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Timetables of Neurogenesis in the Human Brain Based on Experimentally Determined Patterns in the Rat

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INTRODUCTION

The first aim of this paper is to link our developmental studies of the rat central nervous system (CNS) to development of the human CNS. A paper similar to this one will appear in another publication for neuropathologists (Bayer et al., in press). Using quantitative [^{3}H]thymidine autoradiography in rats, we have found that one of the most regular features of CNS development is that each neuronal population is generated during a specific temporal window, what we call *timetables of neurogenesis*. By linking the morphological appearances of human and rat embryos or fetuses at several different developmental stages, this paper shows how rat neurogenetic timetables can be extrapolated to human neurogenetic timetables. The time of origin of all major neuronal populations in the CNS will be summarized here in a tabular form that links them to the probable times of origin in man. It is our hope that these timetables will be a reference for neurotoxicologists and pediatric neurologists dealing with developmental abnormalities in the human CNS. In addition to time of origin studies, much of our [^{3}H]thymidine autoradiographic work deals with cell migration. Because the regularity of neurogenesis sets the stage for coordinated events between different neuronal populations such as neuronal migration, axonogenesis, dendrogenesis and synaptogenesis, we will briefly summarize the times and trajectories of migratory pathways and the initiation of axonal and dendritic growth for the neuronal populations that we have studied up to this time.

The second aim of this paper is to derive some basic principles of neuroanatomical development at the tissue and cellular levels that have been empirically established in rats and probably occur in man. There is growing evidence that the germinal source of neurons is as heterogeneous as their offspring and forms a spatiotemporal mosaic. It can truly be said that neurogenesis occurs in a "chronoarchitectonic" pattern. A series of diagrams will be used to illustrate what we mean by mosaicism in the germinal zones. Finally, the chronology of neurogenesis in two related neuronal populations often correlates with the anatomical connections between them (Bayer and Altman, 1987a). In this chapter, a brief summary of that generalization will be presented using the anatomical connections between the substantia nigra and the striatum as an example.

The third aim of this paper is to deal with the effects of insulting agents (genetic or environmental) that interfere with the normal pattern of development. Insults that occur during neurogenesis result in hypoplasia, a permanent reduction of the normal number of neurons. Insults that affect cell migration often result in ectopia, the abnormal settling of neurons in inappropriate locations. Finally, insults that occur during axonogenesis, dendrogenesis, and synaptogenesis result in dysplasia, characterized by neurons with aberrantly shaped dendrites and axons that often make inappropriate synaptic contacts.

METHODS USED TO LINK HUMAN AND RAT BRAIN DEVELOPMENT

From the early 1960's, our goal was to use the rat as an animal model for the study of human brain development. Here we present a systematic procedure to correlate developmental patterns in the rat central nervous system to those in the human central nervous system.

Statement of the Problem: Gross Differences in the Developmental Time Span Between Rats and Men

Human gestation lasts for approximately 40 weeks (280 days), while the rat gestational period is slightly over three weeks (22-23 days). Rat pups are born more than two weeks before the eyelids open and at a time when neurogenesis of the granule cell populations in the olfactory bulb, hippocampus, and cerebellum is just beginning. Most neurons are generated by the time of weaning (21 postnatal days). In contrast, the human infant is born with the eyelids open and after the bulk of the granular neurons in the cerebellum have been generated. Even if we consider the first three weeks of postnatal life in rats as comparable to middle and late prenatal periods in humans, the rat brain is approaching the appearance of the adult within approximately 6 weeks after fertilization, while the human brain takes nearly 7 times longer to reach the same maturational state. Thus we must make a distinction between absolute chronological age of the developing brain (in terms of days or weeks after fertilization) and relative developmental age (in terms of the time of appearance of specific structural features).

In experimental animals, embryonic age can be exactly determined because the day of fertilization is known. But in human developmental research, the day of fertilization can only be estimated. That has led researchers to rely on the staging method to determine human embryonic age. In the staging method, age is linked to gross morphological development, such as closure of the neural tube, growth of the forelimb bud, etc. With staging, age can at best be narrowed down to a range of days rather than to a specific day. Once most external morphological features have appeared, the embryonic stage is considered to be over and the fetal period begins. The staging method is not used during the fetal period, and age is given in weeks. In order to be consistent throughout the entire prenatal span of human development, we will refer to human ages in weeks and to rat ages in either embryonic (E) or postnatal (P) days.

Strategy Used to Link Development in Rats and Men

Figure 1 diagrams the series of methods that were used. The starting point was the neurogenetic timetables that had been determined in rats using long-survival [^{3}H]thymidine autoradiography (Bayer and Altman, 1974, 1987a, 1991a). Because those data provided the times when specific populations of neurons would be generated in the embryonic brain, single [^{3}H]thymidine injections could be given during the peak times of neurogenesis in selected populations to heavily label the young neurons. By killing the embryos at successive intervals after the injection (short- and sequential-survival) the identities of migrating neurons and early settling neurons could be determined along with the time course of migration. Both methods of [^{3}H]thymidine autoradiography were systematically used from E12 through E21 in rats to produce the large body of data represented by the two top boxes in Figure 1.

The next step was to match rat brain and human brain development (third box from top, Fig. 1). We did not have access to histological material from normal human embryos and fetuses, so we relied on the photographs in several monographs of human brain development (Hochstetter, 1919; Bartelmez and Dekaban, 1962; Larroche, 1966; O'Rahilly and Müller, 1987; Volpe, 1987) to provide an overview of the morphological changes taking place. Taken together, these monographs offer clear evidence that the appearance of the developing human brain closely resembles the developing rat brain, especially during the early stages. We relied most heavily on Hochstetter's (1919) monograph because it considers the longest time span, from crown-rump lengths of 3-5 mm (Stages 12-13) to 102-104 mm (early fetal period). One part of Hochstetter's monograph provides detailed drawings of the entire human brain which we could match with three-dimensional computer reconstructions of the rat forebrain. Another part of Hochstetter's monograph features low-magnification photographs of coronal sections of the same embryos that were drawn at the gross level. These sections could be matched with embryonic rat brain sections. The monograph of Bartelmez and Dekaban (1962) was also helpful because it describes human brains (both at the gross anatomical and the histological levels) from stages 11 to 22. The recent work of O'Rahilly and Müller (1987) was consulted regarding the very early stages (1 to 18) of human development. But none of these monographs dealt with the human brain during the middle and late fetal stages. Those stages in man correspond to postnatal ages in rats and increasing divergence between the two species is apparent. For example, the tremendous expansion of the human cerebral cortex is characterized by an increasing fissurization. Developmental progression during the fetal period can be grossly correlated with the appearance of gyri in the cerebral hemispheres (Dooling *et al.*, 1983). But these regular features in developing human brains could not be used for age-matching with rats because the rat cortex is smooth (lissencephalic). In order to make developmental age matches between man and rat during these later periods,

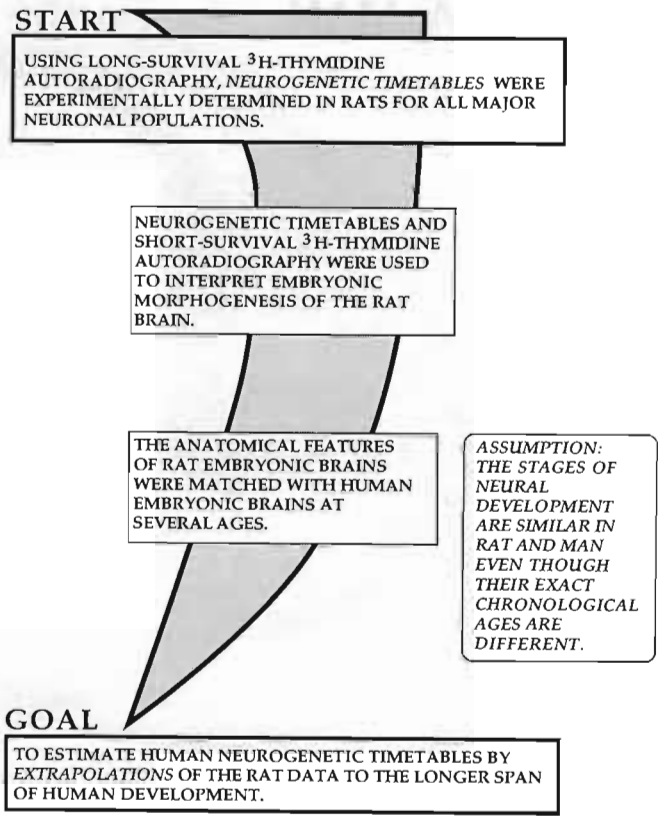


FIG. 1 A diagram of the methods (top three square corner rectangles) that were used to arrive at the determination of human neurogenetic timetables from experimental data gathered in the rat (bottom rectangle). The shaded curved shape in the background represents the "pathway" from one set of data to another. The round-cornered rectangle states the major assumption made during the matching procedure. (From Bayer *et al.*, in press.)

we used similarities in development of the cerebellar cortex and relied mainly on the accounts of Larroche (1966) and Volpe (1987).

In the first part of this article, we match developing human and rat brains at 10 different ages (from rat E11/human week 3.5 to rat E21/human weeks 15-16). Our assumption is that the developmental ages of human and rat embryos or fetuses are comparable when major gross anatomical features and histological landmarks in brain sections are similar in appearance in the two species even though their exact chronological ages are different. Although both gross appearance and histological appearance had to be similar before a developmental age match was made between rat and man, the matches must be considered as approximate rather than exact.

Once we were able to match several different age groups using the procedures described above, correlational time lines for the two species could be established. The neurogenetic timetables determined in the rat were then extrapolated to the approximate times for generation of these same neuronal populations in man (bottom rectangle, Fig. 1). Given the similarities in both the gross appearance and the histological appearance of the brains of man and rat across successive stages of development, it seems valid to assume that the patterns of cell migration

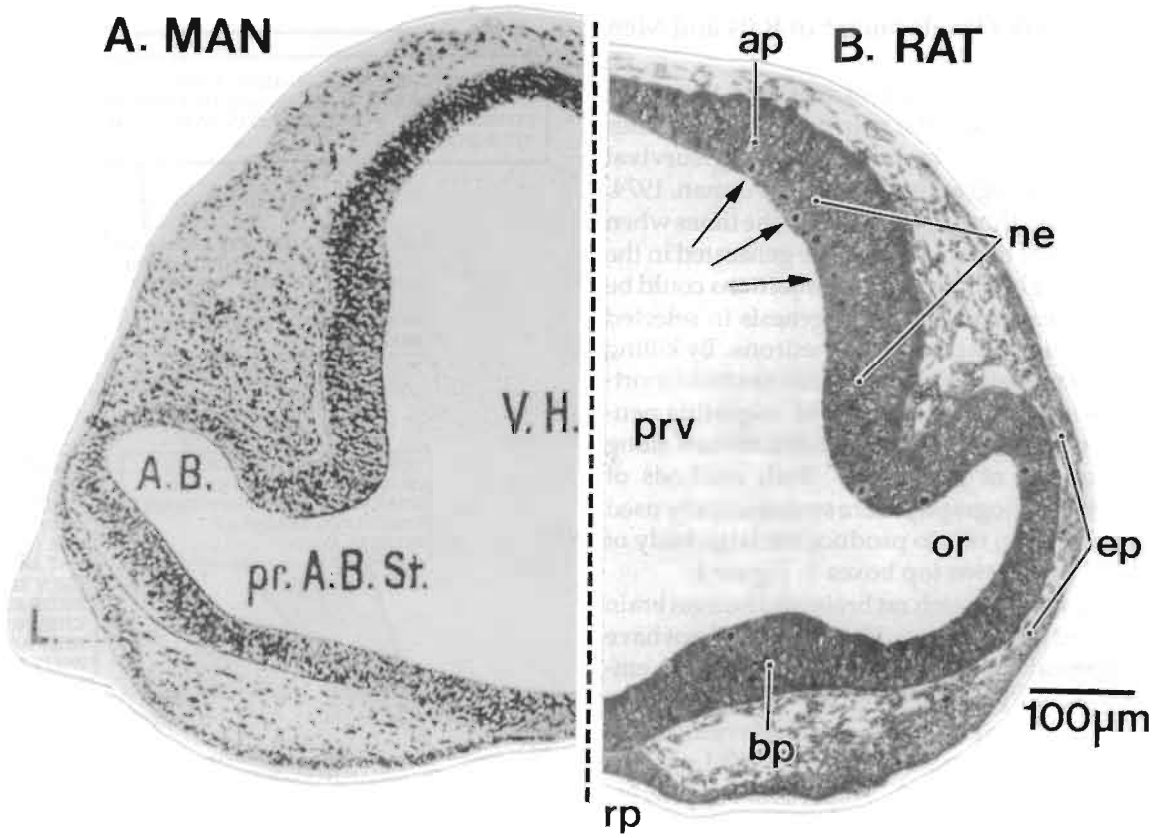


FIG. 2 A. Figure 1 in Plate 10 in Hochstetter (1919). A coronal section of the forebrain and the eye primordium of a 4.84 mm human embryo. Abbreviations: A.B., eye vesicle; L., lens primordium; pr.A.B.St., primordial eye stalk; V.H., forebrain.

FIG. 2 B. The rat forebrain on E11 at a cross-sectional level corresponding to the human embryo in A. Arrows indicate the site where the telencephalic vesicle will evaginate. Abbreviations: ap, alar plate; bp, basal plate; ep, eye primordium; ne, neuroepithelium; or, optic recess; prv, prosencephalic ventricle; rp, Rathke's pouch. (From Bayer *et al.*, in press.)

are similar in the two species. Consequently, the approximate times of cell migration in man were also estimated from our studies in the rat.

MATCHING HUMAN AND RAT BRAIN SECTIONS

The sections from several plates of Hochstetter's (1919) monograph were photographed from an original copy and are reproduced along with photographs of rat brain sections from E11 to E20 (Figs. 2-10).

From 3.5 to 7 Weeks in Man (Rat: E11 to E15)

Shortly after the anterior neuropore and the neural tube closes, frontal sections of a 4.84 mm crown-rump length human forebrain (stages 11-12, 3.5-4 weeks; Fig. 2A) can be nearly superimposed on frontal sections of the rat forebrain on E11.5 (Fig. 2B). In both species, the brain is composed of a large ventricle surrounded by a layer of actively proliferating cells, the neuroepithelium (ne, Fig. 2B). The neuroepithelium will give rise to neurons and glia in the central nervous system and the retina of the eye. At this very early stage in brain development, none of the forebrain neurons have been produced because cells have not yet accumulated outside the neuroepithelium. The shape of the early brain, which forecasts the pattern of future growth, is a result of evaginations and invaginations of the neuroepithelium itself. For example, the eye primordium (ep, Fig. 2B) is due to increased growth in the neuroepithelium of the ventrolateral prosencephalon around the optic recess (or, Fig. 2B), and later on, increased growth in the neuroepithelium of the dorsolateral prosencephalon (arrows, Fig 2B) will signal evagination of the telencephalic vesicles.

Approximately 7-9 days later, the human embryo has grown to a crown rump length of 6.0 mm (Stage 14, approximately 4-5.2 weeks, Fig. 3A) and can be matched with a late E12 rat embryo (E12.5, Fig. 3B). Sections at the level of the eye primordium in the human forebrain shows that its upper part grows over the lens (L., Fig. 3A) in the same way as it does in the E12.5 rat (Fig. 3B). There are other similarities in the two species. The growth of the brain, especially in the dorsal direction, is due to the proliferating cells remaining in the neuroepithelium as they surround the expanding ventricle. The dorsolateral part of the neuroepithelium in rats (arrows, Fig. 3B) is ballooning

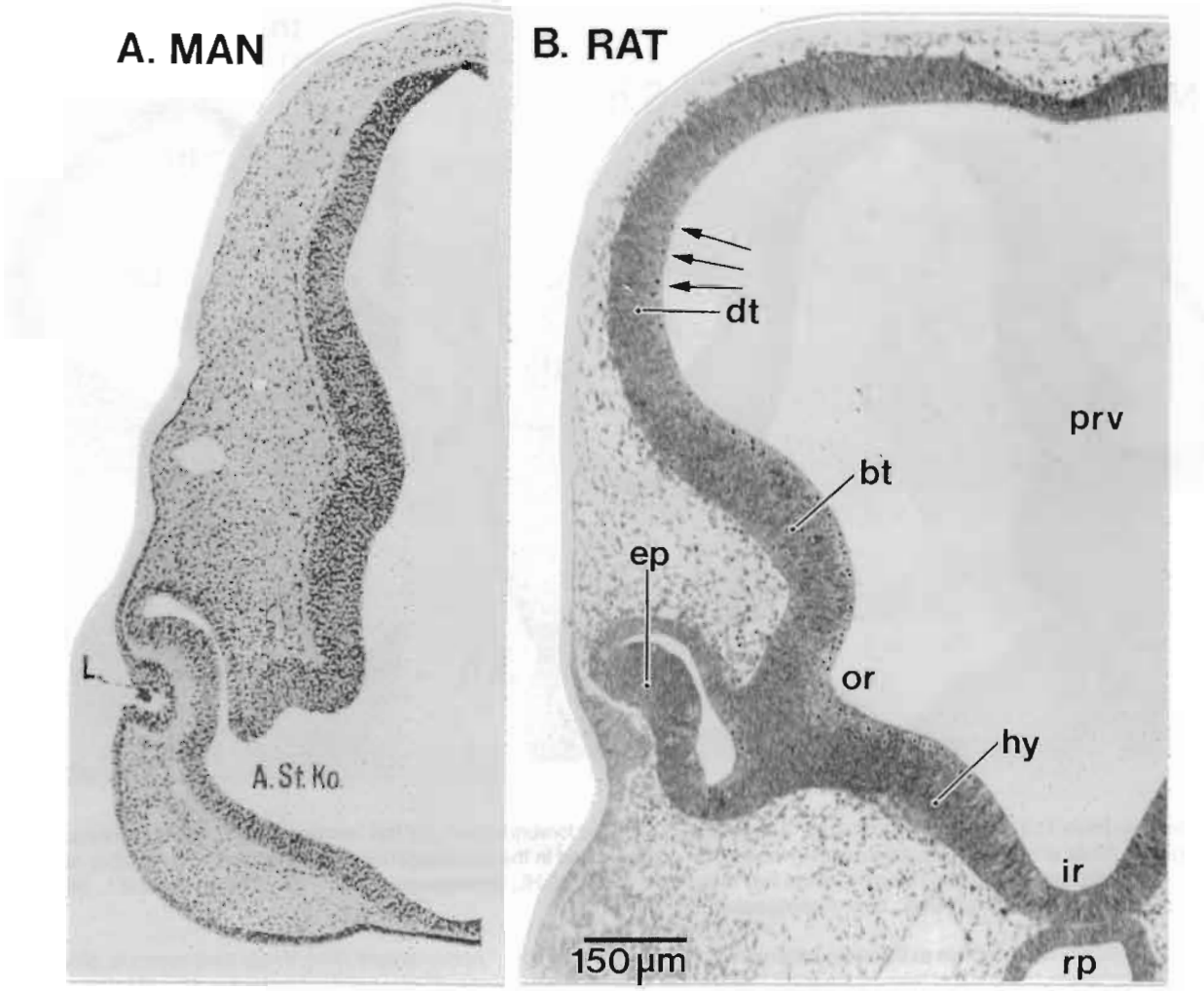


FIG. 3 A. Figure 6 in Plate 10 from Hochstetter (1919). Coronal section through the forebrain and the eye primordium of a 6.0 mm human embryo. Abbreviations: A.St.Ko., cone of the primordial eye stalk; L., lens primordium.

FIG. 3 B. Coronal section of the forebrain at the eye primordium in a rat embryo on E12. Arrows represent the probable sites of expansion of the telencephalic vesicle. Abbreviations: bt, neuroepithelium of the basal telencephalon; dt, neuroepithelium of the dorsal telencephalon; ep, eye primordium; hy, neuroepithelium of the hypothalamus; ir, infundibular recess; or, optic recess; prv, prosencephalic ventricle; rp, Rathke's pouch. (From Bayer *et al.*, in press.)

outward to form the telencephalic vesicles.

After another 7-9 days, the human embryo has grown to a crown rump length of 14.8 mm (Stage 18, approximately 5.8-6.6 weeks, Fig. 4A) and can be matched with an E14 rat embryo (Fig. 4B). Both human and rat brains show the dorsolateral expansion of the telencephalic vesicles around the paired lateral ventricles (LV, Fig. 4B). That evagination better defines the vertically aligned third ventricle (3V) that is surrounded by the diencephalon, the thalamus above and the hypothalamus below (th, hy, Fig. 4B). Within the telencephalon, the dorsomedial position of the hippocampus (Hi., hi) above the anlage of the choroid plexus (A.Ch.) is the same in man and rat. In both species, lightly-staining young neurons have begun to accumulate in the basal telencephalon (BT, Fig. 4B) outside of the basal telencephalic neuroepithelium (bt, Fig. 4B) indicating that neurogenesis is already in progress in some populations (to be discussed in Section 4). Also in both man and rat, young neurons are accumulating outside of the neuroepithelium in the basal hypothalamus.

After another 3-4 days, the human embryo has grown to a crown rump length of 17.0 mm (Stages 18-19, approximately 6.7-7 weeks) and its brain (Fig. 5A) can be matched with that of an E15 rat embryo (Fig. 5B). There is continuing dorsolateral expansion of the paired telencephalic vesicles from the vertically aligned diencephalon in the midline. This is best shown by the ventricular system, where the lateral ventricles branch off from the third ventricle (3V,d, 3V,v, and LV, Fig. 5B). In both species, the neuroepithelium of the basal ganglia (bg, Fig. 5B) is a prominent feature in the floor of the lateral ventricle, and some of its oldest neuronal progeny have accumulated outside it (BG, Fig. 5B) These pile up above the even older neurons in the basal telencephalon (not labeled). In contrast, the future cerebral cortex is less advanced, and contains mainly a thick neuroepithelium (cc, Fig. 5B).

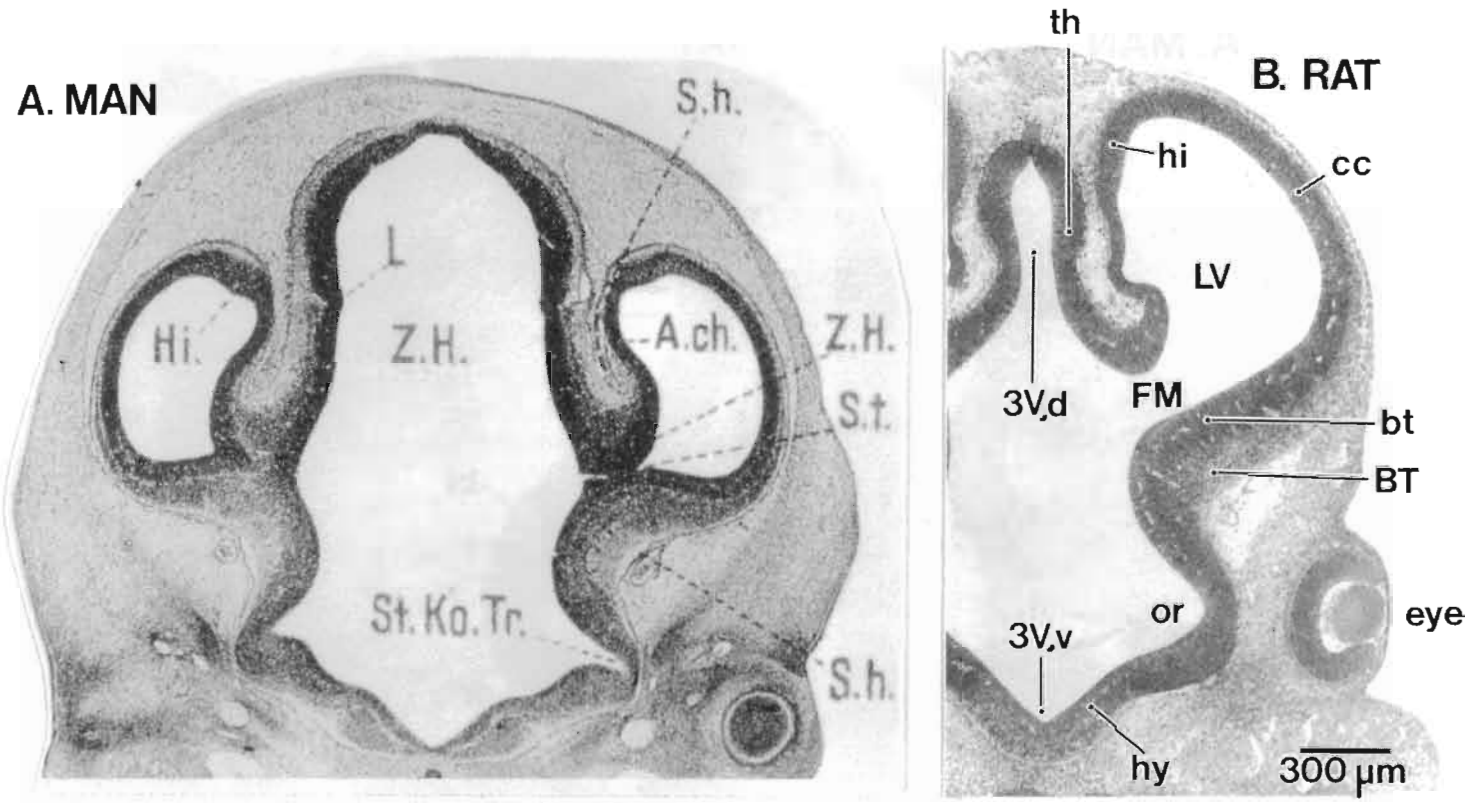


FIG. 4 A. Figure 27 in Plate 11 from Hochstetter (1919). A coronal section of the forebrain in a 14.8 mm human embryo. Abbreviations: (For this and all following Figures, those abbreviations marked with ? were either not explained in the figure legends or were given untranslatable names.) A.Ch., chorioid area; L., (? protuberance dividing two parts of the wall of the third ventricle); Hi., hippocampus; S.h., hemispheric sulcus; S.t., posterior border of the foramen of Monro; St.Ko.Tr., eye stalk; Z.H., diencephalon.

