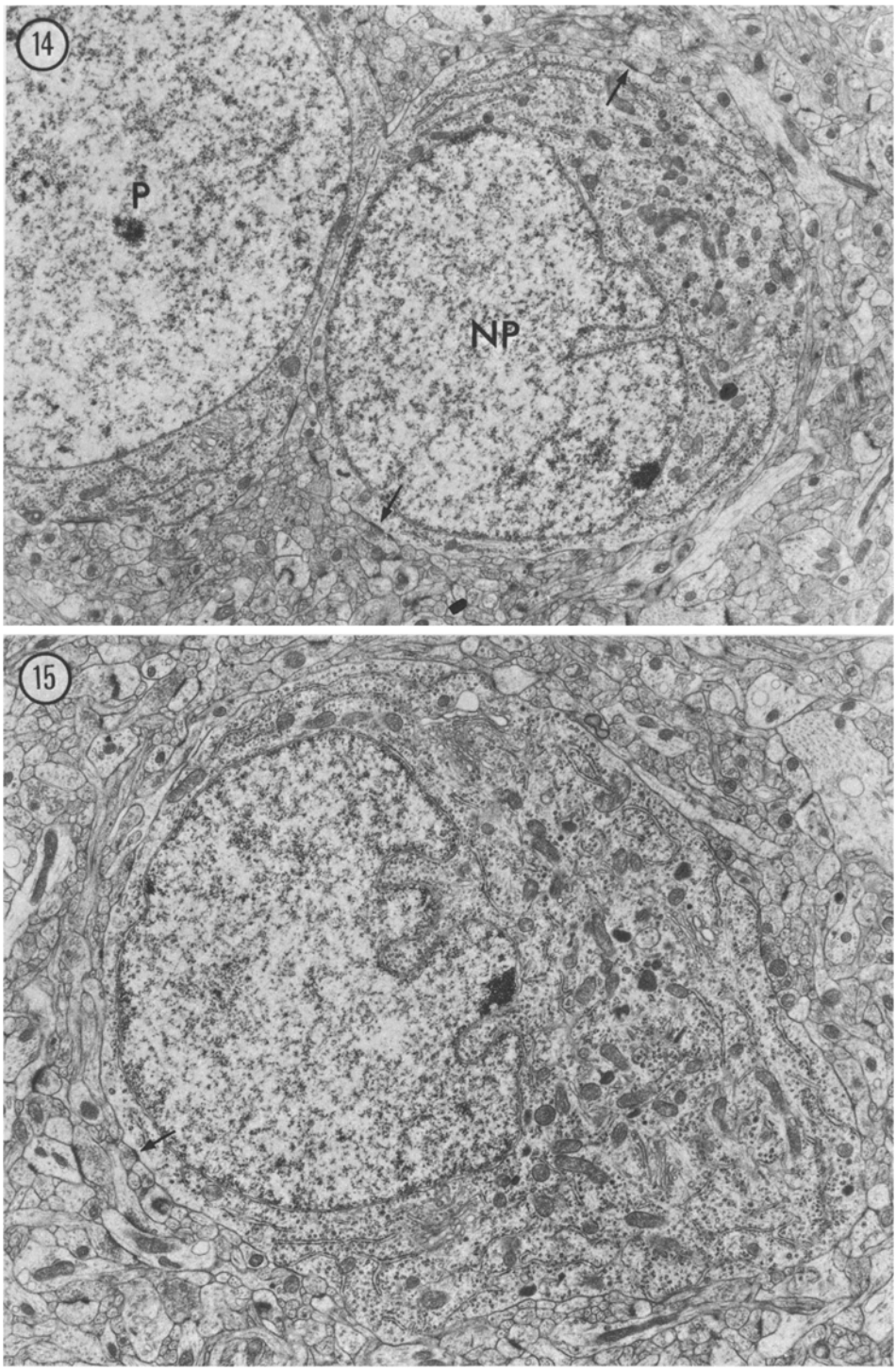
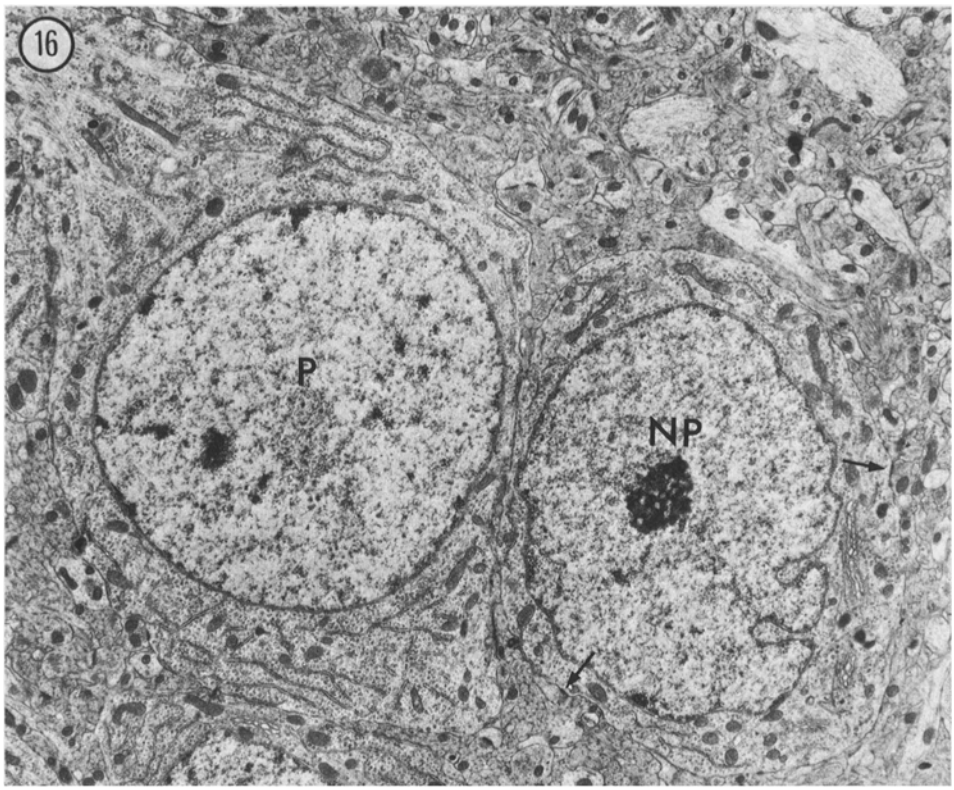