FIG. 4 B. Coronal section of the forebrain at the optic evagination in a rat embryo on E14. Abbreviations: 3Vd, dorsal third ventricle; 3Vv, ventral third ventricle; bt, neuroepithelium of the basal telencephalon; BT, basal telencephalon; cc, neuroepithelium of the cerebral cortex; FM, foramen of Monro; hi, neuroepithelium of the hippocampus; hy, neuroepithelium of the hypothalamus; LV, lateral ventricle; or, optic recess; th, neuroepithelium of the thalamus. (From Bayer *et al.*, in press.)

Some of the differences between the human and rat brains shown in Figure 5 are artifactual. The human brain has been cut so that the top of the section is more posterior than the bottom. The top passes through the most posterior part of the cerebral hemispheres, causing them to appear smaller than the cerebral hemispheres in the rat, which are cut more anteriorly. In more anterior human brain sections, the telencephalic vesicles are much larger. The human brain section cuts the hypothalamus at the level of the optic stalk (St.Ko.Tr., Fig. 5A) and the thalamus in the region where the sensory relay nuclei will develop (d.c.A., Fig. 5A); the rat brain section cuts the hypothalamus behind the optic recess and cuts the thalamus more anteriorly. The hypothalamus appears similar in both man and rat when the basal parts of other sections are matched.

However at stages 18-19, the thalamic neuroepithelium shows some differences between man and rat that can only be explained by species variation, not by the angle of sectioning. The enlarged region in the human thalamus (d.c.A., Fig. 5A) is not found in sections of the rat thalamus. Since the thalamus and neocortex are closely linked, it is not surprising that the neuroepithelium of the human thalamus should be larger than it is in the rat thalamus in relation to the tremendous enlargement of the human neocortex.

From 7 to 15 Weeks in Man (Rat: E16 to E20)

During the early part of the 7th week after fertilization the human embryo has reached a crown rump length of 18-22 mm and is at stage 20 (Lemire *et al.*, 1975). Hochstetter illustrates an embryo with a crown-rump length of 18.4 mm and one of the sections from the level of the foramen of Monro is reproduced in Figure 6A. That can be matched with a coronal section of an E16 rat embryo (Fig. 6B). In both species, the developing cerebral cortex shows several similarities. The most dominant cell layer is the cortical neuroepithelium (cc, Fig. 6B), but the ventrolateral part of the cortex has two additional layers, the intermediate zone and the cortical plate. The intermediate zone (iz, Fig. 6B) contains young neurons that have just moved out of the neuroepithelium, and the cortical plate (cp, Fig. 6B) is a thin layer of young cortical neurons just beneath the pial membrane. These features are present in the human brain (Fig. 6A) but are not labeled by Hochstetter (1919). However, the cortical expanse in man is now much larger than it is in

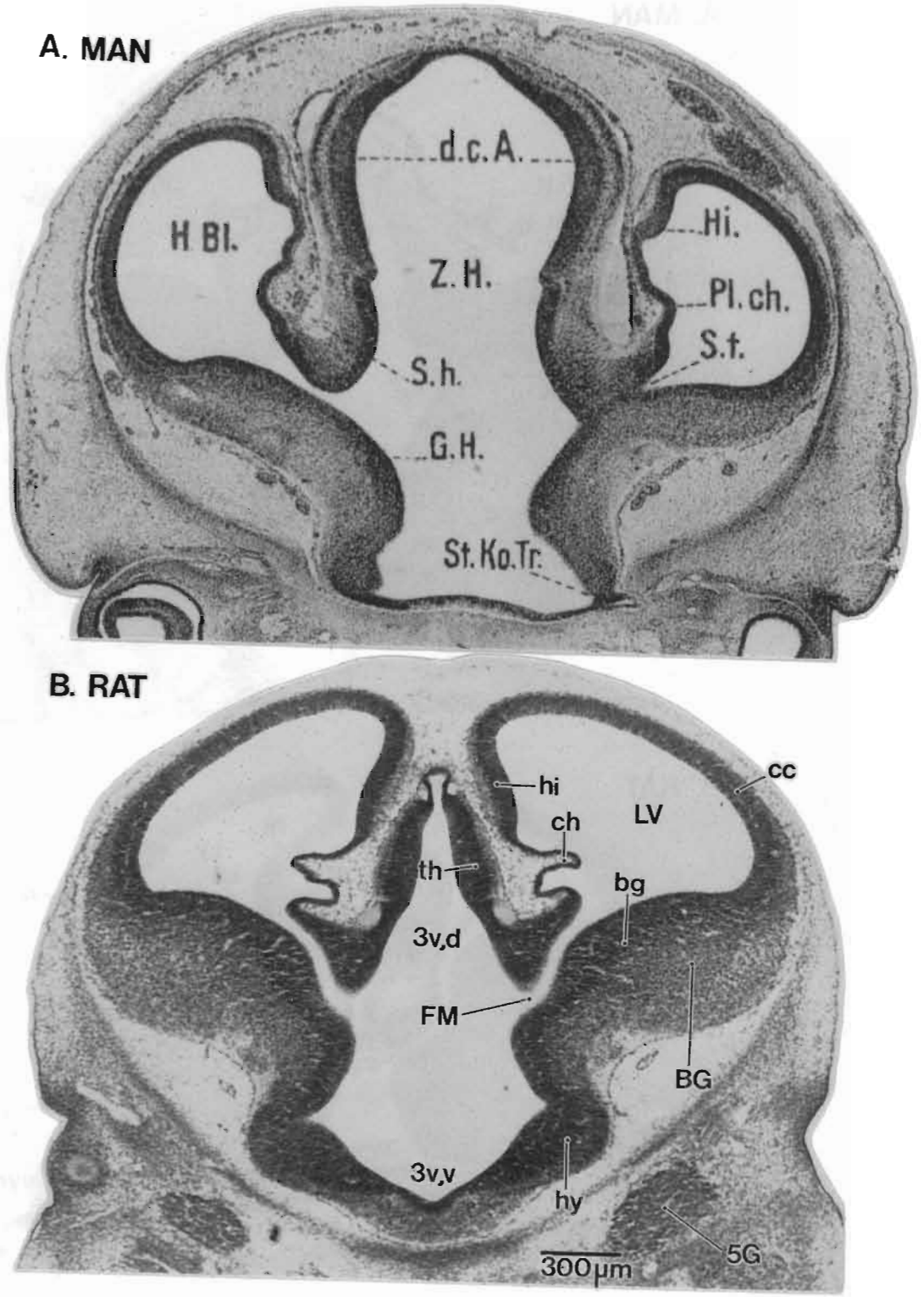


FIG. 5 A. Figure 34 in Plate XII from Hochstetter (1919). Coronal section through the forebrain 17.0 mm human embryo. Abbreviations: d.c.A., dorsocaudal expansion of the diencephalon; G.H., ganglionic eminence; H.Bl., hemispheric vesicle; Hi, hippocampus; Pl.ch., choroid plexus; S.h., hemispheric sulcus; S.t., posterior border of the Foramen of Monro; St.Ko.Tr., eye stalk; Z.H., diencephalon.

FIG. 5 B. Coronal section of the forebrain at the level of the Foramen of Monro (FM) in a rat embryo on E15. Abbreviations: 3V,d, dorsal third ventricle; 3V,v, ventral third ventricle; 5G, trigeminal ganglion; bg, basal ganglia neuroepithelium; BG, basal ganglia; cc, neocortical neuroepithelium; ch, primordium of the choroid plexus; hi, hippocampal neuroepithelium; hy, hypothalamic neuroepithelium; LV, lateral ventricle; th, thalamic neuroepithelium. (From Bayer *et al.*, in press.)

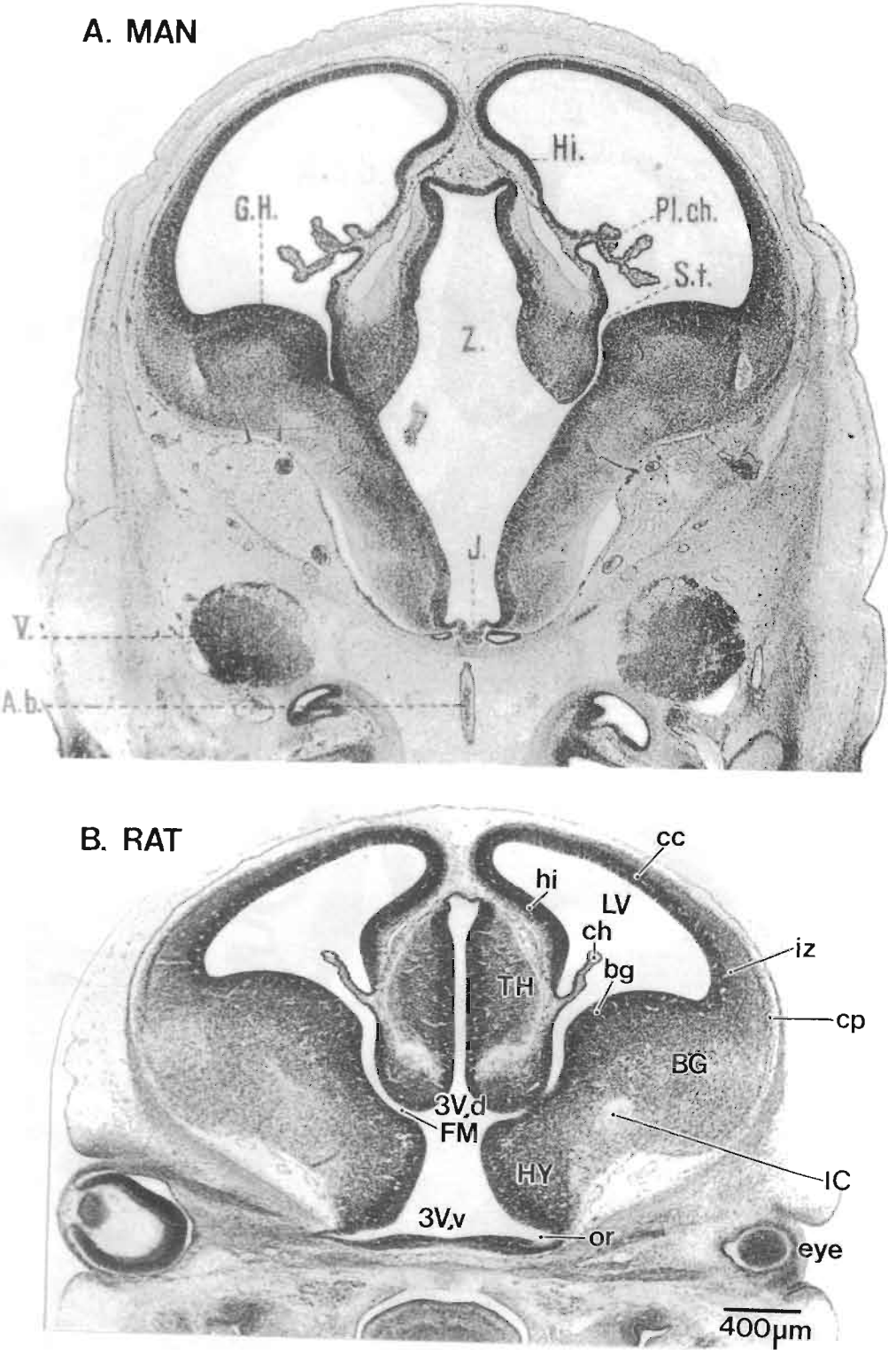


FIG. 6 A. Figure 50 in Plate XIV from Hochstetter (1919). Coronal section through the diencephalon and cerebral hemispheres from an 18.4 mm human embryo. Abbreviations: A.b., basilar artery; G.H., ganglionic eminence; Hi., hippocampus; J., infundibulum; Pl.ch., choroid plexus; S.t., (? posterior border of the foramen of Monro); Z., diencephalon; V., trigeminal ganglion.

FIG. 6 B. Coronal section of the forebrain at the level of the foramen of Monro (FM) in a rat brain on E16. Abbreviations: 3V,d, dorsal third ventricle; 3V,v, ventral third ventricle; bg, basal ganglia neuroepithelium; BG, basal ganglia; ch, choroid plexus; cp, cortical plate; hi, hippocampal neuroepithelium; HY, hypothalamus; IC, internal capsule; iz, intermediate zone; LV, lateral ventricle; cc, neocortical neuroepithelium; or, optic recess; TH, thalamus. (From Bayer *et al.*, in press.)

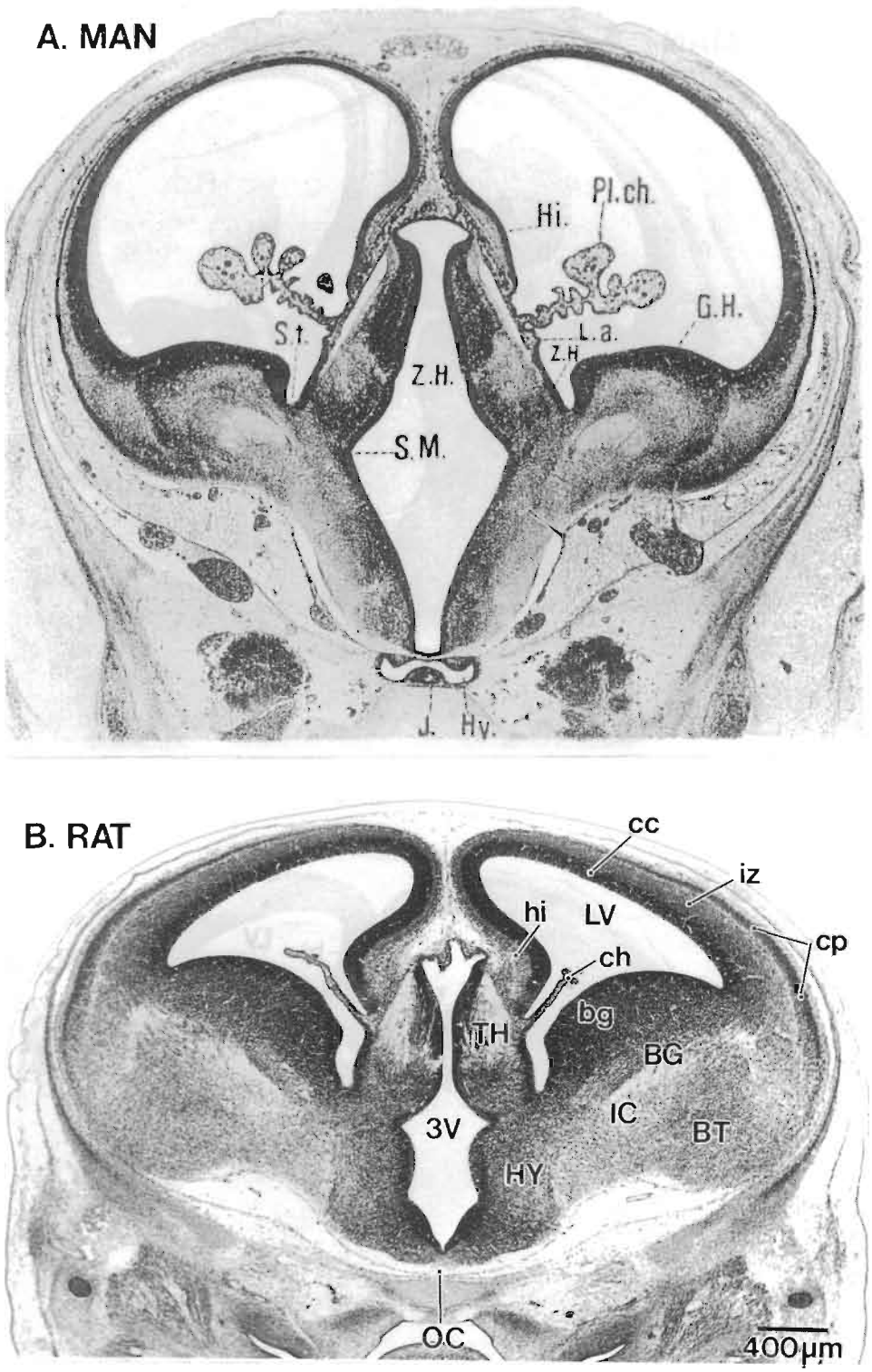


FIG. 7 A. Figure 62 in Plate XVII from Hochstetter (1919). Coronal section through the cerebral hemispheres and diencephalon of a 25.10 mm human embryo. Abbreviations: G.H., ganglionic eminence; Hi, hippocampus; Hy., hypophysis; J. (I), infundibulum; L.a., lamina affixa; Pl.ch., choroid plexus; S.M., sulcus Monroi, and S.t., sulcus terminalis form the posterior border of the foramen of Monro; Z.H., diencephalon.

FIG. 7 B. Coronal section of the forebrain just posterior to the foramen of Monro in a rat brain on E17. Abbreviations: 3V, third ventricle; bg, basal ganglia germinal matrix; BG, basal ganglia; BT, basal telencephalon; ch, choroid plexus; cc, neocortical neuropeithelium; cp, cortical plate; hi, hippocampal primordium; HY, hypothalamus; IC, internal capsule; iz, intermediate zone; LV, lateral ventricle; OC, optic chiasma; TH, thalamus. (From Bayer *et al.*, in press.)

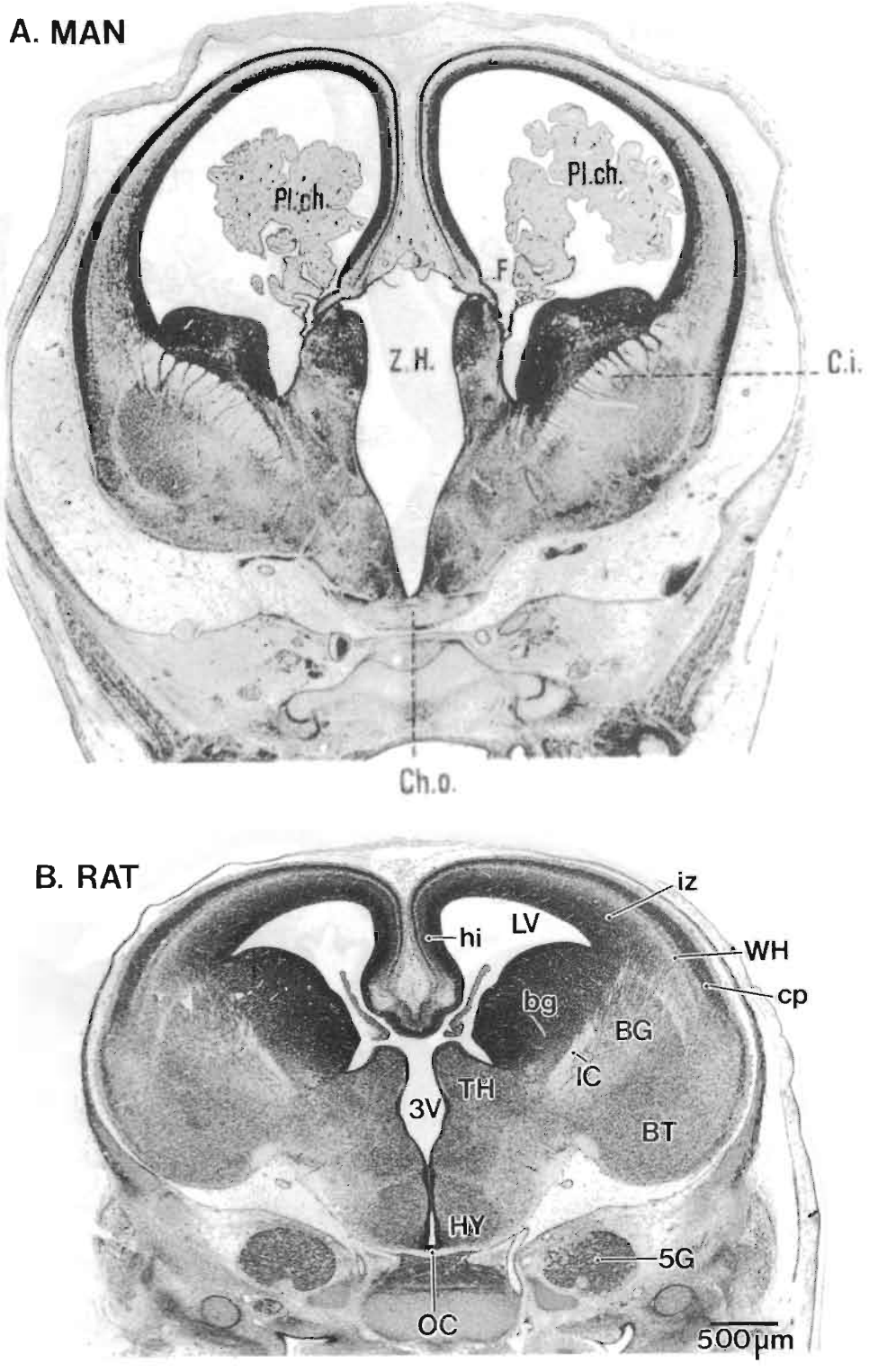


FIG. 8 A. Figure 78 in Plate XX from Hochstetter (1919). A coronal section through the hemispheric vesicles and diencephalon of a 46.5 mm human embryo. Abbreviations: Ch.o., optic chiasma; C.i., internal capsule; F., fornix; Pl.ch., choroid plexus; Z.H., diencephalon.

FIG. 8 B. Coronal section of the rat forebrain on E18. Abbreviations: 3V, third ventricle; 5G, trigeminal ganglion; bg, basal ganglia neuroepithelium; BG, basal ganglia; BT, basal telencephalon; cp, cortical plate; hi, hippocampus; HY, hypothalamus; IC, internal capsule; iz, intermediate zone of the cerebral cortex; LV, lateral ventricle; TH, thalamus; WH, white matter of cerebral cortex. (From Bayer *et al.*, in press.)

the rat, mainly due to the increased length of the neuroepithelium around the larger lateral ventricles. The choroid plexus (Pl.ch., Fig. 6A; ch, Fig. 6B) is also larger in man than in the rat. The most dominant structure in the floor of the telencephalon in both species is the basal ganglia (G.H., Fig 6A; bg, BG, Fig. 6B). Its germinal matrix is very thick, and many young neurons have accumulated outside of it since the previous stage. The diencephalon also shows some similarities in the two species. At the junction between the diencephalon and telencephalon, the internal capsule is beginning to emerge in both man (not labeled in Fig. 6A) and rat (IC, Fig. 6B). However, there are variations in the diencephalic structures found in sections of the two species because the sectioning angles of the human and rat brain are different. In man, the bottom of the section is behind the eye, at the trigeminal ganglion (V., Fig. 6A), while the rat section is at the level of the eye. Other human and rat brain sections can be matched to show similar structures at the base of the brain. The dorsal part of the human brain section cuts through the anterior thalamic pimordium, while the dorsal part of the rat brain section is farther back in the thalamus (TH, Fig. 6B). The difference in size between the dorsal thalamus in man (larger) and in rat (smaller) that was noted in Figure 5 also holds for this age match.

By the latter half of the 7th week after fertilization, the human embryo is between 23-28 mm crown-rump length, and is at stage 22 (Lemire *et al.*, 1975). The coronal section through the forebrain of a 25.1 mm human embryo (Fig. 7A) matches the E17 rat forebrain (Fig. 7B). The similarities seen in the cerebral cortex in both species at stage 20 (Fig. 6) persist at stage 22. The cortical neuroepithelium (cc, Fig. 7B) is still prominent, but both the intermediate zone (iz, Fig. 7B) and the cortical plate (cp, Fig. 7B) have considerably thickened. The human cortical neuroepithelium and choroid plexus are larger than those in rats. In both species, the floor of the telencephalon is greatly enlarged (G.H., Fig. 7A) as a result of the accumulations of three major groups of cells: (1) young neurons in the basal telencephalon (BT, Fig. 7B), (2) young neurons in the basal ganglia (BG, Fig. 7B), and (3) a thick basal ganglia germinal matrix (bg, Fig. 7B). The internal capsule (IC, Fig. 7B) has expanded in both species. The stria medullaris is the fiber bundle that is prominent in the thalamus (TH, Fig. 7B), while there are dorsal and ventral accumulations of young neurons in the hypothalamus (HY, Fig. 7B). Just as it was noted at stage 20 (Fig. 6) the ventricles continue to shrink during this period, especially in the diencephalon.

During the 8th to 9th weeks after fertilization, the human embryo is between 30-55 mm crown-rump length. That is just the beginning of the fetal period (Lemire *et al.*, 1975) and is no longer given a stage number. A coronal section through the forebrain of a 46.5 mm human embryo (Fig. 8A) matches quite closely the E18 rat forebrain (Fig. 8B). The similarities seen between the cerebral hemispheres in the two species at stage 22 are still evident. Both man and rat have a thicker cortical plate (cp, Fig. 8B) that now extends all the way to the hippocampus in the medial wall. The cortical intermediate zone (iz, Fig. 8B) is now quite thick in both man and rat and the deep white matter of the cortex (WH, Fig. 8B) is appearing in its superficial part as the fibers of the internal capsule are penetrating the ventrolateral part of the developing cortex in large numbers. The basal ganglia (bg, BG, Fig. 8B) and basal telencephalon (BT, Fig. 8B) dominate the floor of the lateral ventricle in both species. In both species, the diencephalon shows similar accumulations of young neurons in the developing nuclei of the hypothalamus (HY, Fig. 8B) and thalamus (TH, Fig. 8B). The shape of the human brain beneath the cerebral cortex is beginning to be dictated by growth of the accumulating neurons rather than by structural changes in the neuroepithelium or the ventricles. In rats, the shrinkage of both the lateral and third ventricles is more advanced.

During the 10th and 11th weeks after fertilization, the human embryo is between 60-80 mm crown-rump length, and is in the early fetal period (Lemire *et al.*, 1975). The coronal section through the forebrain of a 73 mm human embryo (Fig. 9A) is matched with the E19 rat forebrain (Fig. 9B). The structure of the cerebral cortex (CC, Fig. 9B) is similar in the two species, in spite of their size differences. The cortical plate (cp, Fig. 9B) continues to thicken, the intermediate zone (iz, Fig. 9B) is large, and the white matter (WH, Fig. 9B) is more prominent. The cortical neuroepithelium (cc, Fig. 9B) is becoming thinner in both man and rat. In both species the basal ganglia are penetrated by the fibers of the internal capsule (IC, Fig 9B) but these fibers are more numerous in man in correlation with the larger cerebral cortex. The brain sections in man and rat contain several fiber tracts in similar positions. Compare the positions of the anterior commissure (Co.a., Fig. 9A, AC, Fig. 9B), the columns of the fornix (C.F., Fig. 9A), the hippocampal commissure (HC, Fig. 9B), the optic nerve (N.o., Fig. 9A), and the optic chiasma (OC, Fig. 9B) in the two species. The third ventricle (3V, Fig. 9B) is now quite small in both man and rat. The lateral ventricle is continuing to shrink in rats (LV, Fig. 9B) but remains prominent in man.

During the 12th to 14th weeks after fertilization, the human embryo is approximately between 90-140 mm crown-rump length and is in the middle fetal period (Lemire *et al.*, 1975). A coronal section through the forebrain of a 87 mm human embryo that is approaching the middle fetal period is shown in Figure 10A. That section is matched with the E20 rat forebrain (Fig. 10B). The similarities noted between the two species on E19 (Fig. 9) are also present on E20. The cortical neuroepithelium (cc, Fig. 10B) continues to become thinner in both man and rat, while the intermediate zone (iz, Fig. 10B) and the white matter (WH, Fig. 10B) have thickened. Even in man, the lateral ventricles are now beginning to shrink, but the choroid plexus is still very extensive. There are many similarities in the structure of the basal ganglia in the two species, except for the larger size of the human internal capsule compared to the rat (IC, Fig. 10B). The hypothalamus (HY, Fig. 10B) appears similar in the two species.

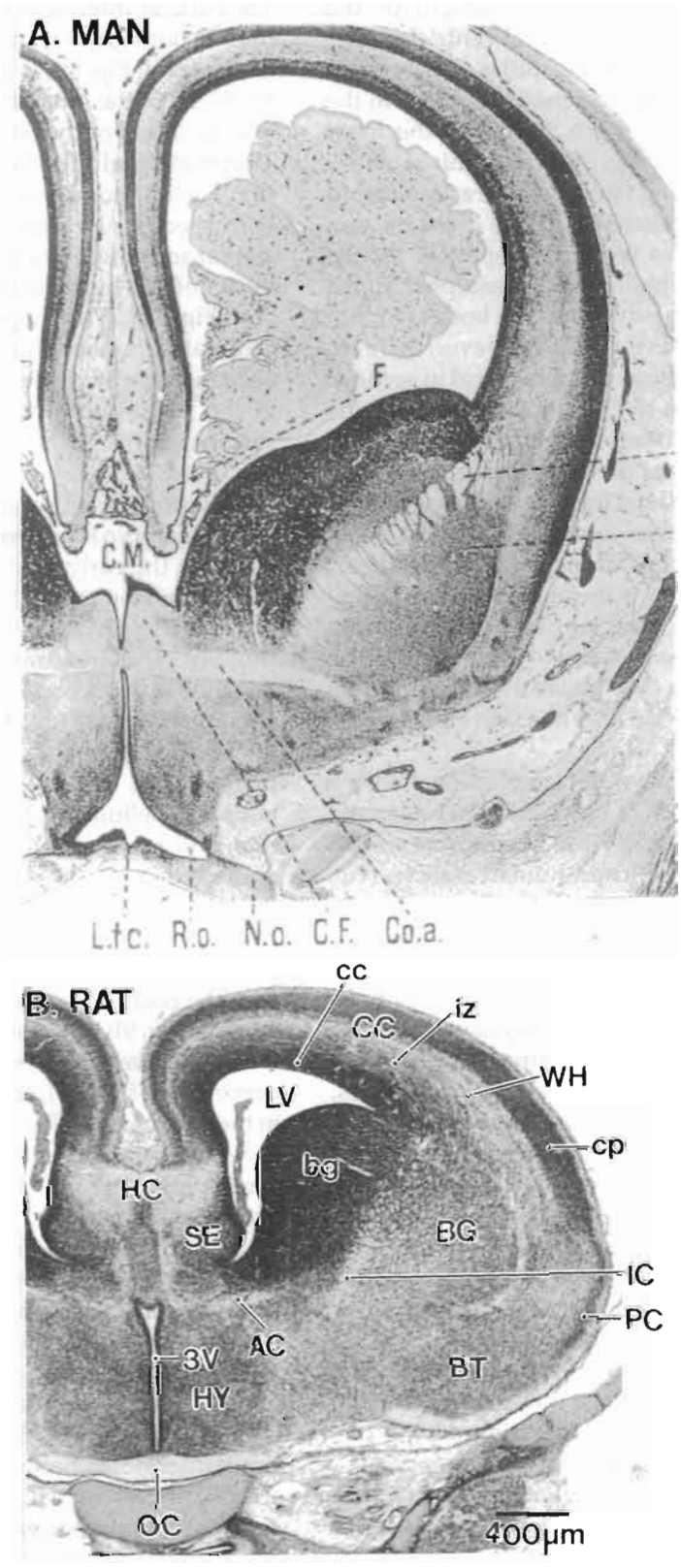


FIG. 9 A. Figure 86 in Plate XXI from Hochstetter (1919). Coronal section through the frontal hemisphere of a 73.0 mm human embryo. Abbreviations: C.F., column of the fornix; C.M., foramen of Monro; Co.a., anterior commissure; F., fornix; L.t.c., lamina terminalis cinerea; N.o., optic nerve; R.o., optic recess.

FIG. 9 B. Coronal section of the rat forebrain on E19. Abbreviations: 3V, third ventricle; AC, anterior commissure; bg, basal ganglia neuroepithelium; BG, basal ganglia; BT, basal telencephalon; cc, cerebral cortical neuroepithelium; CC, cerebral cortex; cp, cortical plate; HC, hippocampal commissure; HY, hypothalamus; IC, internal capsule; iz, intermediate zone; LV, lateral ventricle; OC, optic chiasma; PC, piriform cortex; SE, septum; WH, white matter of cerebral cortex. (From Bayer *et al.*, in press.)

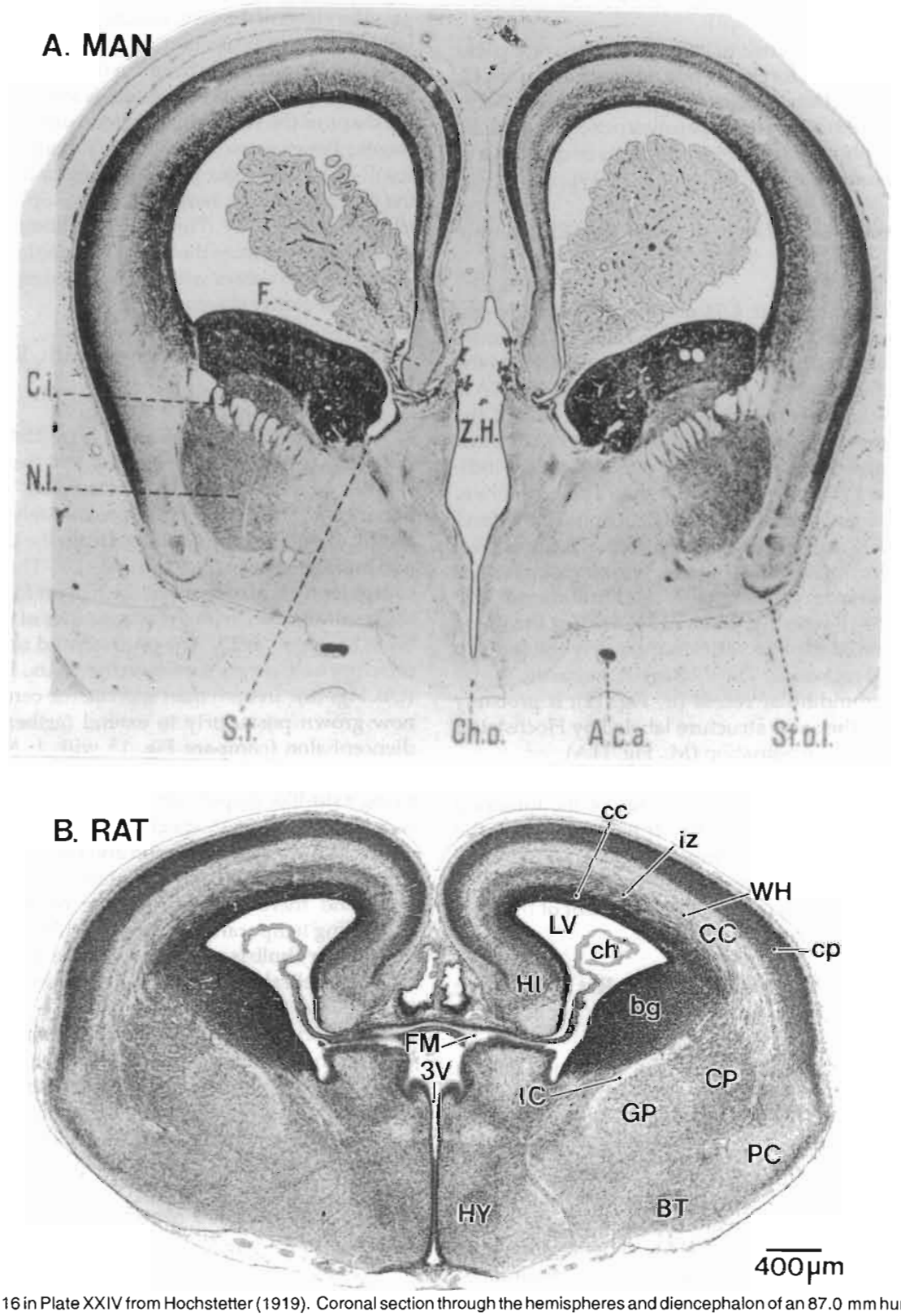


FIG. 10 A. Figure 116 in Plate XXIV from Hochstetter (1919). Coronal section through the hemispheres and diencephalon of an 87.0 mm human embryo. Abbreviations: A.c.a., anterior cerebral artery; Ch.o., optic chiasma; C.i., internal capsule; F., fornix; N.l., (lentiform nucleus?); S.t., (stria terminalis?); St.o.l., lateral olfactory stria; Z.H. diencephalon.

FIG. 10 B. Coronal section of the rat forebrain on E20. Abbreviations: 3V, third ventricle; bg, basal ganglia neuroepithelium; BT, basal telencephalon; cc, germinal matrix of the cerebral cortex (including the neuroepithelium and the subventricular zone); CC, cerebral cortex; ch, choroid plexus; cp, cortical plate; CP, caudate/putamen complex; FM, foramen of Monro; GP, globus pallidus; Hl, hippocampus; HY, hypothalamus; IC, internal capsule; iz, intermediate zone; LV, lateral ventricle; PC, piriform cortex; WH, white matter of the cerebral cortex. (From Bayer *et al.*, in press.)

MATCHING THE GROSS APPEARANCE OF THE HUMAN BRAIN WITH THE RAT BRAIN

Using a three-dimensional computer software package (Skandha), the rat forebrain was reconstructed on E12, E15, E18 and E21. (Details of the methods used are in Bayer and Altman, 1991a.) Those reconstructions could be matched with photographic reproductions of drawings of the entire human brain by Hochstetter (1919).

Human Weeks 4-5 Matched with Rat Embryonic Day 11.5-12

A human embryo at 4.34 mm crown-rump length (Fig. 11) is at stages 12-13 according to Table 1-2 in Lemire *et al.*, (1975) and its approximate age is from the 4th to the early part of the 5th weeks after fertilization. Figure 11A is a lateral view of the entire brain and upper part of the spinal cord showing the forebrain on the right. The trigeminal (V) and facial (VII) cranial nerve roots are indicated. Figure 11B shows the top view of the forebrain. Three dimensional computer reconstructions of the forebrain in an E12 rat embryo viewed from the top (Fig. 12A-C) and front (Fig. 12D-F) show striking similarities with the appearance of the human forebrain at stages 12-13 (compare Fig. 11B with Fig. 12A-C). Notice that the shape and orientation of the eye vesicles are nearly the same in the human and rat brains. The V-shape at the base of the rat brain is the infundibular recess (ir, Fig. 12); it probably corresponds to the same structure labeled by Hochstetter as the mammillary evagination (M., Fig. 11A).

The three dimensional reconstructions of the rat embryo shows the shape and relative size of the forebrain ventricle (Figs. 12B, C, E and F). It is striking that the ventricle is by far the largest component of the brain. As we have shown in sections of human and rat forebrains (Fig. 2), the neuroepithelium is the sole component of the forebrain wall at this early stage.

Late Human Week 6 Matched with Rat Embryonic Day 15

Human embryos at 12.86 mm (Fig. 13A) and 17.0 mm (Fig. 13B) respective crown-rump lengths are at stages 17-19 according to Table 1-2 in Lemire *et al.* (1975), and are in the latter half of the 6th week after fertilization. The forebrain is shown from the frontal (Fig. 13A) and basal (Fig. 13B) aspects. Three dimensional computer reconstructions of the E15 rat forebrain from a top view (Fig. 14A-C) and a front view (Fig. 14D-F) show several similarities with the appearance of the human forebrain at stages 17-19. The telencephalon and diencephalon are now clearly distinguishable, and their shape and orientation are almost exactly the same in the two species. The front views of the rat forebrain (Fig. 14D-F) show the beginning of the olfactory evagination at the same site where the olfactory nerve (R.N., Fig. 13A) is contacting the forebrain in the human embryo and where the olfactory bulb evaginates slightly later.

The views of the ventricular system in the rat brain (Fig. 14B, C, E, F) indicate that the lateral ventricles are now clearly distinguishable from the third ventricle. However, the overall shape of the forebrain is still largely dictated by the shape of the ventricular system, just as it was in earlier stages. For example, the olfactory evagination (oe) is the result of a ventricular protrusion from the anterior tip of the lateral ventricle, best seen in the top view of the ventricular system only (Fig. 14C). Although the third ventricle is receding from the optic stalk, the lateral projections at its base (or) shows where it once extended into the eye vesicles at earlier stages.

Human Weeks 8-9 Matched with Rat Embryonic Day 18

Human embryos at 53 mm (Fig. 15A) and 46.5 mm (Fig. 15B) respective crown-rump lengths are either at or slightly beyond stages 20-23 according to Table 1-2 in Lemire *et al.* (1975), and are approximately 8-9 weeks after fertilization. The brain is shown from the lateral (Fig. 15A) and midline sagittal (Fig. 15B) aspects. Three dimensional computer reconstructions of the E18 rat forebrain (Fig. 16) shows similarities with the appearance of the human forebrain at stages 20-23. The position and orientation of the olfactory bulb is very similar in man (B.o., Fig. 15A) and rat (OB, Fig. 16). In both man and rat, the cerebral cortex has now grown posteriorly to extend farther back than the diencephalon (compare Fig. 15 with 16A-B). The third ventricle (3V, Fig. 16) is also similar in man and rat, occupying a slit-like shape in the midline (compare Figs. 16C, F with 15B). However, species differences are now beginning to show up between man and rat. The cerebral cortex is much larger in man; it completely covers the olfactory bulb, and there is the beginning of an insula and an expanding temporal lobe (S.P., Fig. 15A) laterally. In rats, the olfactory bulb is completely visible in front of the much smaller cerebral cortex, and there is no evaginating temporal lobe.

The view of the rat ventricular system on E18 (Fig. 16B, C, E, F) shows that it is receding as the structures of the brain grow. The overall shape of the brain is no longer influenced by the shape of the receding ventricles and is now dictated by the growth and differentiation of the cellular elements in the brain parenchyma.

Human Weeks 15-16 Matched with Rat Embryonic Day 21

Human embryos at 102 mm (Fig. 17A) and 96 mm (Fig. 17B) respective crown-rump lengths are approximately 15-16 weeks after fertilization according to the crown-rump/age graphs in Chapter 1 of Lemire *et al.* (1975). The brain is shown from the midline sagittal (Fig. 17A) and basal (Fig. 17B) aspects. Three dimensional computer

reconstructions of the forebrain in a rat embryo on the morning of the 21st day after fertilization (Fig. 18) still shows some similarities with the gross appearance of the human forebrain in the 15th and 16th weeks. For example, the position and orientation of the olfactory bulbs (B.o., Fig. 18; OB, Fig. 18) and the slit-like shape of the third ventricle (3V, Fig. 18) are similar in the two species. However, the continual expansion of the human cerebral cortex, even though it is still lissencephalic, now dwarfs the rest of the brain. In rats, the cerebral cortex has grown larger between E18 and E21, but the olfactory bulbs are still completely visible in front of it, and will remain so throughout adult life. The ventricular system continues to recede in the rat forebrain on E21 (Fig. 18B, C, E, F) as it did on E18 (Fig. 16).

LINKING THE TIMES OF NEUROGENESIS AND MORPHOGENESIS IN THE CENTRAL NERVOUS SYSTEMS OF RATS AND MAN

Neurogenetic timetables for every major neuronal population, determined with long-survival quantitative [^{3}H]thymidine autoradiography, are presented in Figures 19 through 40. A few of these figures show migratory pathways and dendritic growth patterns in selected brain structures. These data are shown with the estimated time of neurogenesis in man, using the linking procedures described above. Again, we wish to emphasize that the dates given for man are only approximations. During the following discussion, we will often use the term *neurogenetic gradient*. That refers to the nonrandom spatial accumulation of cells according to age within and between neuronal populations. Stated in another way, in many areas of the central nervous system, earlier-generated (older) neurons settle in different locations than later-generated (younger) neurons. Neurogenetic gradients are very precise in rats. Furthermore, the directions of many neurogenetic gradients can be linked to the pattern of anatomical connections (Bayer and Altman, 1987a).

The Spinal Cord

We will consider four populations of neurons in the spinal gray matter. The somatic lower motor neurons are located in the anterior (ventral) horn. The preganglionic visceral motor neurons are located in the lateral horn. The sensory relay neurons and many interneurons are located in the posterior (dorsal) horn. For a detailed discussion of spinal cord development, see Altman and Bayer (1984).

Motor Neurons. The somatic motor neurons are generated first in the spinal gray (Fig. 19). They originate in a ventrolaterally situated neuroepithelial site, the basal plate, from E11 through E13 in rats, approximately from 3.5 to 5.7 weeks in man. In rats there is a rostral (older) to caudal (younger) neurogenetic gradient (see the top three graphs in Fig. 19; Altman and Bayer, 1984) so that the peak production of the cervical somatic motor neurons is on E12 in rats (human weeks 4.1-5.2), while the peak production of lumbosacral somatic motor neurons is on E13 (human weeks 5.3-5.7). This gradient may be related to the earlier emergence of the forelimb than the hindlimb.

Within 1 day after their generation in rats, somatic motor neurons move out of the neuroepithelium and accumulate ventrolaterally as a mass of randomly oriented cells. During the next day, there is an increasing accumulation of cytoplasmic material and axons begin to leave the spinal cord forming the ventral roots of the spinal nerves. Following axonogenesis, cytoplasmic material continues to accumulate in the motor neuron soma for several days and is presumably the forerunner of multipolar dendrogenesis. If the same pattern takes place in man, we would presume that cell migration and axonogenesis occur within a very short time after cell generation, while dendrogenesis is prolonged.

Visceral motor neurons are most numerous at thoracic and upper lumbar levels; they have a concurrent time of origin with the somatic motor neurons at the same spinal level (Altman and Bayer, 1984; compare times of origin for somatic and visceral thoracic motor neurons in Fig. 19). However, they migrate outward from a neuroepithelial site situated dorsal to the site generating the somatic motor neurons. Like the somatic motor neurons, the visceral motor neurons migrate out of the neuroepithelium within one day after their generation, and cytoplasmic accumulations rapidly occur. The cells in the most lateral part of the intermediate gray (the lateral horn) become dorsoventrally oriented soon after generation; possibly that is associated with axonogenesis, but we could not follow their axons into the ventral roots.

Sensory Relay Neurons. The sensory relay neurons constitute a diverse group. Unlike interneurons that have short axons terminating locally, many spinal relay neurons have long axons terminating in the brain. Some of the relay neurons have ipsilaterally projecting axons, others have contralaterally projecting axons, and still others have axons that project bilaterally. Our developmental study of the spinal cord in rats could differentiate contralateral and ipsilateral cells (Altman and Bayer, 1984).

In terms of neurogenesis, the contralaterally projecting neurons are generated earlier (E12 and E13 in rats, human weeks 4.1-5.7) than the ipsilaterally projecting neurons (E14 in rats, human weeks 5.8-6-6). The neuroepithelium in the spinal cord in rats has alternating microsegments so that one segment produces the ipsilaterally projecting cells, while an adjacent segment produces the contralaterally projecting cells. The contralaterally projecting cells move out of the neuroeithelium within one day after their generation and immediately turn from a horizontal orientation to a vertical one, forming a band of spindle shaped vertical cells along the superficial border of the spinal neuroepithelium. Cytoplasmic material accumulates in the cell bodies, and fibers (presumably axons) course ventrally along the superficial border of the

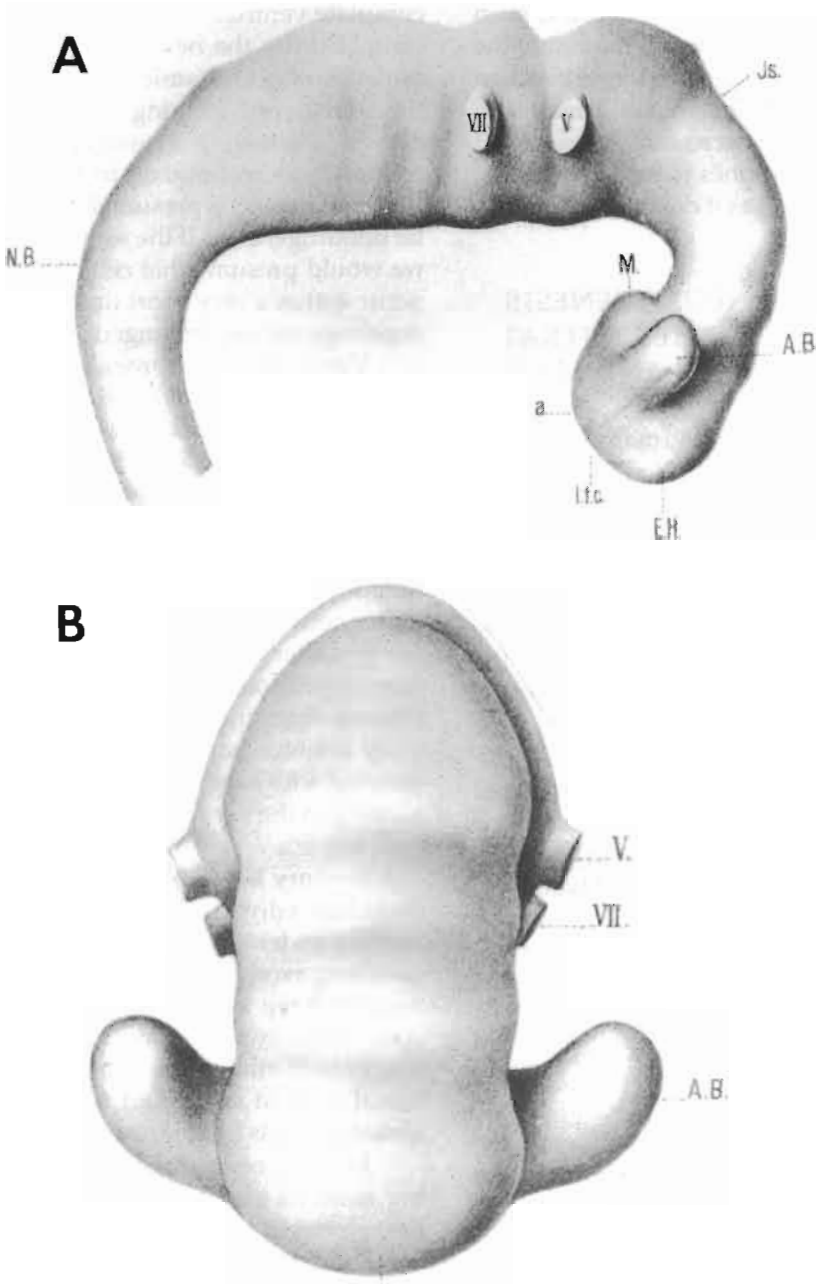


FIG. 11 A. Figure 4 in Plate I from Hochstetter (1919). A lateral view of a 4.34 mm human embryo.

FIG. 11 B. Figure 5 in Plate I from Hochstetter (1919). A dorsal view of the same embryo as drawn in A. Abbreviations: a., postion of the chiasmal plate; A.B., eye vesicle; E.H., forebrain; Js., isthmus; L.t.c., lamina terminalis cinerea; M., mammillary evagination; N.B., cervical flexure; V, trigeminal nerve; VII, facial nerve. (From Bayer *et al.*, in press.)