Fig. 14. Postnatal day 16. A non-pyramidal cell (*NP*) lying immediately adjacent to a pyramidal cell (*P*) in layer IV. Note the eccentric, indented nucleus and the organelle-rich cytoplasm of the non-pyramidal cell. Two of many axo-somatic synaptic contacts on this cell are *arrowed.* ×6,600

Fig. 15. Postnatal day 16; non-pyramidal cell of layer V. The nucleus is eccentrically placed in the pear-shaped cell body and infolded opposite the organelle-rich cytocentrum. The *arrow* indicates a Gray type I axo-somatic synaptic contact. ×8,300



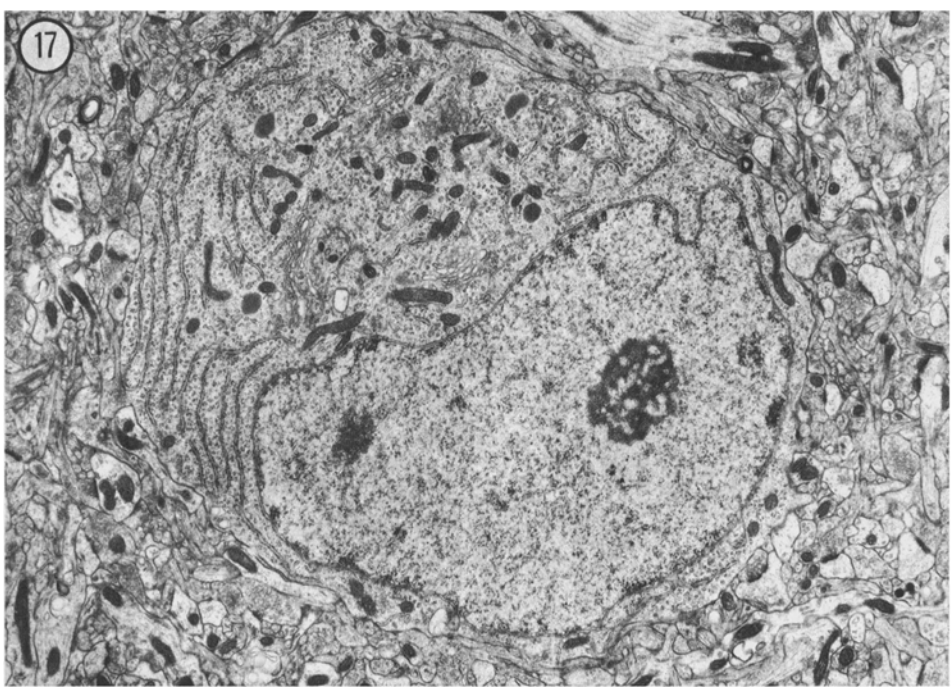
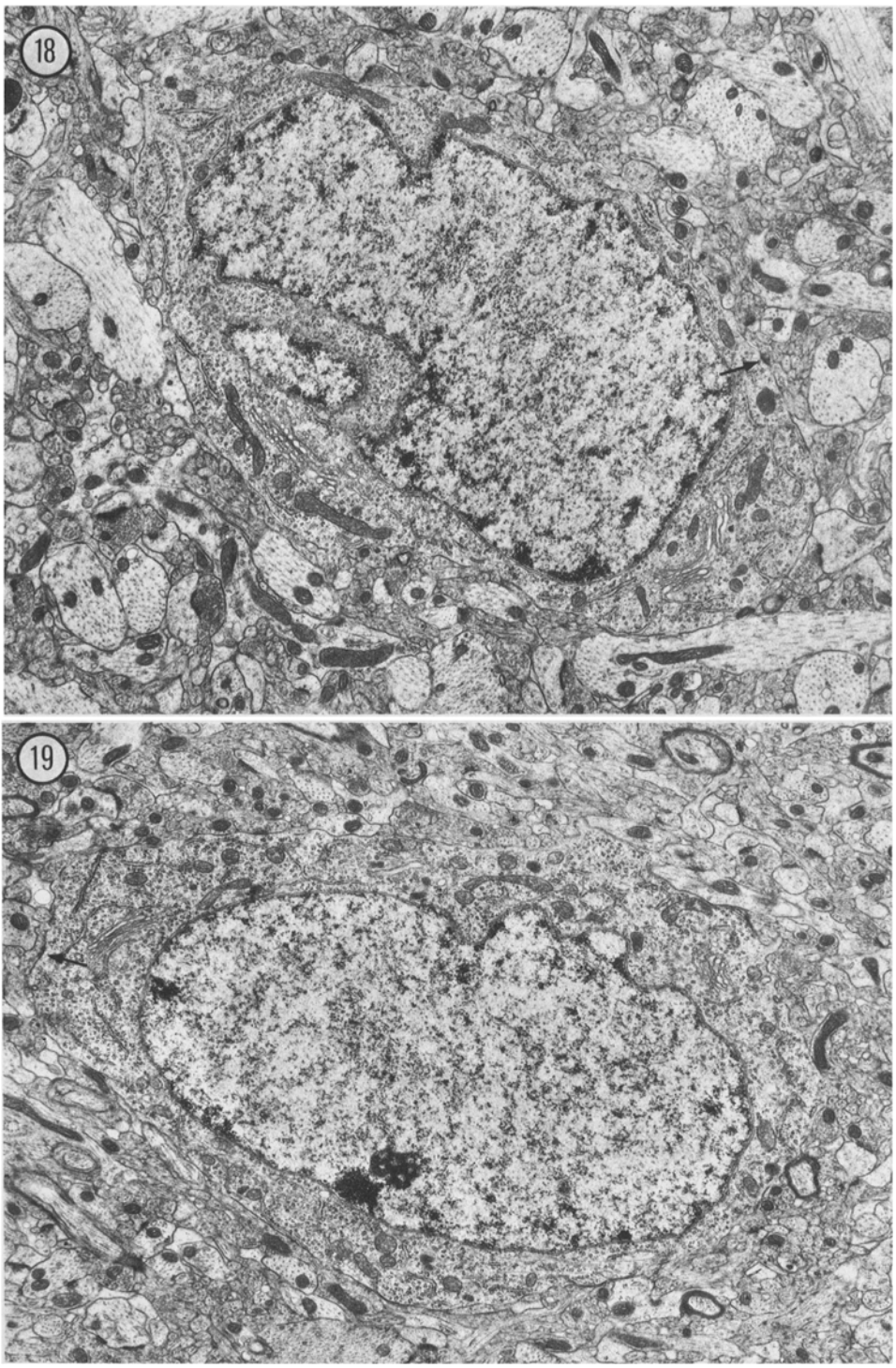