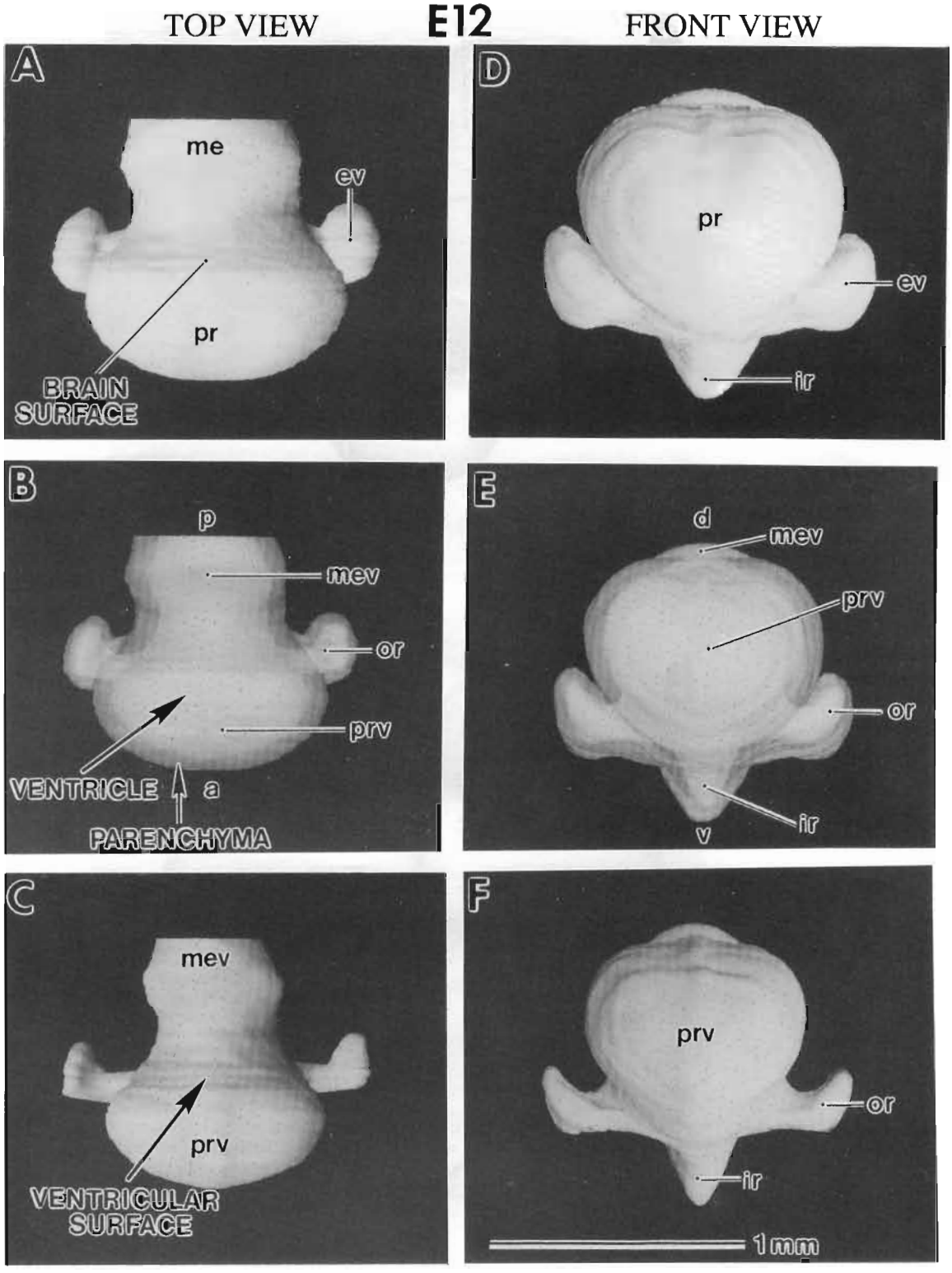
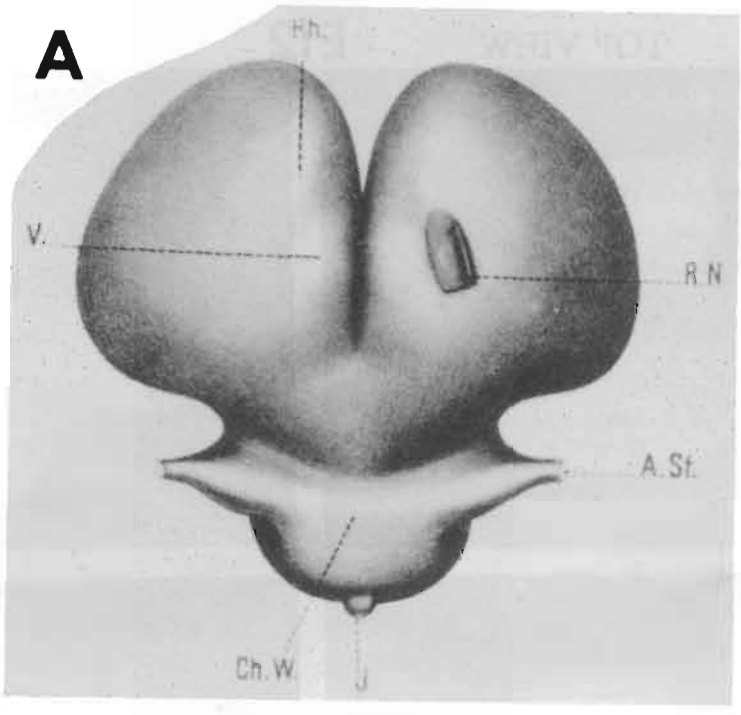


FIG. 12. Three-dimensional computer reconstruction of the forebrain and the most anterior part of the mesencephalon in an E12 rat embryo prior to the separation between the telencephalon and diencephalon. A-C are top views, D-F are front views. The outer surface of the forebrain is shown in A and D. In B and E, the brain surface is shown at 50% opacity so that the outline of the ventricular system (inked line) can be seen within. At this stage, there is no separation between the third ventricle and the lateral ventricle. In C and F the ventricular system is shown alone. Abbreviations: a, anterior; d, dorsal; ev, eye vesicle; ir, infundibular recess; me, mesencephalon; mev, mesencephalic ventricle; or, optic recess; p, posterior; pr, prosencephalon; prv, prosencephalic ventricle; v, ventral. (From Bayer *et al.*, in press.)



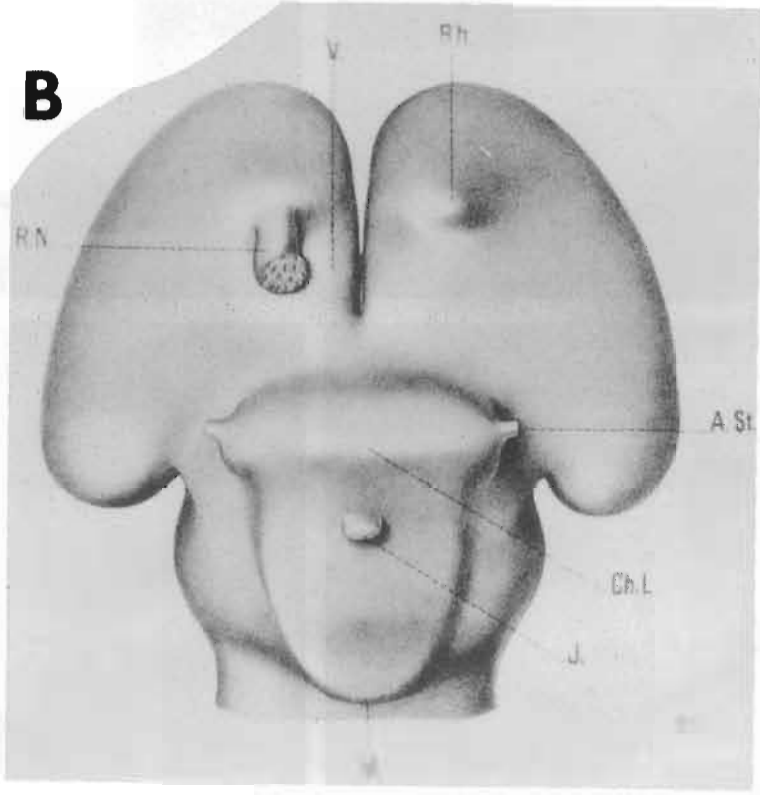


FIG. 13 A. Figure 23 in Plate 4 from Hochstetter (1919). A frontal view of a 12.86 mm human embryo.

FIG. 13 B. Figure 30 in Plate 5 from Hochstetter (1919). Basal view of the forebrain in a 17.0 mm human embryo. Abbreviations: A.St., optic stalk; Ch.L. and Ch.W., primordium of the optic chiasma wulst; J., infundibulum; M., mammillary evagination; Rh., rhinencephalon (olfactory bulb); R.N., olfactory nerve; V., (septum?). (From Bayer *et al.*, in press.)

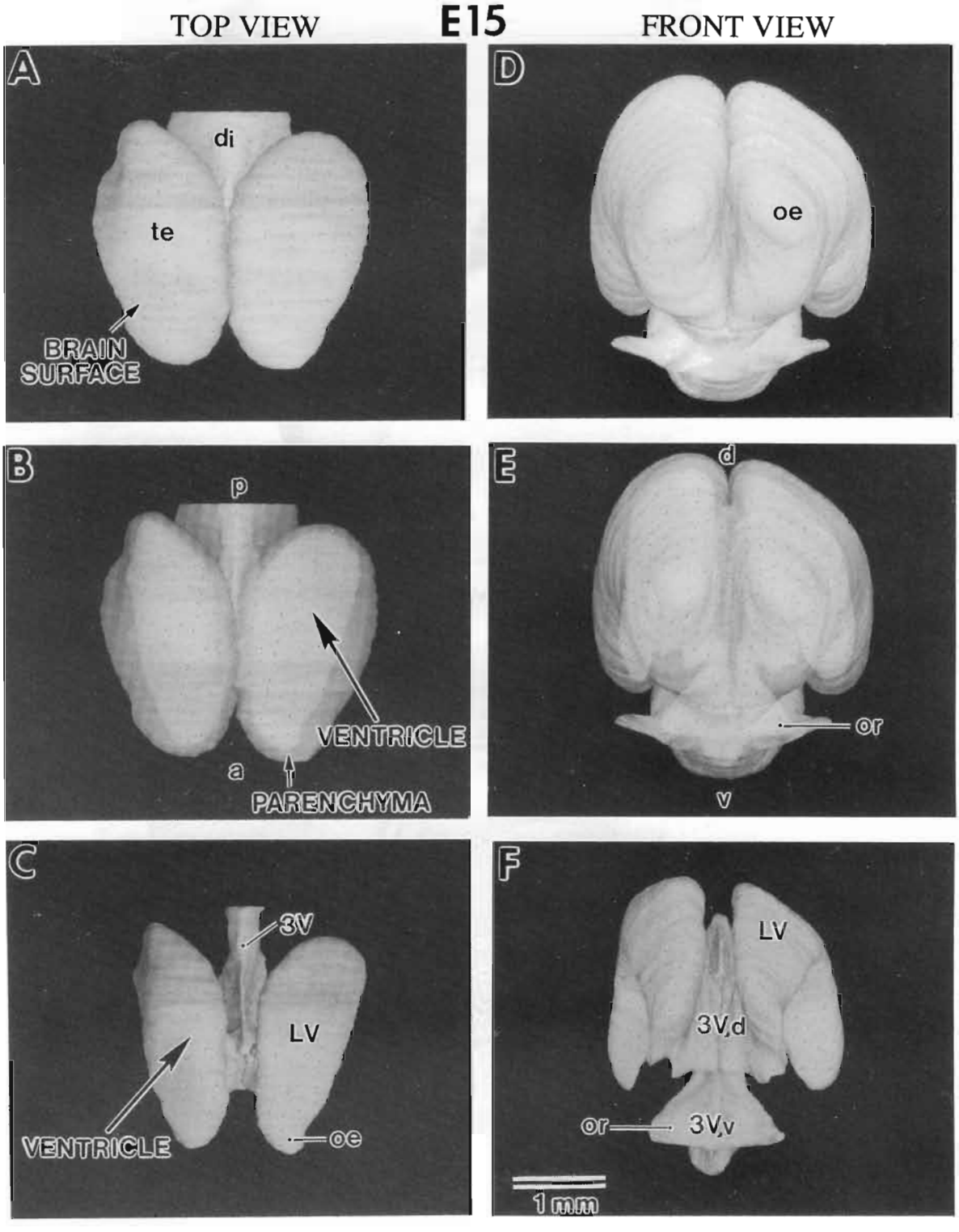


FIG. 14 Three-dimensional computer reconstruction of the forebrain in an E15 rat embryo. A-C are top views, D-F are front views. The outer surface of the entire brain is shown in A and D. In B and E, the brain parenchyma is viewed at 50% opacity so that the outline of the ventricular system can be seen within. In C and F, only the ventricular system is shown. Abbreviations: 3V,d, dorsal third ventricle; 3V,v, ventral third ventricle; a, anterior; d, dorsal; di, diencephalon; LV, lateral ventricle; oe, olfactory evagination; or, optic recess; p, posterior; te, telencephalon; v, ventral. (From Bayer *et al.*, in press.)

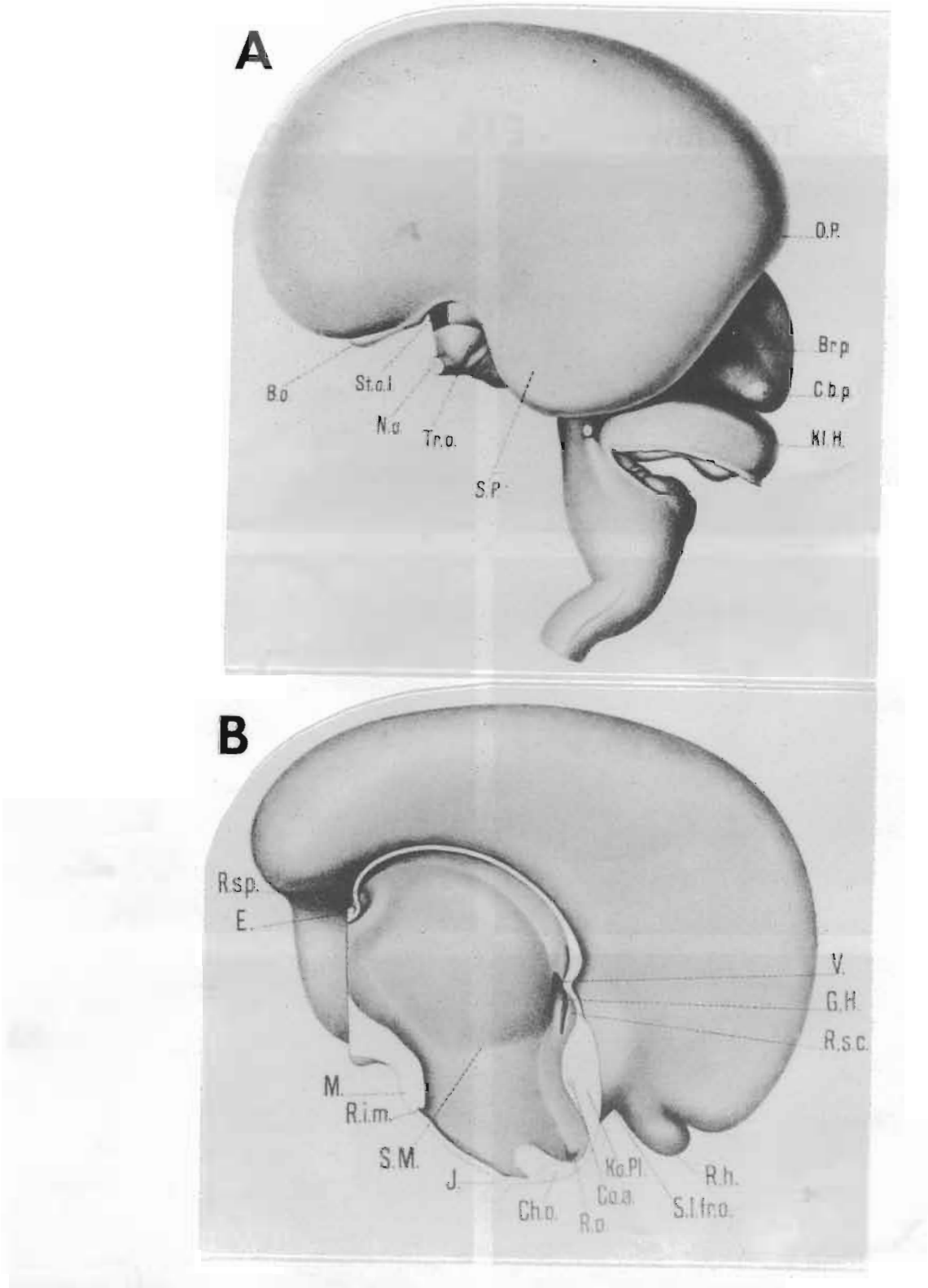


FIG. 15 A. Figure 46 in Plate 8 from Hochstetter (1919). Lateral view of a 53 mm human embryo.

FIG. 15 B. Figure 40 in Plate 7 from Hochstetter (1919). Medial view of a 46.5 mm human embryo. Abbreviations: B.O., olfactory bulb; Br.p., posterior brachium; C.b.p., posterior corpus bigeminum (inferior colliculus); Ch.o., optic chiasma; Co.A., anterior commissure; E., primordium of the pineal gland; G.H., ganglionic eminence; J., infundibulum; Kl.H., cerebellum; Ko.Pl., commissural plate; M., mammillary recess; N.O., optic nerve; O.P., occipital pole; R.h., rhinencephalon; R.i.m., inframammillary recess; R.o., optic recess; R.s.c., supracommissural recess; R.s.p., suprapineal recess; S.l.tr.o., sulcus limitans of the olfactory trigone; S.M., sulcus (foramen) of Monro; S.P., temporal pole; St.O.L., lateral olfactory stria; Tr.o., optic tract; V., (septum?). (From Bayer *et al.*, in press.)

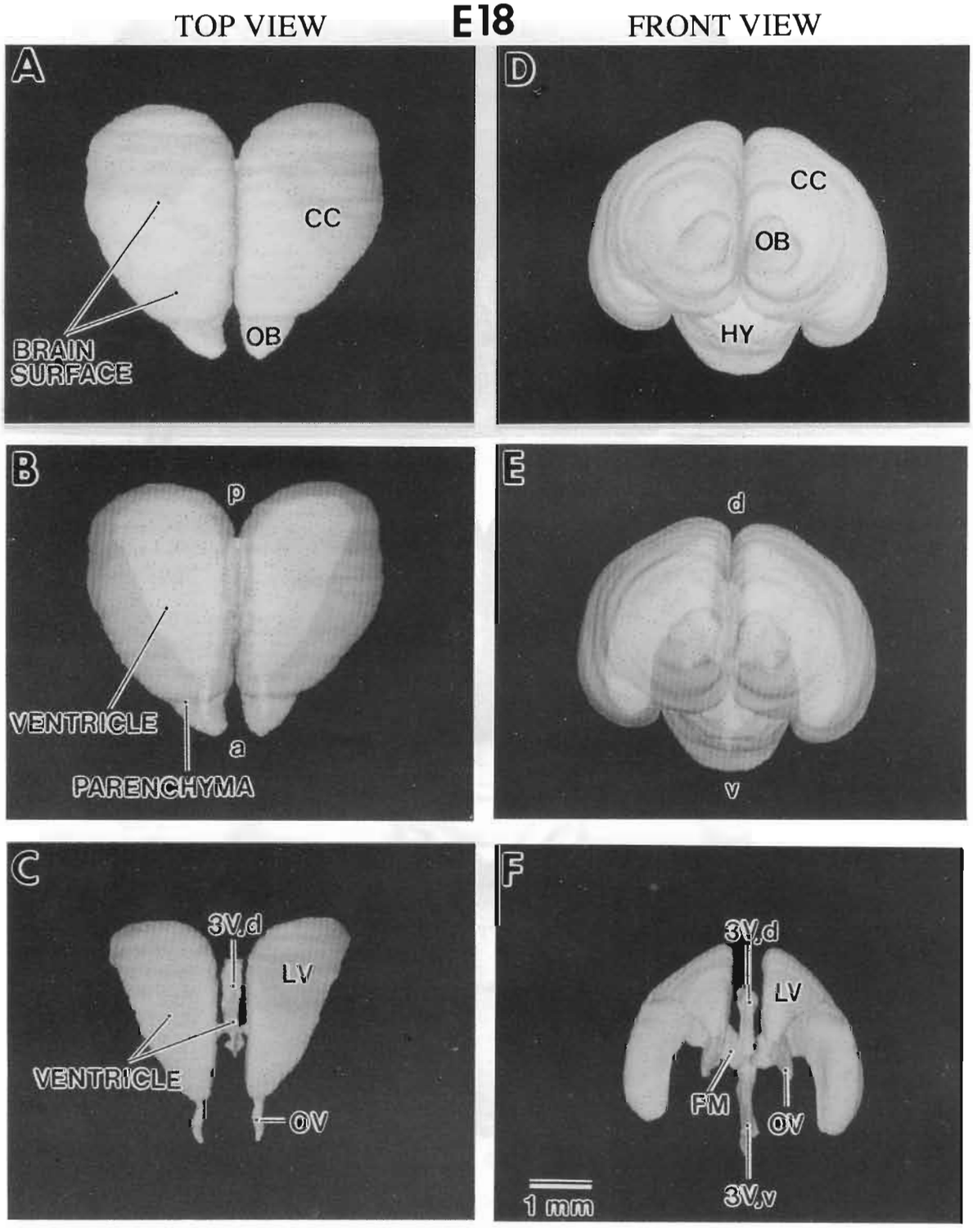


FIG. 16. Three-dimensional computer reconstruction of the forebrain in an E18 rat embryo. The outer surface of the entire brain is shown in A and D. In B and E, the brain parenchyma is viewed at 50% opacity so that the outline of the ventricular system can be seen within. In C and F, only the ventricular system is shown. Abbreviations: 3V,d, dorsal third ventricle; 3V,v, ventral third ventricle; a, anterior; CC, cerebral cortex; d, dorsal; FM, foramen of Monro; HY, hypothalamus; LV, lateral ventricle; OB, olfactory bulb; OV, olfactory ventricle; p, posterior; v, ventral. (From Bayer *et al.*, in press.)

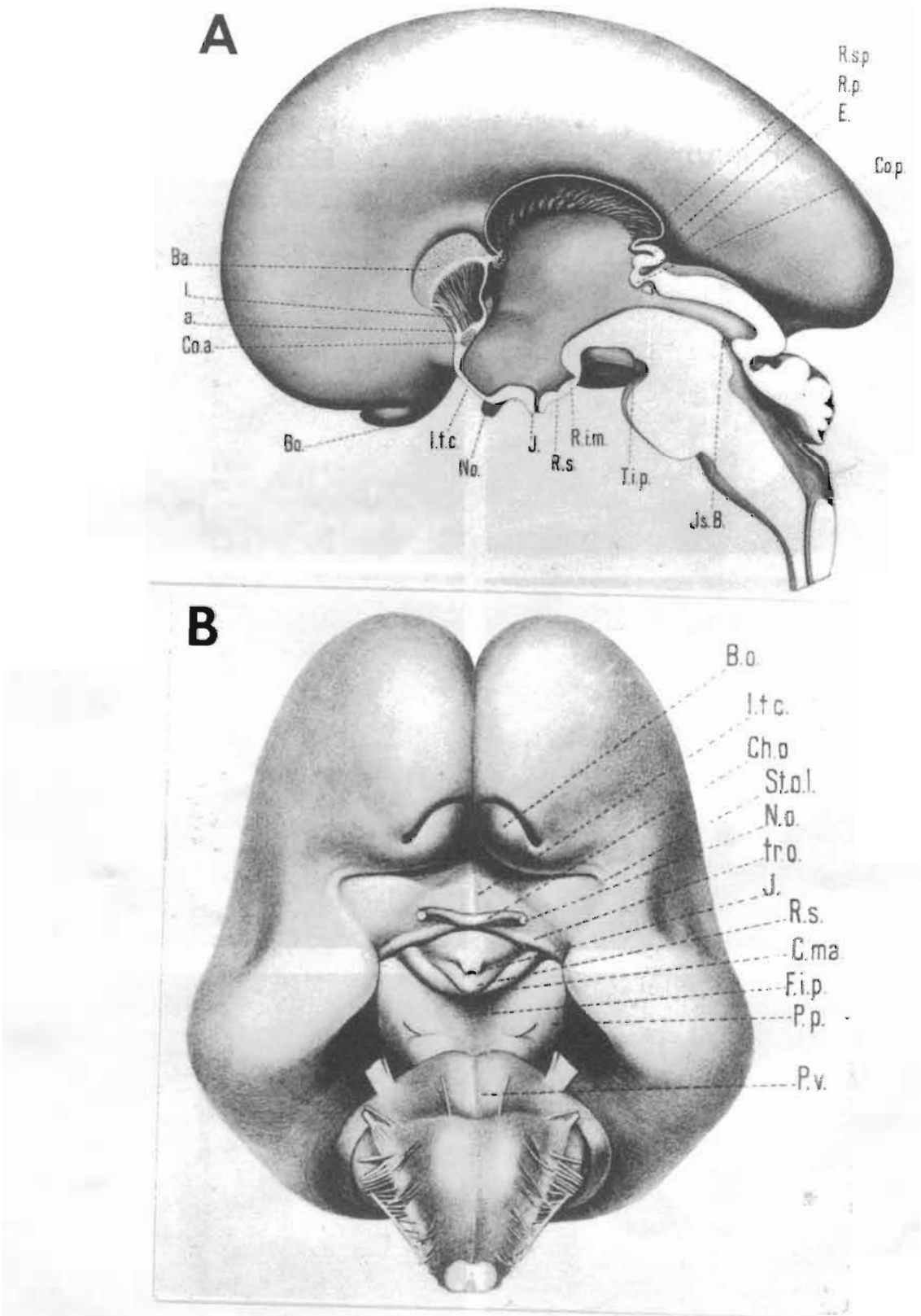


FIG. 17 A. Figure 51 in plate 19 from Hochstetter (1919). Midlateral view of a 102 mm human embryo.

FIG. 17 B. Figure 50 in plate IX from Hochstetter (1919). Basal view of a 96 mm human embryo. Abbreviations: a., (? glial bridge across midline); Ba., (? primordium of the corpus callosum); Bo., olfactory bulb; Ch.o., optic chiasma; C.ma., mammillary body; Co.a., anterior commissure; Co.p., posterior commissure; E., primordium of the pineal gland; F.i.p., interpeduncular fossa; J., infundibulum; Js.B., (? isthmal recess); l., (?); L.t.c., l.t.c. lamina terminalis cinerium; N.o., optic nerve; P.p., cerebral peduncle; P.v., pons; R.i.m., inframammillary recess; R.p., pineal recess; R.s., saccular recess; R.s.p., suprapineal recess; St.o.l., lateral olfactory stria; T.i.p., interpeduncular tubercule; tr.o., optic tract. (From Bayer *et al.*, in press.)

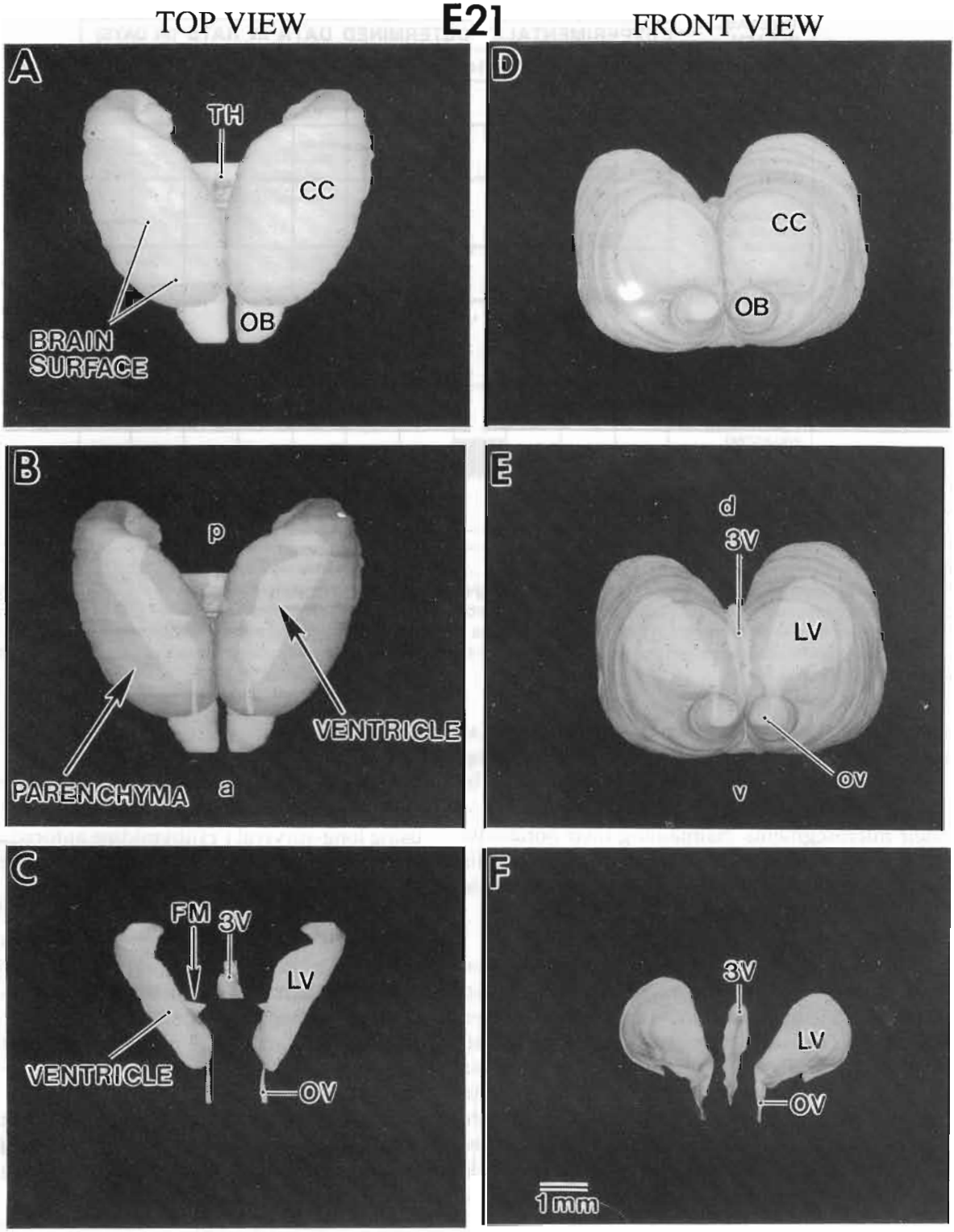


FIG. 18. Three-dimensional computer reconstruction of the forebrain in an E21 rat embryo. The outer surface of the entire brain is shown in A and D. In B and **E**, the brain parenchyma is viewed at 50% opacity so that the outline of the ventricular system can be seen within. In C and F, only the ventricular system is shown. Abbreviations: 3V, third ventricle; a, anterior; CC, cerebral cortex; d, dorsal; FM, foramen of Monro; LV, lateral ventricle; OB, olfactory bulb; ov, olfactory ventricle; p, posterior; TH, thalamus; v, ventral. (From Bayer *et al.*, in press.)

SPINAL CORD DEVELOPMENT

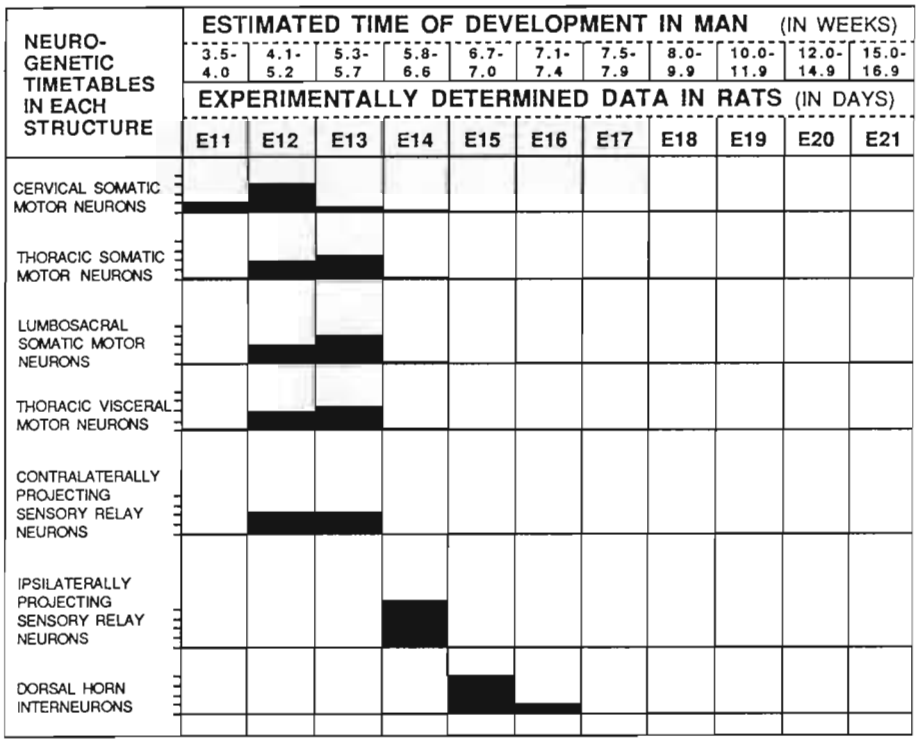


FIG. 19. Timetables of neurogenesis in the spinal cord based on long-survival [^{3}H]thymidine autoradiography in the rat. The bar graphs indicate the proportion of neurons generated in each population on the specified embryonic days (E); the hatch marks on the left side of each graph are in increments of 20%. The estimated time of development in man is shown in weeks above the time line for the experimentally determined data in the rat. The age matches were based on correlations between the gross appearance of the forebrain (Figs. 11-18) and on similarities in histological sections (Figs. 2-10). (From Bayer *et al.*, in press.)

neuroepithelium. These axons reach the thin floor plate at the base of the spinal cord by E14 in rats, and decussating fibers are seen in the ventral commissure on E15. In contrast, one-day-old ipsilaterally projecting cells migrate out of their microsegments maintaining their horizontal orientation. Shortly after the ipsilaterally projecting cells move out of the neuroepithelium, fibers begin to accumulate in the lateral funiculus, presumably their axons.

Dorsal Horn Interneurons. The substantia gelatinosa of the posterior horn contains the most concentrated group of cells considered to be interneurons because their axons terminate locally. These cells form a mushroom-like cap over the dorsal horn. Thymidine autoradiography in rats (Altman and Bayer, 1984) indicates that most of the cells in this part of the spinal gray originate on E15 (bottom graph, Fig. 19). The neurons generated on E15 settle in the neck of the dorsal horn, while the neurons generated on E16 settle in the lower neck and in an area dorsal to the central canal. These dorsal horn interneurons originate in the dorsal spinal cord neuroepithelium and settle within two to three days after their generation. In man, we estimate that these interneurons are produced between 6.7 to 7.4 weeks after fertilization and settle by 9.9 weeks after fertilization.

The Medulla

Our studies on the development of the medulla in rats are restricted to quantitative determinations of neurogenesis using long-survival [^{3}H]thymidine autoradiography after comprehensive labeling. These data were presented in two papers (Altman and Bayer, 1980a,b). We have not yet examined the medulla with short-survival [^{3}H]thymidine autoradiography during the embryonic period. However, short and sequential-survival [^{3}H]thymidine autoradiography has been used to track cell migration of the inferior olive and other precerebellar nuclei in the medulla and pons. Those data will be presented later with the cerebellum.

Motor Nuclei. The upper medulla contains four motor nuclei: the retrofacial, the abducens, the facial, and the superior salivatory (top 5 graphs, Fig. 20). The oldest motor neurons in the entire neuraxis are in the *retrofacial nucleus*. Neurons in the *abducens nucleus* originate later. The large *facial motor nucleus* has a rostral (older) to caudal (younger) neurogenetic gradient. The superior salivatory nucleus is an irregular collection of neurons in the vicinity of the genu of the facial nerve. Most of the neurons originate on E15, a few on E16. In man, we estimate that

DEVELOPMENT OF THE MEDULLA: MOTOR NUCLEI

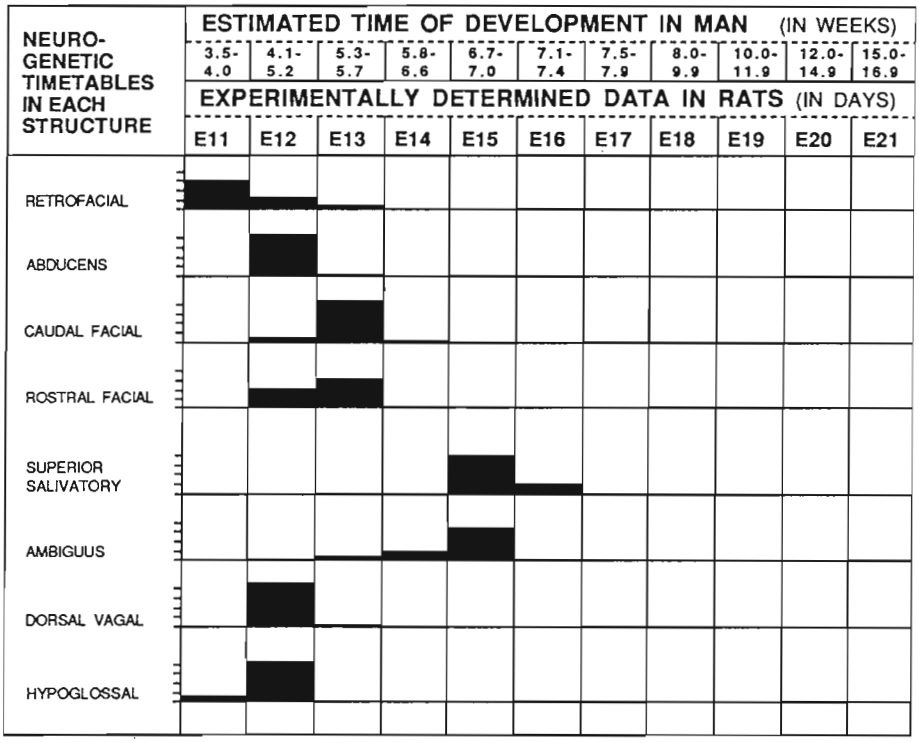


FIG. 20. As in Figure 19 for the motor nuclei of the medulla. (From Bayer *et al.*, in press.)

neurons in the retrofacial, abducens, and facial nuclei are generated 3.5-5.7 weeks after fertilization, while the superior salivatory nucleus is estimated to be generated 6.7-7.4 weeks after fertilization.

In the lower medulla, there are three motor nuclei: the hypoglossal, the dorsal motor nucleus of the vagus and the nucleus ambiguus. The oldest neurons in the rat lower medulla are in the *hypoglossal nucleus*. The *dorsal motor nucleus of the vagus* (graph second from bottom, Fig. 20) closely follows. The latest produced motor neurons in the lower medulla are in the *nucleus ambiguus* (graph third from bottom, Fig. 20). In man, we estimate that the hypoglossal and vagus neurons are generated 4.1-5.2 weeks after fertilization, while the ambiguus neurons are generated 6.7-7 weeks after fertilization.

Sensory Relay Nuclei. The medulla has a large complement of neurons that send sensory information upward to the midbrain and thalamus. All sensory modalities except olfaction and vision have relay stations in the medulla. The quantitative neurogenetic data in the rat were presented in three papers (Altman and Bayer, 1980a,b,c).

The sensory *trigeminal complex* relays input from the face and jaw and includes the nucleus oralis in the upper medulla and the nucleus interpolaris, and subnuclei of the caudalis (magnocellularis, gelatinosus, and zonalis) in the lower medulla. The time of origin of neurons in rats is shown in the top 5 graphs in Figure 21. Most of the neurons in the trigeminal sensory complex originate between days E13 to E15. Only the oralis and the magnocellularis contain a few neurons that are generated on E12. In rats, the peak time of neurogenesis is E13 for oralis, E14 for interpolaris, magnocellularis, and gelatinosus, and E15 for zonalis. We estimate that neurons in the human trigeminal sensory nuclei are generated mainly 5.3-7 weeks after fertilization.

The *gracilis and cuneate nuclei* are located adjacent to each other in the superficial parts of the lower medulla, and they relay touch and light pressure information to the thalamus from the entire body surface except that supplied by the trigeminal nerve. Neurons in these nuclei are mainly generated on E13 in rats with a medial (older) to lateral (younger) neurogenetic gradient (Fig. 21). In man, we estimate that neurons in these nuclei are generated mainly 5.3 to 6.6 weeks after fertilization.

Considering the gracilis nucleus, cuneate nucleus, and nuclei of the trigeminal complex together, there is an overall neurogenetic gradient that can be related to the body surface. Neurons relaying information from the most distant parts of the body (the lower trunk and hindlimbs) in the gracilis nucleus are the oldest, those relaying information from less distant body parts (upper trunk and

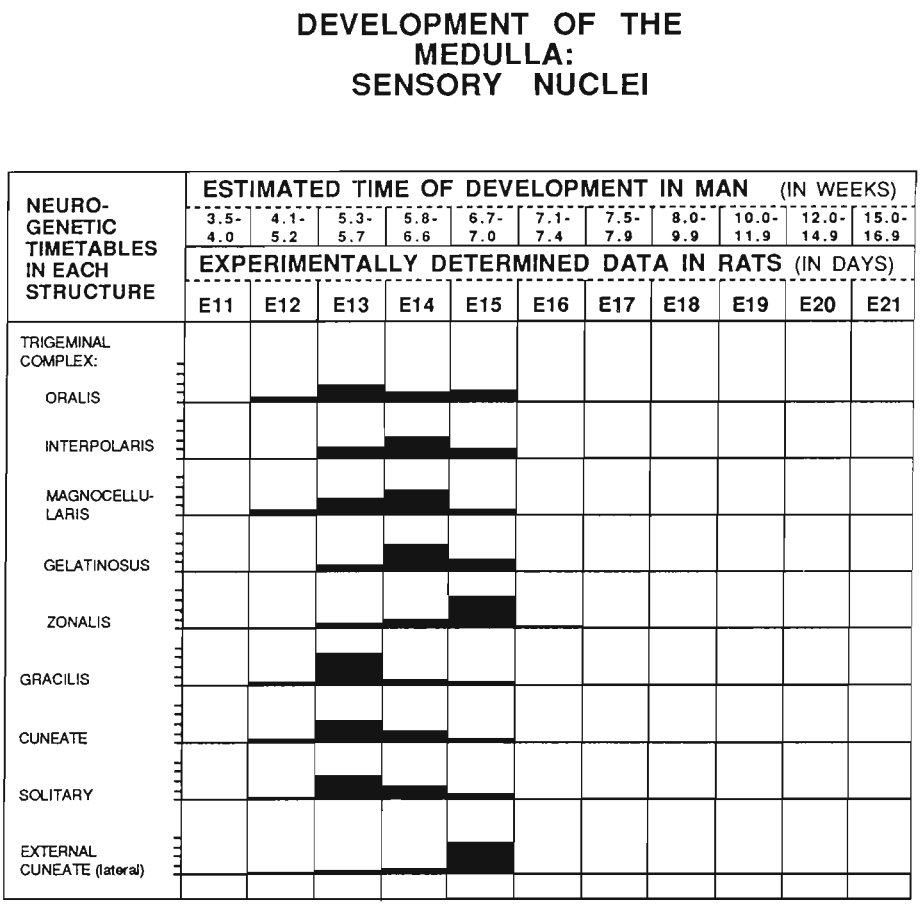


FIG. 21. As in Figure 19 for the sensory nuclei of the medulla. (From Bayer *et al.*, in press.)

forelimb) are in the cuneate nucleus and are slightly younger, while those relaying information from nearest body parts (face) in the nuclei of the trigeminal complex are the youngest. Possibly this neurogenetic gradient is related to the order of incoming sensory axons from the primary sensory neurons in the peripheral nervous system.

The *solitary nucleus* is the principal relay for taste. In rats, 50% of the neurons in the solitary nucleus originate on E13, 30% on E14, and 15% on E15 (graph second from bottom, Fig. 21). In man, we estimate that taste relay neurons are generated between 5.3 to 7 weeks after fertilization.

The *external cuneate nucleus* relays proprioceptive input from muscles in the upper trunk, forelimb, and neck to the cerebellum. In rats, neurons in the external cuneate nucleus originate quite late, 70% on E15 (bottom graph, Fig. 21). In man, we estimate that these neurons are generated 6.7 to 7 weeks after fertilization.

The neurons relaying vestibular input to the cerebellum include the *lateral, superior, inferior, and medial vestibular nuclei* and the *hypoglossal prepositus nucleus*. The hypoglossal prepositus nucleus is included in the group because of the similarity of its anatomical connections and functions with the other vestibular nuclei (for a review of the literature, see Altman and Bayer, 1980c). In rats, most of the neurons in these nuclei are generated between E12 and E14 (top 5 graphs, Fig. 22). We estimate that neurons in these nuclei are generated 4.1 to 6.6 weeks after fertilization in man.

In rats, most cells in the *cochlear nucleus* originate on E15 (graphs 6-9 from top, Fig. 22). The dorsal cochlear nucleus has a lengthy period of neurogenesis from E12 to E17, with a peak on E15 and only a small proportion originating on the other days. The anteroventral and posteroventral parts also peak on E15 (Altman and Bayer, 1980c). In man, we estimate that cochlear nuclear complex neurons are mainly generated 6.7-7 weeks after fertilization, but the entire range of neurogenesis could extend from 4.1 weeks to 7.9 weeks. The *trapezoid nuclei* have a very pronounced lateral (older) to medial (younger) neurogenetic gradient (graphs 10-11 from top, Fig. 22). It is interesting that neurons in the *superior olive* nuclear complex have a pronounced neurogenetic gradient in exactly the opposite direction: medial (older) to lateral (younger). These strong neurogenetic gradients have been related to the tonotopic representation in the auditory pathways (Altman and Bayer, 1981b). In man, we estimate that the two peaks of neurogenesis in the trapezoid body occur during weeks 4.1-5.2 and during weeks 6.7-7 after fertilization. The neurogenetic peaks in the superior olive nuclei are likely to occur during the fifth (5.3-5.7) and seventh (7.1-7.4) weeks.

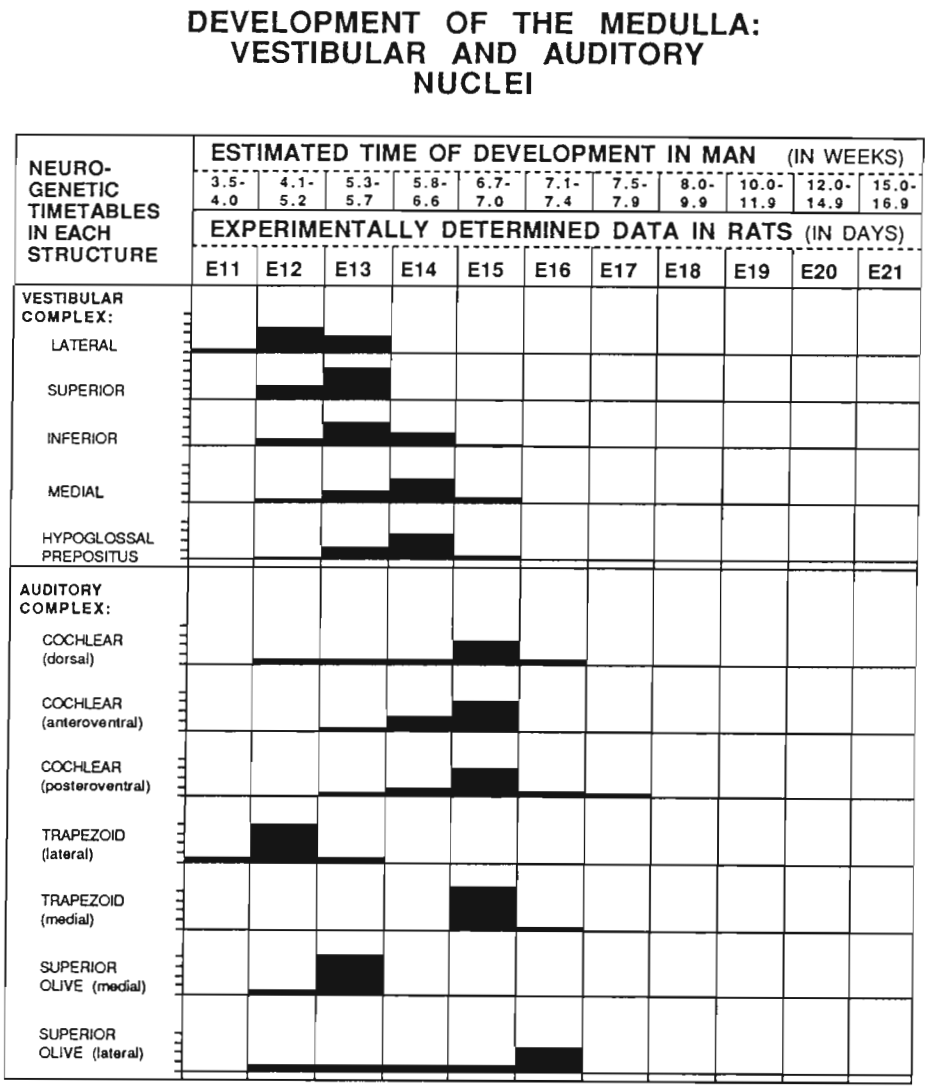


FIG. 22. As in Figure 19 for the vestibular and auditory nuclei in the medulla. (From Bayer *et al.*, in press.)

The Raphe Complex and the Reticular Formation. The medulla contains three of the nuclei in the *raphe complex*, the raphe obscurus and raphe pallidus in the lower medulla, and the raphe magnus in the upper medulla. In rats, neurogenesis extends from E11 to E15, with the majority of the neurons originating on E12 and E13 (three top graphs, Fig. 23). There is a rostral (older) to caudal (younger) neurogenetic gradient between neurons in the raphe magnus while neurons throughout the raphe obscurus and raphe pallidus originate simultaneously. Midline raphe neurons are generated mainly on E16. In man, we estimate that raphe neurons in the medulla are generated mainly during 4.1 to 5.7 weeks after fertilization, but some of the midline raphe neurons are probably generated as late as the 7th week after fertilization.

The *reticular formation* is divided into a rostral part in the upper medulla and dorsal and ventral parts in the lower medulla. In rats, neurogenesis extends over a period of 4 days, from E12 to E15 (bottom three graphs, Fig. 23). In man, we estimate that neurons are generated in the medullary reticular formation from the 4th through the 7th weeks after fertilization.

The Pons

Our experimental studies of development in the pons, as in the medulla, are limited to the determination of the time of neuron origin based on long-survival [^{3}H]thymidine autoradiography (Altman and Bayer, 1980d).

Trigeminal Complex. The large neurons in the *mesencephalic nucleus* are similar to the typical primary sensory neurons in the cranial sensory ganglia and the spinal dorsal root ganglia. These neurons relay proprioceptive input from the muscles of mastication and from the tissues surrounding the teeth. These neurons originate mainly on E11 (top graph, Fig. 24). These neurons are believed to be produced in the periphery and then migrate into the central nervous system. A more complete account of the development of these neurons is in Altman and Bayer (1980d). In man, we estimate that these neurons are generated mainly during latter half of the third week, while a few

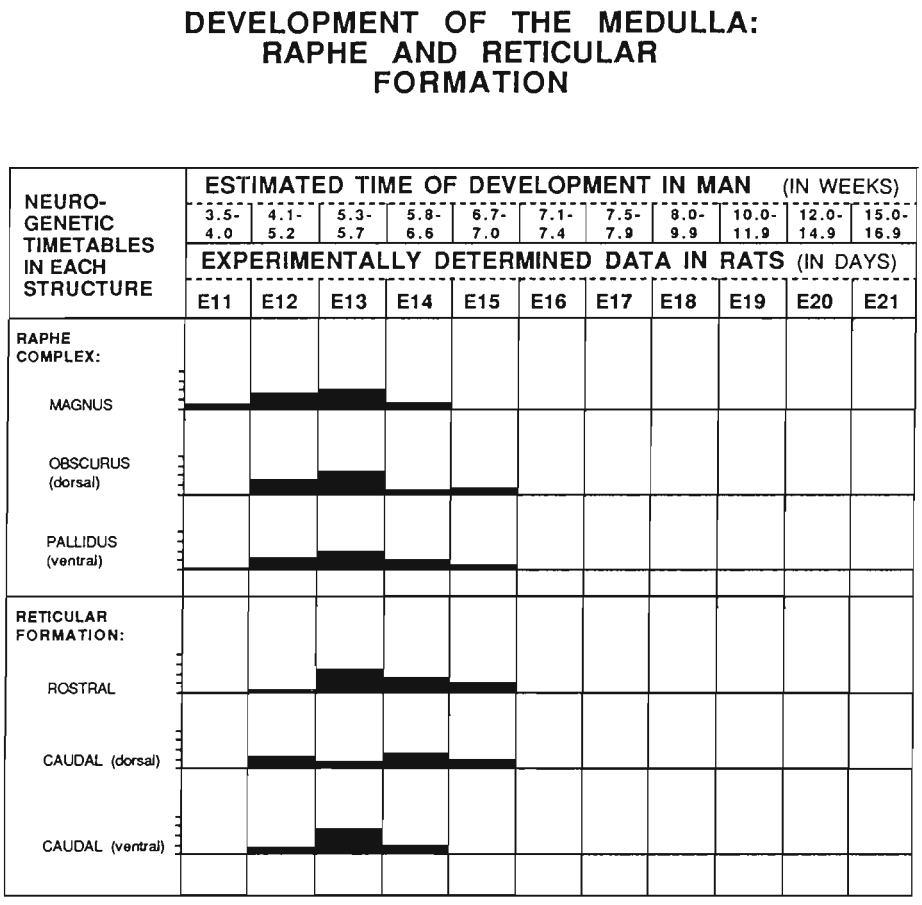


FIG. 23. As in Figure 19 for the medullary raphe nuclei and the medullary reticular formation. (From Bayer *et al.*, in press.)

neurons may still be generated during the 4th and early part of the 5th week.