Fig. 16. Postnatal day 20. A small non-pyramidal cell (*NP*) lies immediately adjacent to a small pyramidal cell (*P*) of layer III. Note the mature appearance of the neuropil and of the cytoplasm of both cells. Two type I axo-somatic synaptic contacts onto the non-pyramidal cell are *arrowed*. $\times 7{,}000$

Fig. 17. Postnatal day 20; non-pyramidal cell of layer IV. The cell has an eccentric nucleus, and a prominent nucleolus. Large aggregates of GER and numerous free ribosomes partially surround a prominent Golgi zone. $\times 8{,}300$



Figs. 18 and 19. Postnatal day 20; non-pyramidal cells of similar size and ultrastructural characteristics in layer II (Fig. 18) and layer VI (Fig. 19). Both cells receive axo-somatic Gray type I synapses (*arrows*) and are surrounded by a neuropil of mature appearance. Note the high density of ribosomes in both cells. $\times 9{,}000$

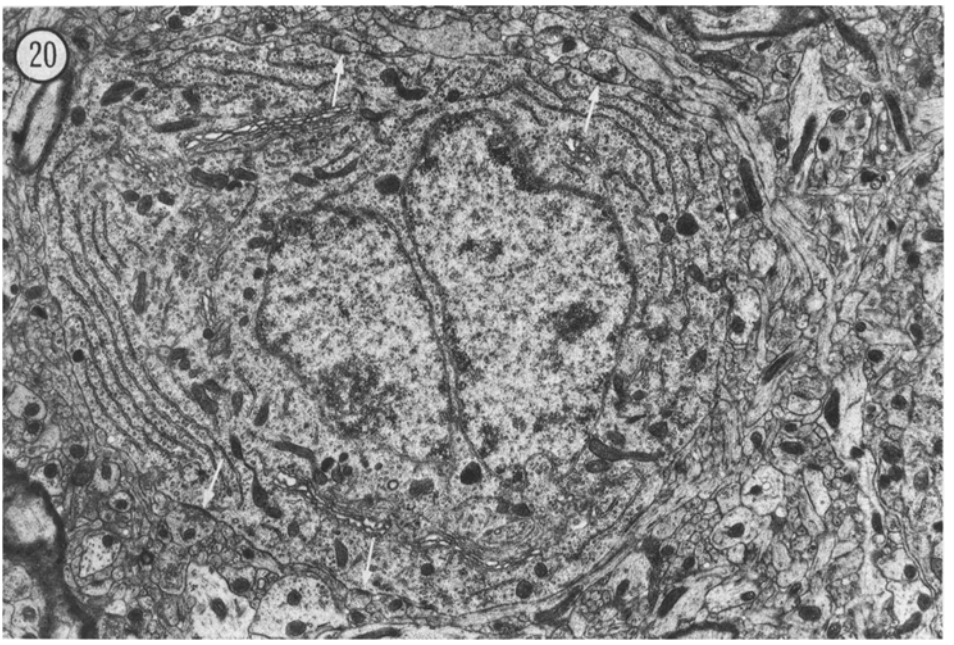


Fig. 20. Postnatal day 24; large non-pyramidal cell of layer IV with rich GER, an extensive perinuclear Golgi apparatus, and several axo-somatic synapses (*arrows*). ×8,300

Discussion

It is widely accepted, that in the development of the cerebral neocortex pyramidal cells of the deep layers are generated earlier, attain their laminar position earlier, and differentiate earlier than the neurons situated more superficially. It also appears to be generally accepted that, with the exception of the Retzius-Cajal cells of layer I (Bradford et al., 1977), non-pyramidal cells mature significantly later than the pyramidal cells with which they are associated. These concepts of cortical histogenesis are based on numerous Golgi studies (e.g. Poliakov, 1961; and see Rakic, 1975) and more recent autoradiographic data (e.g. Berry, 1974; Rakic, 1974, 1975) and are consistent with a more general concept of neuronal development and differentiation, according to which large projection neurons (Golgi type I cells; principal neurons) are generated earlier, differentiate earlier, and have a more rigidly specified form and pattern of connections with other neurons, than the smaller non-projection neurons (Golgi type II cells; interneurons; local circuit neurons) (e.g. Altman, 1967; Morest, 1969; Jacobson, 1974, 1978; Rakic, 1975).