Neurons in the *motor nucleus* supply the muscles of mastication (masseter, temporalis and pterygoids); some axons also supply the tensor tympani, the tensor palati, and parts of the digastric muscle. Cell dating studies with [^{3}H]thymidine autoradiography in rats indicates that about 80% of the neurons originate on E12 and about 20% originate on E11. In man, we estimate that these neurons are generated mainly during the 4th and early part of the 5th weeks.

The *principal sensory nucleus* is the rostral continuation of the nucleus oralis (discussed above with the medullary sensory nuclei), and relays sensory input from the face and jaw to the contralateral ventrobasal complex in the thalamus. In rats, these neurons originate from E13 to E16 (Fig. 24). In man, we estimate that the majority of these neurons originate during the latter half of the 5th week and up to the middle part of the 6th week.

The *infratrigeminal nucleus* in rats is composed of neurons of various sizes interspersed between and around the fibers of the trigeminal nerve as it courses through the ventrolateral pons. Their peak time of origin is on E15 and E16 (Fig. 24). In man, we estimate that these neurons are generated mainly during the latter part of the 6th week and the early part of the 7th week.

Other Pontine Nuclei. There is a sequential time of origin between the neurons in the pontine *reticular formation* and the raphe pontis nucleus. In the reticular formation, the large neurons are mainly generated on E12 and E13, while small and medium-sized cells are generated mainly on E14 and E15 (5th graph from top, Fig. 24). The prolonged time of neurogenesis is probably related to the cellular heterogeneity in this region. We estimate that these neurons are generated from the 4th to the beginning of the 7th week in man. In rats, the time of origin of the large and small cells in the *raphe pontis nucleus* is exactly the reverse. The parvicellular portion lies just beneath the central gray and is composed mainly of small neurons that originate early from E13 to E15 (6th graph from top, Fig. 24), while the magnocellular portion contains large neurons that are generated later, mainly on E15 and E16 (7th graph from top, Fig. 24). We estimate that both large and small neurons of the raphe pontis nucleus originate during the 5th to the middle part of the 7th weeks in man.

The rat *locus coeruleus* neurons are generated from E11 to E13. These neurons are noted for their widespread connections throughout the central nervous system (connections reviewed in Altman and Bayer, 1980d). In man, we estimate that locus coeruleus neurons are generated mainly during the 4th and early part of the 5th week.

Second-order auditory afferents terminate in the *nuclei*

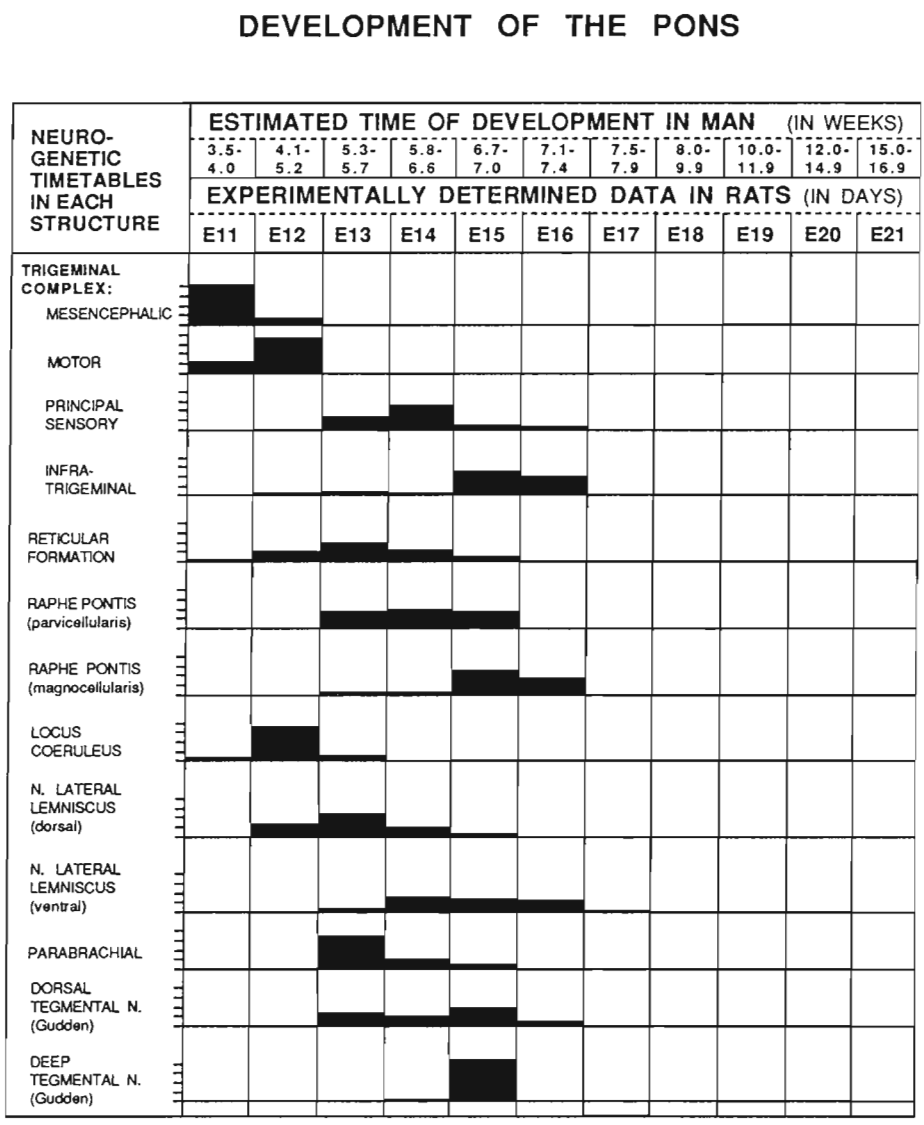


FIG. 24. As in Figure 19 for the pons. (From Bayer *et al.*, in press.)

of the lateral lemniscus (literature reviewed in Altman and Bayer, 1980d). The neurons in the dorsal and ventral subnuclei originate sequentially. Those in the dorsal part are generated mainly on E12-E14, with a peak on E13. Those in the ventral part are generated mainly on E14 to E16. In man, we estimate that these neurons are generated mainly during the 4th week to the middle part of the 7th week.

The *parabrachial nuclei* are part of the gustatory pathway (literature reviewed in Altman and Bayer, 1980d). In rats, nearly 70% of its neurons are generated on E13, while the remaining cells are generated on E14 and E15. In man, we estimate that these neurons are generated during the 5th and 6th weeks.

Neurons in the *dorsal tegmental nucleus of Gudden* send axons to the mammillary complex in the hypothalamus. In rats, these neurons are generated from E13-E16 in a biphasic pattern, with peaks on E13 and E15. The two peaks may be related to differential time of origin between the earlier originating small cells and the later generated large cells. The *deep tegmental nucleus of Gudden* also projects to the mammillary body in the hypothalamus. In rats, most of these neurons are generated on E15, concurrently with many of the large cells in the dorsal tegmental nucleus. In man, we estimate that the neurons in Gudden's tegmental nuclei originate mainly during the 5th and 6th weeks after fertilization.

The Cerebellum and the Precerebellar Nuclei

The cerebellum has been one of the most thoroughly studied brain structures in our laboratory. Normative studies of the time of origin of neurons in the cerebellar cortex (Altman, 1969; Altman and Bayer, 1978a), the deep nuclei of the cerebellum (Altman and Bayer, 1978a), and the precerebellar nuclei in the medulla and pons (Altman and Bayer, 1978b) were done with long-survival [^{3}H]thymidine autoradiography after comprehensive labeling. Short- and sequential-survival [^{3}H]thymidine autoradiography were used to study the migration of the

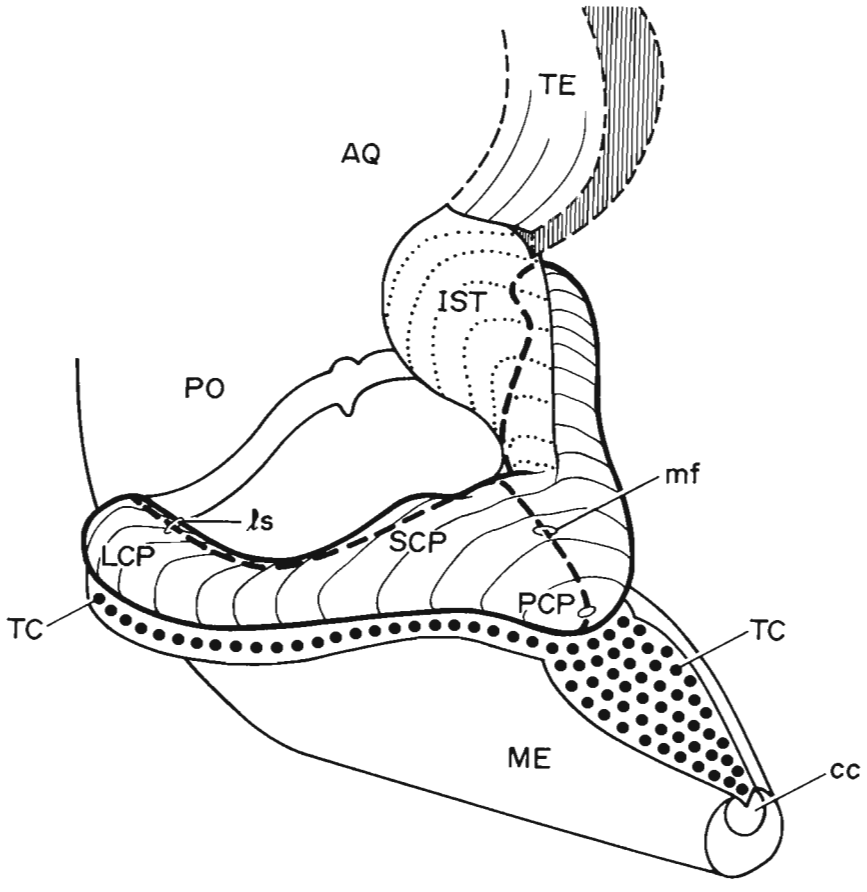


FIG. 25. The cerebellar primordium in a day E16 rat (heavy outline) in relation to the tela choroidea (TC) caudally and ventrolaterally and in relation to the embryonic lateral fissure (lf, broken lines) ventromedially. On the left side, the isthmus (IST) is not shown. The dorsomedial boundary between the isthmus and the cerebellar primordium shown on the right side is not certain. The three components of the cerebellar primordium are the lateral (LCP), the subisthmal (SCP), and the postisthmal (PCP). Other labels: AQ, cerebral aqueduct; cc, central canal in upper spinal cord; lf, embryonic lateral fissure; ME, medulla; mf, embryonic medial fissure; PO, pons; TE, mesencephalic tectum. (Figure 24 from Altman and Bayer, 1985a).

Purkinje cells and deep nuclear neurons (Altman and Bayer, 1978a, 1985a,b,c) and neurons in the precerebellar nuclei (Altman and Bayer, 1978b, 1987a,b,c,d). Cytodifferentiation of the Purkinje cells and the interneurons in the cerebellar cortex were investigated with electron microscopy (Altman, 1972a,b,c,). In addition, experimental manipulations using low-level X-irradiation during the early postnatal period have been used to determine the factors responsible for the morphogenesis of the elaborate Purkinje cell dendritic tree (Altman, 1973a,b, 1976b; Altman and Anderson, 1972, 1973). Based on findings in the cerebellum, we will propose several general principles that are likely to operate during the morphogenesis of other central nervous structures, but are difficult to test experimentally.

The Cerebellum as a Whole. The cerebellum is derived from the neuroepithelium that surrounds the lateral recess of the IVth ventricle in the pons and medulla. The cerebellar anlage is located in the roof plate of the hindbrain, above the anlage of the pons and forms the two anterior prongs of the diamond-shaped tissue that surrounds the velum (tela choroidia) overlying the IVth ventricle (Altman and Bayer, 1985a). Further anteroposterior growth of the mesencephalon and forebrain forces the cerebellar anlage backwards so that it lies above the upper medulla and the pons; the drawing in Figure 25 shows the cerebellar anlage (heavy outline) in this orientation. A bridge of neuroepithelium, the isthmus (IST, Fig. 25), is laterodorsal to the cerebellar anlage and is directly connected with the posterior tectal neuroepithelium in the roof of the mesencephalon (TE, Fig. 25). The cerebellar anlage is separated from both the pons and the isthmus by a shallow embryonic cerebellar fissure (Altman and Bayer, 1985a). The isthmus contains primordia of cell groups in the dorsal pons, such as the locus coeruleus and the vestibular nuclei. As the hindbrain doubles back on itself, the tela choroidea of the IVth ventricle separates it into an upper compartment, the isthmal and postisthmal recesses, and a lower compartment, the IVth ventricle proper. The cerebellar anlage itself has three components. (1) The lateral primordium (LCP, Fig. 25) lies adjacent to the lateral recess of the IVth ventricle; it is contiguous with the pons below and is separated from the anlage of the cochlear nuclei by the tela choroidea (TC, Fig. 25). (2) The subisthmal primordium (SCP, Fig. 25) is located beneath the isthmus and adjacent to the lateral primordium. (3) The postisthmal

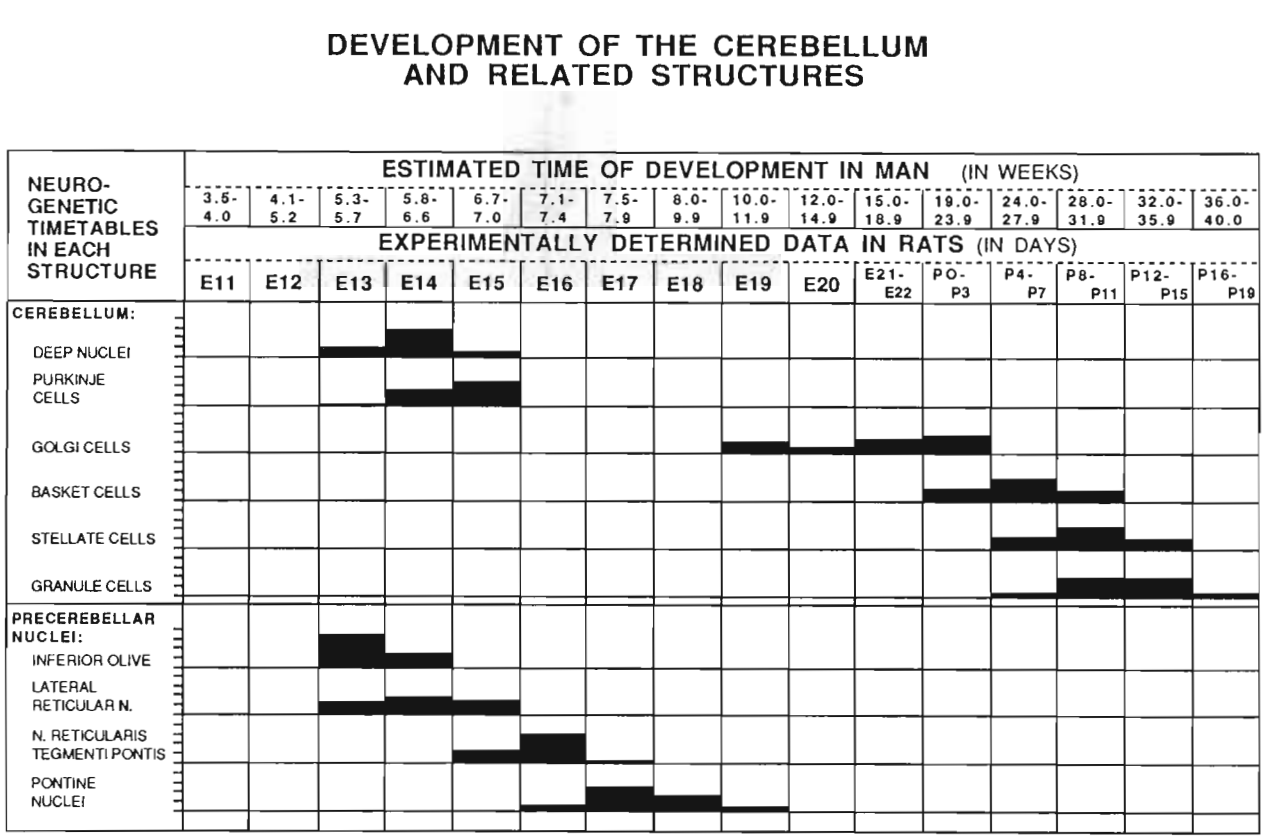


FIG. 26. As in Figure 19 for the cerebellum and precerebellar nuclei. (From Bayer *et al.*, in press.)

primordium (PCP, Fig. 25) is a region of neuroepithelium that is fused across the midline and forms a cap around the postisthmal recess of the IVth ventricle. As we will explain below, each of these primordia is the source of different classes of cerebellar neurons.

Deep Nuclei. The neurogenetic timetables of all three cerebellar deep nuclei have been combined and are presented in the top graph of Figure 26. In rats, E14 is the peak time of neuron origin (61% arise), while approximately 22% of the neurons are generated on E13 and 17% on E15. There is no difference in the time of origin of small vs. large neurons. Neurons in the most lateral dentate nucleus are slightly older than those in the more medial interpositus nucleus and those in the most medial fastigial nucleus (see Fig. 14 in Altman and Bayer, 1978a). In man, we estimate that deep nuclear neurons are generated from the early 5th week through the 6th week after fertilization.

Young neurons destined to reside in the cerebellar deep nuclei are generated in the lateral cerebellar primordium and initially migrate medially (arrows, Fig. 27A) from E14 to E16 (Altman and Bayer, 1985b). Between E16 and E18, the migrating neurons remain on the surface of the cerebellar primordium and begin to grow axons. Between E18 and E21, the earlier produced deep nuclear neurons migrate downward, while the later produced Purkinje neurons in the cerebellar cortex migrate around and above them. The deep neurons descend in the direction of the fibers of the inferior cerebellar peduncle that is first seen on E17 in rats. The three deep nuclei, the dentate, the interpositus, and the fastigial, can be distinguished from each other before their descent, and by E22, a small-celled and a large-celled component can be seen in each nucleus. Although it has not been demonstrated that such cell movements occur in man, it is likely that the human deep cerebellar nuclei have the same pattern of cell migration. If so, the migration should last from approximately the 6th through the 19th weeks after fertilization.

Cerebellar Cortex. The cerebellar cortex contains 5 neuronal populations. The Purkinje cells are the output neurons that have axons projecting out of the cortex, mainly to the deep nuclei, but some extend to the lateral vestibular nucleus (Deiters). Golgi cells, basket cells, stellate cells, and granule cells are classified as interneurons because they all have short axons that arborize within the cortex itself.

Purkinje Cells. The Purkinje cells in rats are generated somewhat later than the deep nuclear neurons (graph second from top, Fig. 26) with peak time of neurogenesis on E15 rather than E14. There is a lateral (older) to medial (younger) neurogenetic gradient within the Purkinje cell population (see Fig. 14 in Altman and Bayer, 1978a). In man, we estimate that Purkinje cell neurogenesis extends from the early 5th through the 6th weeks after fertilization.

The Purkinje cells are derived from all three parts of the cerebellar primordium (LCP, SCP, PCP, Fig. 25); how-

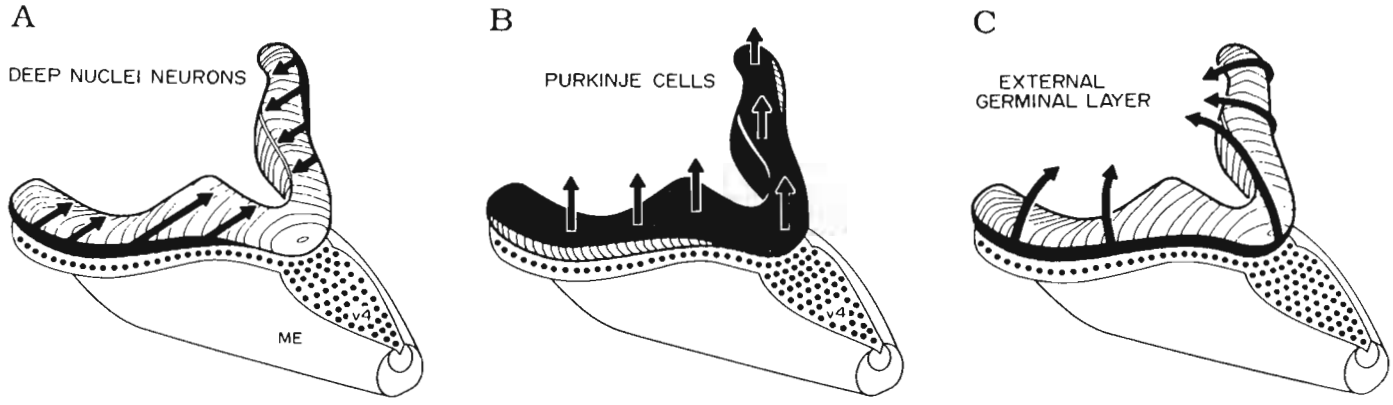


FIG. 27. Schematic illustrations of the initial migratory routes of young neurons (A and B) or of germinal cells derived from the neuroepithelium (C) in the cerebellar primordium. The deep nuclear neurons (A) are derived from the lateral cerebellar primordium (LCP, Fig. 25) and migrate medially. The Purkinje cells (B) are derived from the subisthmal and postisthmal primordia (SCP, PCP, Fig. 25) and migrate radially. The proliferative cells in the external germinal layer (C) are derived from the border region where the neuroepithelium is adjacent to the tela choroidea and grow anteriorly and medially to eventually cover the entire cerebellar cortex; these germinal cells are the source of the interneurons in the cerebellar cortex. Abbreviations in (A): ME, medulla; v4, fourth ventricle. (Figures 25-27 from Altman and Bayer, 1985a.)

ever, the source of the deep nuclei in the lateral cerebellar primordium (striped outline, Fig. 27B) is postulated to be spatially segregated from the sources of the Purkinje cells (solid black, Fig. 27B). The lateral cerebellar primordium is the source of Purkinje cells in the hemispheres, the subisthmal primordium is the source of those in the anterior vermis, and the postisthmal primordium of those in the posterior vermis. The Purkinje cells move out of their respective neuroepithelial sources and accumulate in a cortical transitory zone outside the neuroepithelium within one day after their generation (arrows, Fig. 27B; Altman and Bayer, 1985a,c). The subsequent radial migration of the Purkinje cells toward the surface of the cerebellar cortex awaits growth of the external germinal layer (to be described below) over the cerebellar primordium. In man, we estimate that Purkinje cell migration begins in the 8th week and continues at least through the 19th week after fertilization.

The Golgi Cells. These are the first interneurons to be generated in the cerebellar cortex, beginning on E19 and extending to the early postnatal period (P2; Fig. 26). Probably Golgi cells are derived from the receding neuroepithelium of the cerebellar primordium because those in the anterior vermis are generated at least two days before the external germinal layer has grown to the most anterior part of the cerebellum (Altman and Bayer, 1978a). We have not studied the migration of the Golgi cells. In man, we estimate that the Golgi cells are generated from the beginning of the 10th week through the 23rd week of development.

Basket, Stellate, and Granule Cells. These three populations of interneurons are noted for their late time of origin. In rats, most of them originate during the first three weeks after birth (Fig. 26). The basket cells have their peak time of origin between P4-P7, the stellate cells peak on P9-P10, while neurogenesis of the large population of granule cells occurs mainly between P8 and P15 (Altman, 1969) (Fig. 26). [^{3}H]thymidine injections that begin on P19 label few granule cells, and only an occasional granule cell is labeled when injections begin on P21. Cerebellar interneurons are not labeled by injections that begin at later times. In man, some of the basket, stellate, and granule interneurons must be generated during the fetal period. That is because the cerebellar cortex at birth already contains many neurons in the granular layer and scattered interneurons are in the well-defined molecular layer (Larroche, 1966). Basing our determinations on the histological sections shown in Figure 15 of Larroche (Larroche, 1966), we estimate that most of the basket, stellate, and granule cells are generated from the 19th week (corresponding to P0 in rats) to birth in the 40th week (corresponding to P19 in rats). However, the human cerebellum still has a prominent external germinal layer at birth that is retained for a variable period in infancy and childhood (ranging from the 7th postnatal month to the end of the 2nd year, see Fig. 10-6 in Lemire et al., 1975). That indicates that some granule cells (possibly basket and stellate cells as well) must also be generated after birth, just as they are in rats.

We have shown experimentally in rats that basket, stellate, and granule cells are generated by proliferating cells in the external germinal layer (Fig. 27C). This layer first appears on E17 in rats at the junction between the neuroepithelium of the cerebellar primordium and the tela choroidea, forming what we have called a germinal trigone (Altman and Bayer, 1978a). One prong of the trigone is the proliferating cells of the neuroepithelium in the cerebellar primordium, another prong is the proliferating cells of the tela choroidea (choroid plexus), and the third prong is the proliferating cells of the external germinal layer. The source of the external germinal layer is most likely the neuroepithelial cells along the lateral and posterior edges of the cerebellar primordium. As development proceeds,

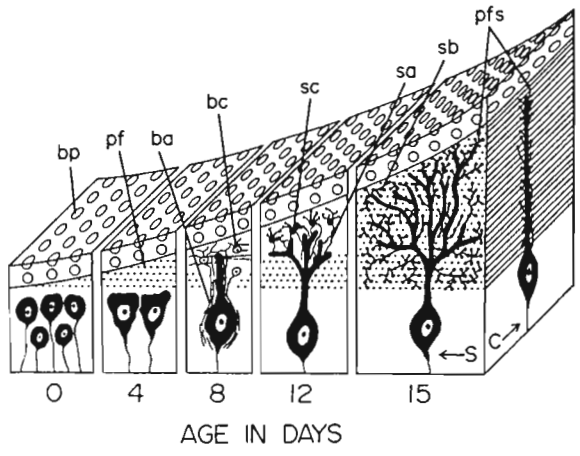


FIG. 28. Diagram of the development of the Purkinje cell dendritic tree as it is shaped by the basket, stellate, and granule cell axons (parallel fibers). Abbreviations: ba, basket cell axons; bc, basket cells; pf, parallel fibers; pfs, parallel fiber synapses; sa, stellate cell axons; sb, spiny branchlets; sc, stellate cells. (From Altman, 1976c.)

the external germinal layer grows anteriorly and medially beneath the pia to eventually cover the entire cerebellar primordium (Altman and Bayer, 1978a, 1985a) (arrows, Fig. 27C). In most rats, the external germinal layer persists to postnatal day 21 and its dissolution signals the cessation of granule cell neurogenesis.

The time course of the migration and settling of the basket, stellate, and granule cells has been investigated with electron microscopy and Golgi staining (Altman, 1972a,c). As early as 6 hrs after [^{3}H]thymidine injection on P6 in rats, labeled young neurons leave the proliferative compartment of the external germinal layer and accumulate in its premigratory compartment which is composed of densely packed, nonproliferating cells beneath the zone of proliferating cells. By 24 hrs after [^{3}H]thymidine injection, some labeled young neurons are already migrating through the primitive molecular layer. The basket and stellate cells settle in the molecular layer, above the Purkinje cells, while the granule cells continue to migrate into the granular layer, below the Purkinje cells. Basket and stellate cells settle within 1-2 days after their generation, while labeled granule cells are first seen in the granular layer 3 days after [^{3}H]thymidine injection. Because of the prolonged period of neurogenesis, the times for generation, migration, and settling of the basket, stellate, and granule interneurons overlap extensively. The oldest neurons in each population have settled several days before the youngest neurons are generated.

The cytoarchitecture of the cerebellar cortex is built as basket, stellate, and especially the granule cells migrate from the external germinal layer. These observations are based mainly on those presented in Altman (Altman, 1972a,c). While in the premigratory compartment, the presumptive young granule cell begins to grow its axon, called a parallel fiber. First, the cross bar of the T-shaped part of the parallel fiber grows from opposite poles of the horizontally-oriented cell body. Next, the granule cell body turns vertically as it migrates downward through the molecular layer and continues to extrude a trailing process that forms the vertical part of the T-shaped parallel fiber. During growth, the granule cell axons are strictly oriented so that the cross bar of the T is parallel to the long axis of the lobule; in the vermis that is perpendicular to the midline. As we will describe later, that has an important bearing on the orientation of the Purkinje cell dendritic tree parallel to the midline. Another important organizational aspect of the parallel fibers is their accumulation in the molecular layer strictly according to age. The first parallel fibers from the oldest granule cells occupy the bottom of the molecular layer, while the last parallel fibers from the youngest granule cells occupy the top. The young neurons in the molecular layer that are variably oriented are postulated to be the basket and stellate cells that are arrested in their downward migration by the gridwork of parallel fibers piling up in the molecular layer.

Purkinje Cell Dendrogenesis. In all mammalian brains thus far studied with the Golgi technique, Purkinje cells are noted for their large flattened fan-shaped dendritic arborizations extending from the base to the surface of the molecular layer. The planar branches are oriented perpendicular to the long axis of the lobule, at a right angle to the parallel fiber bundles, as shown at P15 in Figure 28. By using low level X-irradiation to eliminate either some or all of the basket, stellate, and granule cell populations, factors responsible for shaping the Purkinje cell dendritic tree have been determined. The following paragraphs are summarized from several papers on experimental studies in the rat cerebellar cortex after X-irradiation (Altman, 1973a,b, 1976b; Altman and Anderson, 1972, 1973).

When the precursors of all basket, stellate, and granule cells are eliminated by prolonged X-irradiation starting either at birth or P4 and continuing to P14, the Purkinje cell dendrites develop no preferential orientation. Several primary dendrites grow in all directions, some into the very reduced molecular layer, others extending downward or horizontally (Altman and Anderson, 1972, 1973). Since climbing fiber axons (which originate in the inferior olive) already have synaptic contacts with Purkinje cells, the conclusion is that the climbing fibers are not responsible for any of the orientation features found in normal Purkinje cell dendrites.

When the X-irradiation exposures begin on P8 and extend to P15, normal numbers of basket cells are generated, but stellate and granule cells are greatly reduced. In these animals, the Purkinje cells develop an unusually long primary dendrite that extends into the molecular layer; some of the primary dendrites are so long that they actually reach the pial membrane (Altman, 1976b). Long spiny branchlets grow downwards from the top of the primary dendrite into the lower molecular layer where there are a few parallel fibers, giving the appearance of a weeping willow tree. The primary dendrites are covered with the descending axons of basket cells. Since basket cells are the

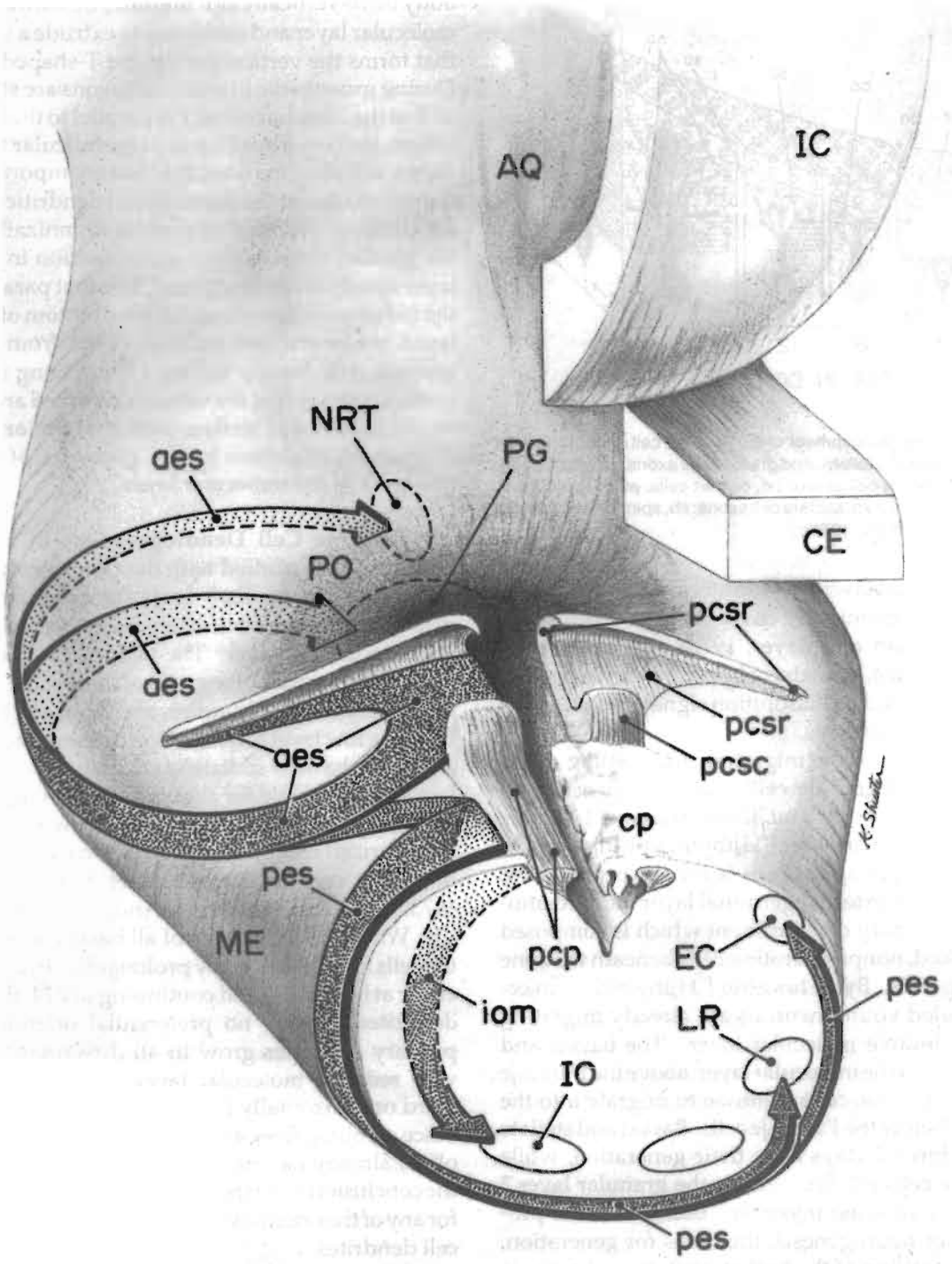


FIG. 29. Divergent migratory routes (arrows) of neurons of the precerebellar nuclei to widely spaced destinations in the medulla (ME) and pons (PO). All neurons are sequentially generated in various parts of the precerebellar neuroepithelium (pcp,pcsr, pcsc) in the dorsal medulla (From Altman and Bayer, 1987d). Other abbreviations: aes, anterior extramural (subpial) migratory stream; AQ, cerebral acqueduct in mesencephalon; CE, cerebellar plate; cp, choroid plexus of the IVth ventricle; EC, external cuneate nucleus; IC, inferior colliculus; LR, lateral reticular nucleus; IO, inferior olive complex; iom, intramural migratory stream (within the parenchyma) of inferior olive neurons; BRT, nucleus reticularis tegmenti pontis; pes, posterior extramural (subpial) migratory stream; PG, nuclei of the basal pontine gray.

predominant interneurons, they have unchecked influence on the growth of the Purkinje cell dendrites. The conclusion is that the basket cells induce the Purkinje cell dendrite to grow a single primary dendrite into the molecular layer (P8, Fig. 28).

When the X-irradiation exposures begin on P8 and are stopped on P11, the external germinal layer regenerates in time to produce some stellate cells and some granule cells. In these animals, the Purkinje cell dendrites form exceptionally long primary dendrites in the lower half to two-thirds of the molecular layer. But in the upper half to one-third of the molecular layer where stellate cells are present,

there are profuse smooth secondary branches extending from the primary dendrite, and a plethora of spiny branchlets among the parallel fibers. The parallel fibers may be reoriented in the reconstituted molecular layer. If that happens, the Purkinje cell dendritic planes are turned perpendicular to the long axis of the parallel fibers (Altman, 1973b). Evidently, the normal orientation of the later generated granule cells (long axis perpendicular to the midline) is lost when the external germinal layer regenerates after X-irradiation; the parallel fibers continue to fasciculate, but the orientation of the fascicles is no longer related to the orientation of the cerebellum as a whole. There are several conclusions to be drawn from these studies. Since smooth secondary and tertiary branches only appear when stellate cells are present, we postulate that stellate cells are responsible for these features of the Purkinje cell dendrite (P12, Fig. 28). Since spiny branchlets are always directed toward parallel fibers, we postulate that granule cell axons induce the growth of the spiny branchlets (P15, Fig. 28). Finally, since the planar part of the Purkinje cell dendritic tree is always perpendicular to the bundles of parallel fibers, we conclude that the fascicular orientation of the granule cell axons induces the Purkinje cell dendrite to arborize in a planar fashion (Altman, 1976c) (compare S and C in P15, Fig. 28).

The Precerebellar Nuclei. The precerebellar nuclei in the medulla and pons are remarkable for their sequential neurogenetic timetables (Altman and Bayer, 1978b) (4 bottom graphs, Fig. 26). The first is the inferior olive, where 72% of the neurons are generated on E13. The second is the lateral reticular nucleus, where neurons are generated from E13 to E15 with a shallow peak on E14 (39%). The third is the nucleus reticularis tegmenti pontis, where the neurogenetic peak is on E16 (64%). Finally, neurons in the pontine nuclei are mainly produced on E17 (53%) and E18 (29%). In man, we estimate that the precerebellar nuclei are generated from the early 5th week through the 11th week of development.

The neurogenetic pattern in the precerebellar nuclei suggests a common neuroepithelial source, where populations of neurons are produced one after the other. Indeed, a common site has been identified in the two posterior prongs of the diamond-shaped neuroepithelium that surrounds the velum of the IVth ventricle in the roof of the hindbrain (pcp, pcsr, pcsc, Fig. 29; Altman and Bayer, 1987a,d). That region successively produces neurons of the inferior olive, the lateral reticular nucleus, the nucleus reticularis tegmenti pontis, and the pontine nuclei. In spite of their common site of origin, the precerebellar nuclear neurons follow divergent migratory pathways to diverse settling sites. Those in the inferior olive begin to migrate one day after their generation and form a ventrally directed migratory stream within the parenchyma of the medulla (iom, Fig. 29; Altman and Bayer, 1987b). After another day of migration, the young neurons settle in the ventral part of the lower medulla (IO, Fig. 29). The neurons destined to reside in the lateral reticular nucleus also leave their site of origin within 24 hrs, but migrate circumferentially around the edge of the medulla beneath the pia (pes, Fig. 29) in a posteroventral route (Altman and Bayer, 1987c). By E17, the first neurons in the migratory stream reach the midline at the ventral surface of the medulla and continue to migrate across the midline; they settle in the ventrolateral medullary parenchyma on the opposite side of the brain by E19 (LR, Fig. 29). The youngest neurons follow sequentially a few days later and are settling by E22. Also within one day after their generation, neurons of the nucleus reticularis tegmenti pontis follow a subpial anteroventral migratory route (aes, Fig. 29) to their settling site in the depths of the pons (NRT, Fig. 29) and reach their target approximately three days after their generation (those generated on E16 settle by E19; Altman and Bayer, 1987c). The neurons of the pontine nuclei also follow a subpial anteroventral migratory route (aes, Fig. 29) and settle in the superficial ventral pons (PO, Fig. 29) approximately three days after their generation (Altman and Bayer, 1987c). The settling pattern is highly ordered with respect to time of neurogenesis: the oldest neurons arrive first and form a core, younger neurons arrive later and settle around the old cell core in concentric arcs. In man, we would estimate that precerebellar nuclear neurons are migrating from the end of the 5th week through the 18th week of development.

The Mesencephalon

Our developmental studies in the mesencephalon are limited to the determination of the time of neuron origin using long-survival [^{3}H]thymidine autoradiography (Altman and Bayer, 1981a).

Motor Nuclei and Others Related to the Visual System. The midbrain tegmentum contains five nuclei that are part of the visual system. When all of these nuclei are considered together in rats, there is a sequential time of origin between them (top 5 graphs, Fig. 30). Somatic motor neurons are oldest. In the trochlear nucleus (cranial nerve IV), 60% of these neurons originate on E12, 40% on E13. In the oculomotor nucleus (cranial nerve III), 52% of the somatic motor neurons originate on E12, 48% on E13 (Altman and Bayer, 1981a). Next in line are neurons related to the somatic motor output pathway in the nucleus of Darkschewitsch; 38% on E12, 45% on E13, 9% on E14 and 8% on E15. Visceral motor neurons in the Edinger-Westphal nucleus are next; 15% on E12, 71% on E13, 6% on E14 and 14% on E15. Finally, the latest neurons to be generated in the tegmental part of the visual system are part of the visual sensory pathway and reside in the parabigeminal nucleus. Parabigeminal neurons peak on E14 (50% originate) with approximately 25% of the population originating on E13 and E15 (Altman and Bayer, 1981a). In man, we estimate that the mesencephalic tegmental neurons in the visual system are generated during the 4th, 5th, and 6th weeks after fertilization.

Other Tegmental Nuclei. The *red nucleus* is composed of a caudal magnocellular and a rostral parvocellular division. The rubrospinal tract originates in the magnocellular division, and its termination field overlaps with that of the corticospinal tract. For a review of the connections of the red nucleus, see Altman and Bayer (Altman and Bayer, 1981a). In rats, the magnocellular part of the red nucleus mostly contains large neurons with some scattered medium-sized and smaller neurons; these neurons are generated mainly on E13 (90%), the remainder on E14 (6th graph from top, Fig. 30). The parvocellular part contains mostly medium-sized neurons with a few scattered large neurons; here neurogenesis also peaks on E13 (7th graph from top, Fig. 30). In man, we estimate that most of the neurons in the red nucleus (both parts) are generated in the middle part of the 5th week after fertilization, while those in the parvocellular portion continue to be generated up to the middle of the 6th week after fertilization.

The *interpeduncular nucleus* has several subdivisions with different neurochemical properties (Lenn and Bayer, 1986). For purposes of simplicity, only two neurogenetic timetables are presented that separate neurons in dorsal and ventral parts of the nucleus (Fig. 30). Dorsal neurons originate mainly on E14 and E15 and ventral neurons originate mainly on E13. The various chemically distinguishable subnuclei of the interpeduncular nucleus have different timetables of neurogenesis (see Fig. 1 in Lenn and Bayer, 1986). That implies that chemical and anatomical differentiation of the interpeduncular nucleus is related to an orderly pattern of neurogenesis. In man, we estimate that neurons in the interpeduncular nucleus are generated from the middle of the 5th and during all of the 6th week after fertilization.

The *dorsal and median raphe nuclei* constitute groups B7 and B8, respectively, of the serotonergic neurons in the central nervous system. Mostly ascending fibers to the diencephalon and telencephalon originate in the dorsal raphe, while the median raphe is the source of many descending fibers to the pons, cerebellum, and medulla. A more complete discussion of the connections of the raphe nuclei in rats is in Altman and Bayer (Altman and Bayer, 1981a). The dorsal raphe neurons are located just beneath

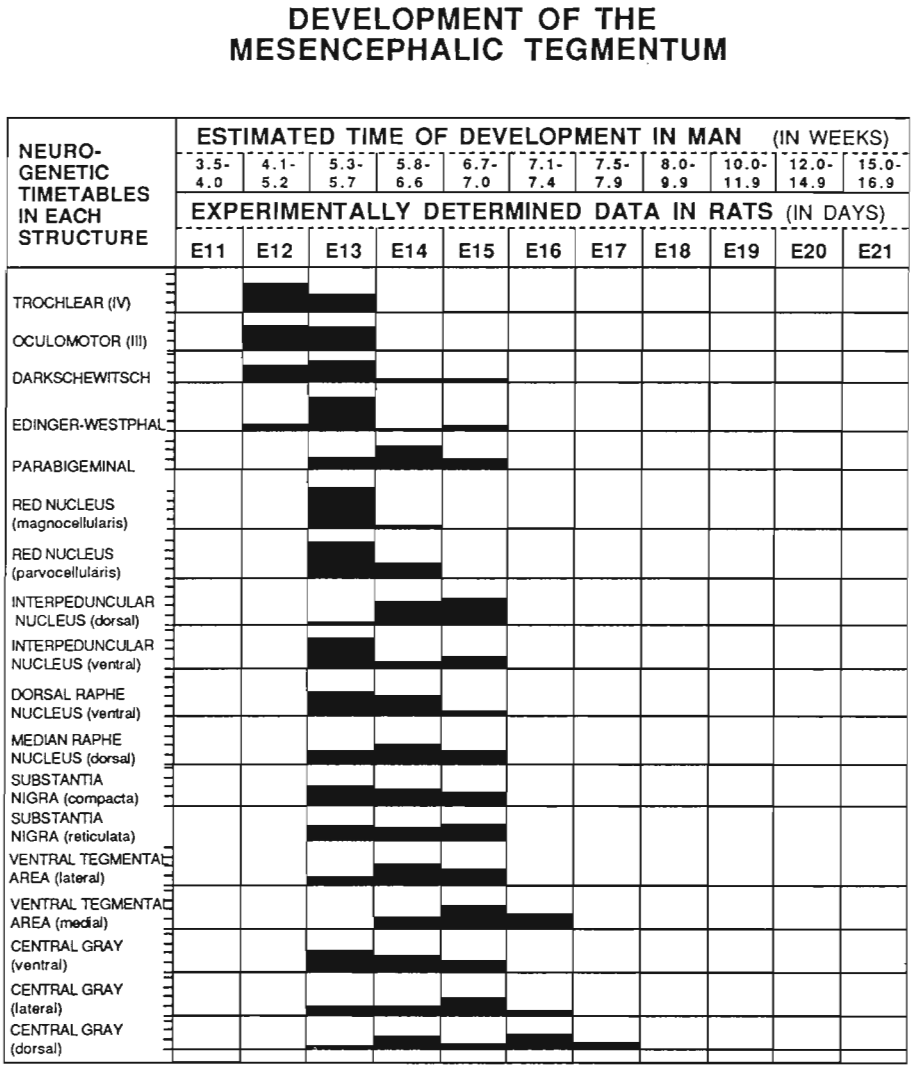


FIG. 30. As in Figure 19 for the mesencephalic tegmentum. (From Bayer *et al.*, in press.)

and within the ventral part of the central gray, but they can be distinguished from central gray neurons by their larger size. However, the data presented in Figure 30 represents the neurogenetic timetable for neurons in the ventral part of the dorsal raphe nucleus only, where there is little intermingling with the central gray. Most of the dorsal raphe neurons are generated on E13 and E14, with some arising on E15. The neurogenetic timetable for the median raphe nucleus in Figure 30 is restricted to the dorsal part of the nucleus, where smaller neurons predominate. These neurons are generated from E13 to E15, with a peak on E14. Neurogenesis of the large neurons in the relatively small ventral part of the median raphe nucleus was not determined quantitatively, however, most of these neurons have already been generated by E14. In man, we estimate that mesencephalic raphe neurons are generated from the early 5th through the 6th week after fertilization.

There is a sequential neurogenetic gradient between the *substantia nigra* and the *ventral tegmental area*. Substantia nigra neurons are generated earlier (E13-E15 for both pars compacta and pars reticulata, Fig. 30) than those in the ventral tegmental area (mainly on E14-E16, Fig. 30). In the ventral tegmental area, lateral cells are generated mainly on E14 and E15, medial cells on E15 and E16. In man, we estimate that most of the dopaminergic neurons are generated from the early 5th through the middle part of the 7th week after fertilization.

The *central gray* surrounds the cerebral aqueduct, and is believed to be related to nociceptive functions (for a review, see Altman and Bayer, 1981a). In terms of its development, the central gray can be divided into three parts, a ventral part surrounded by the tegmentum, a lateral part at the tegmental/tectal border, and a dorsal part surrounded by the tectum. In rats, there is a ventral (older) to dorsal (younger) neurogenetic gradient between these subdivisions (three bottom graphs, Fig. 30). Neuron production begins in all three components on E13, but it peaks on E13 ventrally, on E15 laterally, and on E16 dorsally. The dorsal part of the nucleus actually has a biphasic pattern of neurogenesis (a peak on E14 as well as on E16). In man, we estimate that central gray neurons are being generated from the early 5th week through the end of the

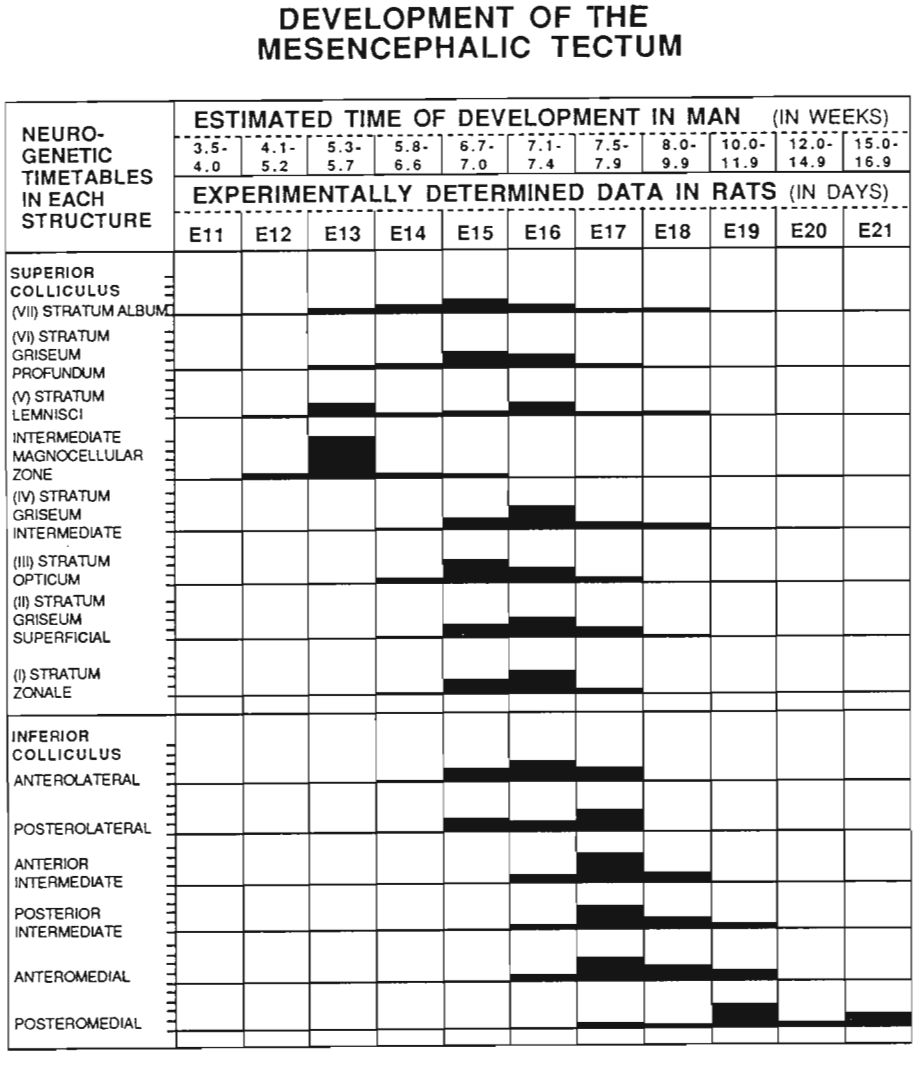


FIG. 31. As in Figure 19 for the mesencephalic tectum. (From Bayer et al., in press.)

7th week after fertilization.

Superior Colliculus. The lamination pattern in the rodent and human superior colliculus is much less distinct than in the chick optic tectum (Brodal, 1981). The cell layers are not sharply segregated from each other and the fibrous layers do not offer clear landmarks because they contain an appreciable concentration of neuronal perikarya. The stratum zonale (layer I) is composed of sparsely packed small cells while similar cells are packed more densely in the stratum griseum superficiale (layer II). The typical cells of the stratum opticum (layer III) are larger, spindle-shaped (with horizontal orientation in the coronal plane) and usually have pale nuclei. The stratum griseum intermediate (layer IV) contains a high concentration of small cells together with some large cells. The cell population of the stratum lemnisci (layer V) is quite heterogeneous and includes many large, multipolar cells, particularly laterally. The stratum griseum profundum (layer VI) is characterized by intermediate-sized multipolar cells. The stratum album profundum (layer VII) contains most large cells but they are not as large as some of those seen in layer V.