Recent investigations, however, have brought into question the generality of these concepts and some of the specific data on which they are based. Firstly, autoradiographic studies of neocortical development in the rat by Rickmann et al. (1977) have shown that non-pyramidal cells are produced and added to all layers of the developing cortex throughout the period of neurogenesis.

Secondly, systematic Golgi studies in a variety of mammalian species (e.g. Åström, 1967, sheep; Lund et al., 1977, monkey; Parnavelas et al., 1978, rat) demonstrate that, with the exception of the Retzius-Cajal cells of layer I, all cortical neurons reach maturity at approximately the same stage of development, at least in so far as maturity can be judged on the basis of Golgi preparations.

The present study demonstrates that the pattern of maturation seen in the Golgi preparations (Parnavelas et al., 1978) is reflected in the ultrastructural appearance of these same neurons. Non-pyramidal cells, when first clearly recognizable by electron microscopy (towards the end of the first postnatal week), are less well differentiated in terms of their cytoplasmic organelles and the development of their processes than the associated pyramidal cells, particularly the pyramidal cells of the deeper layers. The number of identifiable non-pyramidal cells increases dramatically over the next few days and during the second week the conspicuous gradient of maturation from deep to superficial cortex ceases to be apparent. By the end of the second postnatal week the proportion of identifiable non-pyramidal cells is approximately the same as in the adult. At the end of the second week, which coincides with eye-opening, there is also a conspicuous increase in the amount of GER and other cytoplasmic organelles in these cells, and as judged by the ultrastructural characteristics of their nuclei, perikaryal cytoplasm and processes, the non-pyramidal cells appear to be mature. From the middle of the second postnatal week onwards, there is no apparent difference in maturity (as judged by these features) between the non-pyramidal and the pyramidal cells, and cells of both types achieve their adult appearance at the end of the third week of postnatal life. Thus, if the patterns of connectivity of cortical non-pyramidal cells are in fact more modifiable than those of the pyramidal cells (e.g. Jacobson, 1974), then such plasticity is not readily explained in terms of a substantially greater immaturity of these cells during the period of first exposure to the influences of the environment.

There is, however, a sense in which the present observations are entirely compatible with the suggestion that the early postnatal period is a period of great activity and plasticity in the non-pyramidal cell population. During the period from towards the end of the second postnatal week, through the third postnatal week and into the first part of the fourth week, the non-pyramidal cells, or at least many of the non-pyramidal cells, appeared to have an extremely rich complement of cytoplasmic organelles, in particular GER, ribosomes, and Golgi apparatus. Not only did these cells appear to be more richly endowed with large orderly arrays of GER and other cytoplasmic organelles than their counterparts at earlier developmental stages but they also appeared to be hypertrophic by comparison with non-pyramidal cells in mature animals (although not larger in perikaryal diameter). The presence in many of these cells of eccentric nuclei with prominent nucleoli and a folded nuclear periphery facing into the organelle rich cytocentrum, strengthened the impression that these cells were in a highly active state. These observations require confirmation by quantitative means, but if it is the case that the non-pyramidal cells are in a state of intense synthetic activity – involving especially proteins and glycoproteins – it might well be that this activity is directed towards the provision of materials to terminal

regions of the nerve cell processes in connection with the formation of large numbers of transient and/or permanent synaptic contacts.

Our earlier Golgi studies indicate that this period is not one during which there is conspicuous growth in length or diameter of dendritic shafts. However, during this period a greater proportion of spinous non-pyramidal cells is impregnated than in adult animals and in such cells, the density of dendritic spines – which are major sites for synaptic interaction with other nerve cells – is higher than in the adult. Furthermore, our Golgi studies provided inadequate information on the growth of the axonal processes of non-pyramidal cells, and it may well be that there is rapid growth and synapse formation by the terminal portions of the axon during this important period, which follows eye opening.

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