Neurogenetic patterns in the rat superior colliculus (top 8 graphs, Fig. 31) indicate that neuronal populations may be grouped into three cytogenetic zones (Altman and Bayer, 1981c). The first is the intermediate magnocellular zone that is composed of the large multipolar neurons in layers IV (fewer) and V (more). These large neurons are distinguished from others in the same layers by their early and brief span of neurogenesis on E13 (4th graph from top, Fig. 31). That early-forming zone divides the superior colliculus into upper and lower cytogenetic zones where the time span of neurogenesis typically lasts for 5-6 days. In the deep layers (3 top graphs, Fig. 31), a deep (older) to superficial (younger) neurogenetic gradient delineates a second cytogenetic zone between layers VII, VI, and V. In the superficial layers, a sandwich neurogenetic gradient distinguishes a third cytogenetic zone (5th to 8th graphs from top, Fig. 31). Older neurons tend to congregate in layer III (peak on E15), and younger neurons in layer IV below and in layers II and I above (all have peaks on E16). The three cytogenetic zones may be correlated with the structural-functional parcellation of the superior colliculus into an efferent spinotectal subdivision (intermediate magnocellular zone), a somatomotor subdivision (deep zone), and a visual sensory subdivision (superficial zone). In man, we estimate that neurons in the superior colliculus are generated from the 5th to the 9th weeks of development, possibly in similar neurogenetic patterns.

Inferior Colliculus. The neurogenetic timetables in the rat inferior colliculus (bottom set of graphs, Fig. 31) indicate a complex gradient (Altman and Bayer, 1981b). Older neurons settle anterolaterally (peak production on E16). Younger neurons settle anteromedially to posterolaterally (all have peak production on E17). Finally, the youngest neurons settle posteromedially (peak production on E19, but many are generated on E21). In addition, ventral cells tend to be older than dorsal cells (not quantified). These neurogenetic gradients suggest that neurons of the inferior colliculus migrate in a ventral, lateral, and anterior direction away from the posterior tectal neuroepithelium and settle according to time of origin in a ventrolateral (older) to dorsomedial (younger) gradient. The tonotopic order of inputs into the inferior colliculus also runs from ventrolateral (high tones) to dorsomedial (low tones) and can be superimposed on the pattern of neurogenetic gradients (see Fig. 8 in Altman and Bayer, 1981b). In man, we estimate that neurons in the inferior colliculus are generated from the late 6th week up to the 17th week of development and postulate that strict neurogenetic gradients exist that may be related to tonotopically ordered anatomical projections.

The Thalamus

The time of origin and embryonic development of most thalamic nuclear groups have been studied with both long survival and short-survival [^{3}H]thymidine autoradiography. The following account is summarized from several previous publications (Altman and Bayer, 1979a,b,c, 1988a,b,c, 1989a,b,c).

The *anterodorsal, anteroventral, anteromedial* and *lateral-dorsal* thalamic nuclei are included in the anterior complex. They have been described as major components of the Papez circuit in the limbic system because of their strong anatomical connections with the hippocampal region and the retrosplenial cortex (Altman and Bayer, 1988b; Bayer and Altman, 1991a). In rats, the oldest neurons in the complex are in the lateral dorsal nucleus (peak on E15); the anterodorsal, anteroventral, and anteromedial nuclei have neurogenetic peaks on E16 (top 4 graphs, Fig. 32). In man, we estimate that neurons in the anterior thalamic nuclear complex are generated from the latter half of the 6th week through the 8th week of development. Neurons of the anterior complex are generated in a discrete neuroepithelial source, the anterior lobule (Altman and Bayer, 1988b). The young neurons leave that source within 24 hours after their generation. On E16 and E17, three migratory streams can be distinguished, a dorsal one to the anterodorsal nucleus, an intermediate one to the anteroventral and anteromedial nuclei, and a ventral one to the lateral dorsal nucleus. Generally, the anterior thalamic neurons settle about three days after they are generated. In man, we estimate that neurons are migrating to and settling in the anterior thalamic nuclear complex from the 7th through the 11th weeks of development.

The *ventrobasal nucleus* serves as the principal thalamic relay station in the somesthetic and somatomotor pathways to the somatosensory cortex; the *ventrolateral nucleus* is the relay of cerebellar input to the motor cortex, and the *ventromedial nucleus* relays tactile information from the tongue and taste input to the gustatory and insular cortex (reviewed in Bayer and Altman, 1991a). In rats, most of the neurons in the ventrobasal complex are generated on E15 (Fig. 32) but more neurons are generated on E14 in the

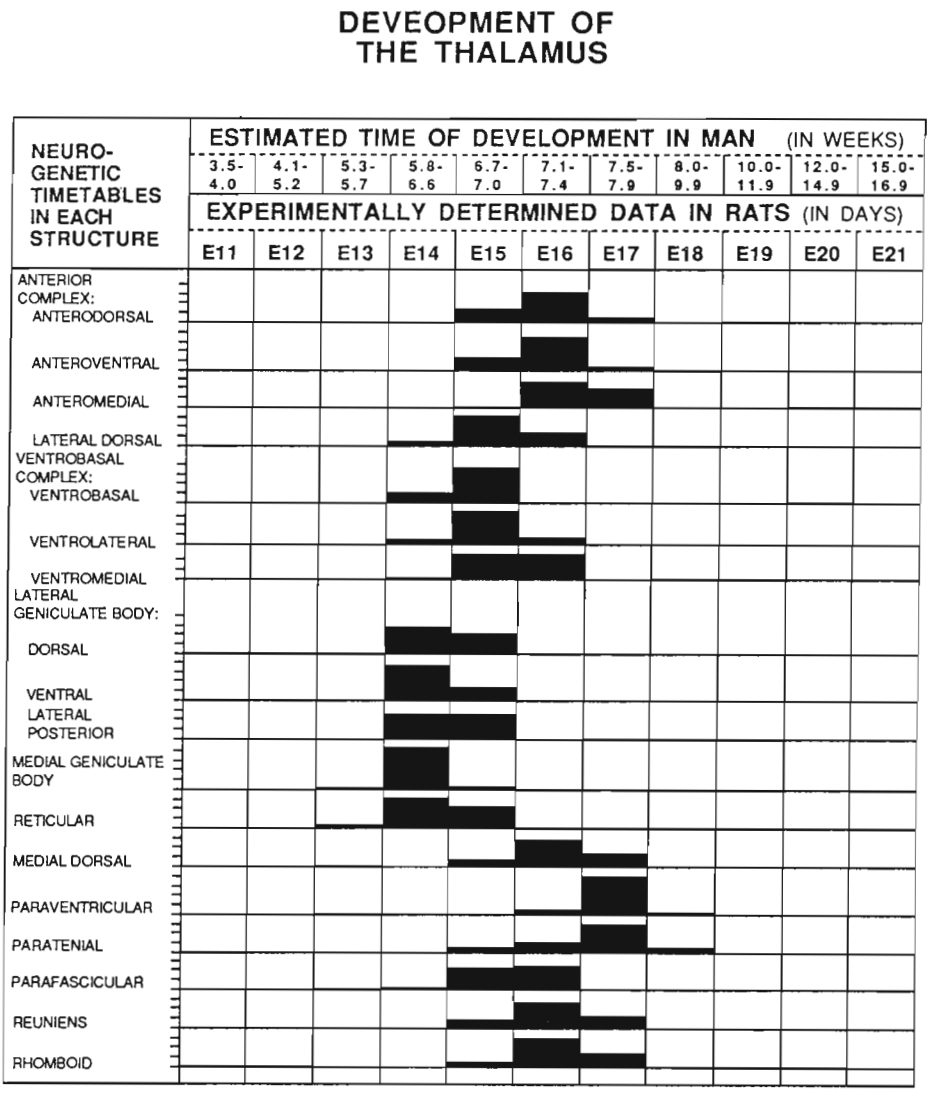


FIG. 32. As in Figure 19 for the thalamus. (From Bayer *et al.*, in press.)

ventrobasal nucleus and more on E16 in the ventromedial nucleus. In man, we estimate that the ventrobasal complex neurons are generated from the late 5th up to the middle 7th weeks of development. Neurons of the ventrobasal nuclear complex originate in the unique intermediate thalamic neuroepithelial lobule, which is distinguished from the rest of the thalamic neuroepithelium by the presence of a mitotically active secondary germinal matrix-a subventricular zone (Altman and Bayer, 1989a). Two sublobules can be distinguished, an earlier producing posteroventral site that is inferred to be the source of the ventrobasal nucleus and a later producing anterodorsal site that is inferred to be the source of the ventrolateral nucleus. The neurons of the ventromedial nucleus appear to originate from the intermediate neuroepithelial lobule after its two sublobules are no longer visible. Migration, settling, and axonogenesis occurs within two days after generation. In man, we estimate that ventrobasal complex neurons are migrating and settling from the 7th to the 9th weeks of development, and postulate that these neurons begin to grow axons to the cerebral cortex also during this time.

The major thalamic components of the mammalian visual system are in the lateral geniculate body. The *dorsal lateral geniculate nucleus* has probably received more attention by anatomists and physiologists than any other thalamic structure because of its rich associations with the retina and the primary visual cortex (see literature cited in Altman and Bayer, 1989c). In primates, the dorsal lateral geniculate nucleus has 6 layers of neurons, but there are variations in lamination patterns between different primate species. There is more structural variation in the dorsal lateral geniculate nucleus of lower mammals; there are only three layers in cats and there is no visible lamination in rats (Altman and Bayer, 1979a,b, 1989c). In contrast, the *ventral lateral geniculate nucleus* is more prominent in lower mammals than it is in man. The *lateral posterior nucleus* in lower mammals is considered to be the homologue of the pulvinar in primates and the lateral posterior-pulvinar complex in carnivores. Like the primate pulvinar, the rat lateral dorsal nucleus has rich associations with the secondary visual cortex (Olavarria, 1979). In rats, neurogenesis in the ventral lateral geniculate nucleus peaks on E14. In

the dorsal lateral geniculate nucleus, more neurons are generated on E14 than on E15. In the lateral posterior nucleus, equal proportions of neurons are generated on E14 and E15 (Fig. 32). Each of these nuclei have intranuclear neurogenetic gradients (Altman and Bayer, 1989c). In man, we estimate that neurons in these nuclei are generated from the late 5th through the 6th weeks of development. Given the more complex structure of these nuclei in man, we predict that sharp intranuclear neurogenetic gradients exist in the human thalamus, especially between cell layers in the dorsal lateral geniculate nucleus. Neurons bound for the dorsal and ventral lateral geniculate nuclei and the lateral posterior nucleus are generated in three discrete neuroepithelial sites just below the pineal recess, and above the site of origin of the ventrobasal complex. The source of the lateral posterior nucleus is directly adjacent to the pineal recess, the source of the dorsal lateral geniculate nucleus is just below that followed more ventrally by the source of the ventral lateral geniculate nucleus (Altman and Bayer, 1989c). Within one day after their generation, young neurons move out of their respective neuroepithelial sources and migrate for 1-2 days before they settle. In man, we estimate that neurons destined for the lateral geniculate body migrate during the 7th to 9th weeks of development. There is no evidence in the rat that the lateral posterior nucleus contains a late-generated group of neurons that migrates in from the ventromedial telencephalon, as reported by Sidman and Rakic (1982) in primates.

The *medial geniculate body* is the principal thalamic relay station in the mammalian auditory pathway. Several subdivisions have been proposed, mainly based on anatomical and physiological work in other species than the rat. However, the rat medial geniculate body contains subdivisions that compare to those of other mammals (reviewed in Altman and Bayer, 1989b). For purposes of simplicity, the time of origin of all neurons in the medial geniculate body have been combined in the data shown in Figure 32; neurons are generated mainly on E14. In man, we estimate that these neurons are generated from the late 5th to the late 6th weeks of development. Intrinsic neurogenetic gradients can be related to the anatomical connections with auditory cortical areas (Bayer and Altman, 1991a). The site of origin of medial geniculate neurons is a caudally situated eversion of neuroepithelium ventroposterior to the source of the ventral lateral geniculate nucleus (Altman and Bayer, 1989b). Young neurons leave that germinal source within one day after their generation (by E15) and migrate caudally for at least two more days before settling (on E17) in the most caudal and lateral part of the thalamus, where the medial geniculate body comes to lie adjacent to the mesencephalon. In man, we estimate that medial geniculate neurons migrate from the end of the 6th week through the 8th week of development.

Unlike most thalamic nuclei, the *reticular nucleus* does not project to the cerebral cortex; instead, its axons terminate in the thalamus (for review, see Altman and Bayer, 1988c). In rats, some neurons are generated on E13 but most arise on E14 and E15 (Fig. 32). The reticular nucleus is divisible into a very early forming small central part (peak on E13) and later forming medial and lateral parts (peaks on E14; see Fig. 3 in Altman and Bayer, 1988c). The central subnucleus is distinguished as the earliest originating neuronal population in the thalamus, and its neurons are generated in a unique neuroepithelial site, the reticular protuberance, while the sites of origin of the medial and lateral subnuclei are in the reticular lobule located beneath the protuberance. One day after they are generated, young neurons destined for various reticular subnuclei migrate away from their respective germinal sources and settle. The ventrally situated migrating reticular cells ride along the top of the internal capsule. Most of the reticular neurons have settled by E19. In man, we estimate that reticular neurons are generated from the late 5th through the 7th week of development. We estimate that these neurons are migrating from the late 6th week through the 11th week of development.

The *medial dorsal, paraventricular, paratenial, parafascicular, reuniens,* and *rhomboid nuclei* are the intralaminar and medial thalamic nuclei. In rats, neurons in the medial dorsal nucleus are generated E15-E17 with a peak on E16. E17 is the peak day of neurogenesis in the anterior paraventricular and the paratenial nuclei (Altman and Bayer, 1988b). The sites of origin of the medial dorsal, anterior paraventricular, and paratenial nuclei are presumably in the anterior lobule (Altman and Bayer, 1988a), but the migration of these neurons from their sites of origin has not yet been followed. Neurons in the parafascicular nucleus are generated about equally on E16 and E17. The neuroepithelial source of the parafascicular nucleus has not yet been identified in rats, but it is likely to be in the vicinity of the intermediate sublobule, which on earlier days gives rise to the ventrobasal complex (Altman and Bayer, 1988a). Neurons in the reuniens and rhomboid nuclei are generated with peaks on E16. As with the other nuclei in this group, the neuroepithelial sources of the reuniens and rhomboid nuclei have yet to be determined (manuscripts in preparation). In man, we estimate that neurons in these nuclei are generated from the latter part of the 6th week through the 9th week of development.

The Preoptic Area and the Hypothalamus

All hypothalamic nuclei, and most of those in the preoptic area are derived from the neuroepithelium in the ventral part of the third ventricle, below the neuroepithelium generating thalamic neurons. Just as for the thalamus, there appears to be a high degree of neuroepithelial mosaicism, where discrete sites can be linked to specific nuclei. The hypothalamus proper is distinguished from the preoptic area at the optic recess and is subdivided into the lateral hypothalamus, the core hypothalamus, the mammillary body, and the midline hypothalamus. The following discussion is summarized from the observations presented in several journal articles

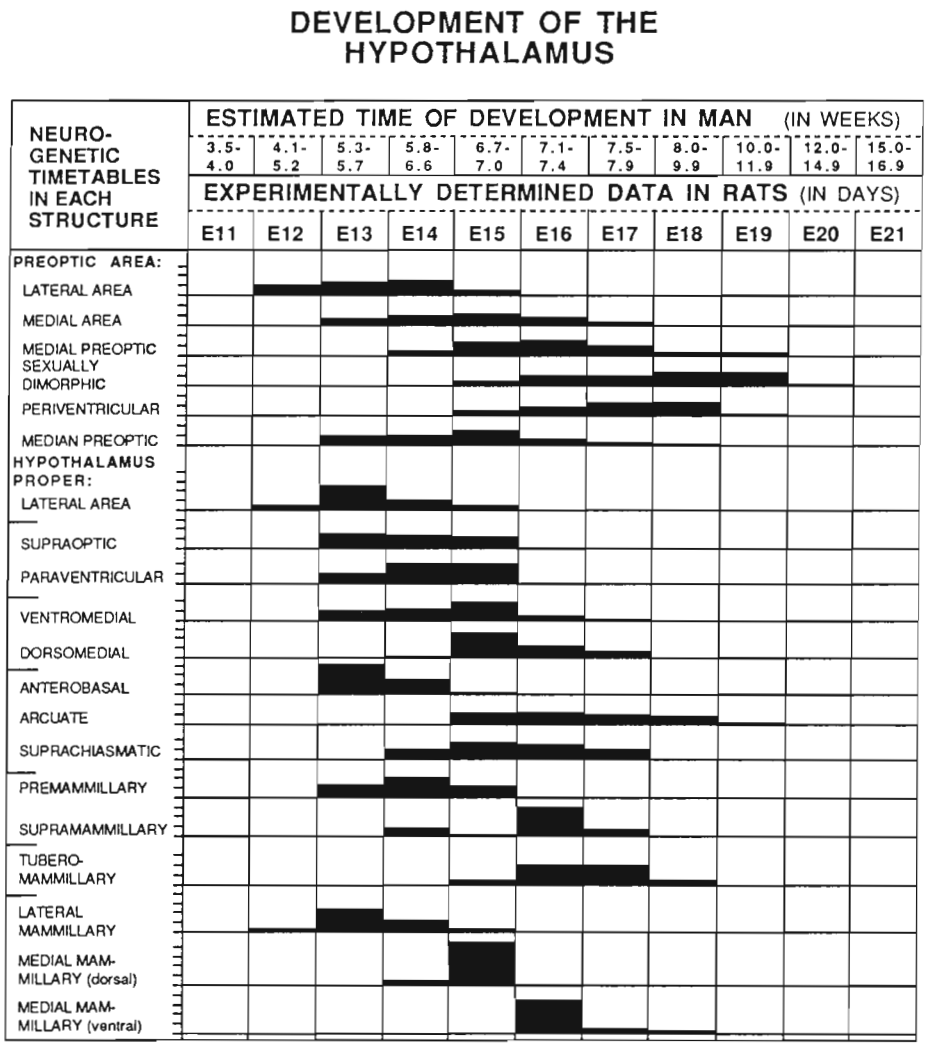


FIG. 33. As in Figure 19 for the hypothalamus. (From Bayer *et al.*, in press.)

(Altman and Bayer, 1978c,d,e; Bayer and Altman, 1987b) and a monograph on hypothalamic embryonic development (Altman and Bayer, 1986).

Preoptic Area Nuclei. The preoptic area has been the subject of controversy for many years in the anatomical literature because it blends with the basal telencephalon. Indeed, some of its components (magnocellular preoptic nucleus, the preoptic continuation of the bed nucleus of the stria terminalis) have been shown to originate in the telencephalon and migrate into the preoptic area to settle (Bayer and Altman, 1987b). But throughout most of its extent, the preoptic area strongly resembles the hypothalamus. There has been considerable recent interest in the preoptic area since sexually dimorphic nuclei have been found here in both rodent and human brains. The anterior hypothalamus also has sexually dimorphic areas. Thus, on the basis of its functional associations with the endocrine system and on its anatomical configuration, the major part of the preoptic area appears to be an anterior continuation of the hypothalamus (see review in Bayer and Altman, 1987b).

Throughout most of the preoptic area in rats there is a lateral (older) to medial (younger) neurogenetic gradient (top 6 graphs, Fig. 33). Neurons originate mainly between E12 and E15 in the lateral preoptic area, between E13-E16 in the medial preoptic area, between E14-E17 in the medial preoptic nucleus, and between E15-E18 in the periventricular nucleus. There are two atypical structures: (1) the sexually dimorphic nucleus originates exceptionally late (E15-E19) and is located farther away from the third ventricle than older neurons. (2) The median preoptic nucleus has a reversed neurogenetic gradient with respect to the third ventricle, older neurons generated on E13-E14 are located closer to the ventricle than younger neurons generated on E15-E17. In man, we estimate that preoptic neurons are generated, presumably with a lateral to medial gradient, from the 4th through the 11th weeks of development.

The preoptic neuroepithelium in the third ventricle is in front of the optic recess and forms its front wall. We postulate that this germinal matrix contains a mosaic of spatiotemporally defined neuroepithelial zones, each containing precursor cells for specific preoptic nuclei (Bayer and Altman, 1987b). Within one day after their generation,

young neurons leave their respective sites of origin in the neuroepithelium. Throughout most of the preoptic area, neurons migrate predominantly laterally. The older neurons in the lateral preoptic area migrate earlier and settle within 1-2 days adjacent to the telencephalon. Younger neurons migrate in successively later waves and accumulate medially. The sexually dimorphic neurons are exceptional since they migrate past older cells to settle in the core of the medial preoptic nucleus. The median preoptic nucleus originates from a midline neuroepithelial zone that is continuous with the neuroepithelium in the midline basal telencephalon, and is, therefore, considered to represent a transitional area between the telencephalon and diencephalon. In man, we postulate that the migration of preoptic area neurons begins soon after neurogenesis of the oldest populations, just as in the rat. The oldest neurons probably migrate and settle from the 5th to the 7th weeks. Possibly the youngest preoptic neurons do not settle until the end of the 16th week of development, shortly after they are generated.

Hypothalamic Nuclei. The *lateral hypothalamic area* extends from the preoptic area to the mammillary body. It contains neurons that are intimately related to the medial forebrain bundle that courses through the lateral preoptic area and the lateral hypothalamus. In rats, the lateral hypothalamic and lateral preoptic areas are structurally indistinguishable. Neurogenesis has the same span (E12-E15), but more neurons are generated on E12 in the lateral preoptic area than in the lateral hypothalamus (Altman and Bayer, 1978c) (compare the two graphs in Fig. 33). In man, we estimate that lateral hypothalamic neurons are generated mainly from the early 5th to the beginning of the 7th weeks after fertilization. Lateral hypothalamic neurons originate in the neuroepithelium ventrally adjacent to the source of the zona incerta and dorsally adjacent to the sources of more defined hypothalamic structures, such as the dorsomedial and ventromedial nuclei. The young neurons generated on E13 exit the neuroepithelium in a lateroventral direction on E14, and settle by E15 in the same area where the first fibers of medial forebrain bundle have just arrived (See Fig. 21 in Altman and Bayer, 1986). This process continues for two more days so that the lateral hypothalamus is already quite large in the brains of rat embryos on E17 (see Fig. 22 in Altman and Bayer, 1986). The young neurons become randomly dispersed according to age among the medial forebrain bundle fibers. In man, we estimate that lateral hypothalamic neurons are migrating and settling from the late 5th through the 7th weeks of development.

The *supraoptic* and *paraventricular nuclei* contain neurons that produce oxytocin and vasopressin (anti-diuretic hormone) that are secreted into the blood capillaries in the posterior lobe of the pituitary gland or neurohypophysis (reviewed in Altman and Bayer, 1986). Neurons in both nuclei are generated from E13 to E15 in rats (Fig. 32; Altman and Bayer, 1978c). In man, we estimate that the neurons in the supraoptic and paraventricular nuclei originate from the early 5th to the beginning of the 7th weeks of development. These nuclei originate from a common neuroepithelial site in a diamond-shaped evagination of the anteroventral third ventricle, what Herrick called the sulcus ventralis (Altman and Bayer, 1978d). That site eventually generates a specialized convuluted ependymal lining in the third ventricle that may be related to the function of these nuclei (Altman and Bayer, 1978e). Supraoptic neurons migrate farther than paraventricular neurons in a lateroventral course; older neurons (E13 birthdays) settle dorsolaterally by E15, while younger neurons (E15 birthdays) settle ventromedially adjacent to the optic tract by E17. The majority of the paraventricular neurons have also settled by E17. In between the supraoptic and paraventricular nuclei, a few scattered large neurosecretory neurons, the internuclear magnocellular neurons, form arrays adjacent to blood vessels that course through the core of the hypothalamus (Altman and Bayer, 1978c). Possibly, these neurons migrate with the supraoptic neurons and settle in midcourse. In man, we estimate that supraoptic and paraventricular neurons migrate soon after their generation and are settled by the middle of the 7th week after fertilization.

The *ventromedial nucleus* has received considerable attention because of its involvement in a variety of physiological and behavioral regulations, among them appetite and feeding; less is known about the function of the *dorsomedial nucleus* (see reviews in Altman and Bayer, 1986). The two nuclei are considered together because they form a butterfly-shaped collection of neuronal cell bodies in the anterior hypothalamus, originate from adjacent sites in the hypothalamic neuroepithelium, and have mirror-image neurogenetic gradients. The neurons of the ventromedial nucleus are produced between E13 and E17 in rats (Fig. 33) in a ventrolateral (older) to dorsomedial (younger) neurogenetic gradient (Altman and Bayer, 1978c). The neurons of the dorsomedial nucleus are produced between E14 and E17 in rats (Fig. 33) (Altman and Bayer, 1978c) in a dorsolateral (older) to ventromedial (younger) neurogenetic gradient. In man, we estimate that the neurons in both nuclei are generated from the early 5th to the end of the 7th weeks of development. The sources of the of the dorsomedial and ventromedial nuclei in the third ventricle neuroepithelium are lined up beneath the source of the paraventricular and supraoptic nuclei. Cells at these sites are still proliferating on E16 and E17, and their final product is a specialized ventricular lining where ependyma forms rows of cells instead of a single layer (Altman and Bayer, 1978e). Young neurons destined for each nucleus leave their respective sources one day after they are generated and migrate in divergent directions on the next day, the dorsomedial neurons head dorsolaterally, the ventromedial neurons head ventrolaterally. The oldest neurons form the leading edges of the two migratory streams and settle first, while younger neurons settle later, closer to the ventricle (see Fig. 72 in Altman and Bayer, 1986). The oldest neurons settle as early as E16; the youngest neurons settle as late as E19. In the human hypothalamus, these

neurons are probably migrating and settling from the late 5th through the 11th weeks of development.

The *anterobasal nucleus* lies in the midline at the base of the third ventricle in front of the arcuate nucleus and behind the optic chiasma. It is considered part of the arcuate nucleus by some, but it has unique developmental and structural characteristics. First, the neurons have a much earlier time of origin than those in the arcuate nucleus; second, the anterobasal neurons are larger than those in the arcuate nucleus; third, the anterobasal nucleus surrounds a portion of the third ventricle where the ependymal lining is different from that in the arcuate nucleus. On the basis of these considerations and its embryonic development, we proposed that it was a separate nucleus (Altman and Bayer, 1978c,d). Most of the anterobasal neurons are generated on E13 and E14, and a small fraction on E15 (Fig. 33). Neurons destined for the anterobasal nucleus originate in the neuroepithelium in the midline just behind the optic chiasma and migrate ventrally to accumulate in a conspicuous midline mass on E14, more migrate in on E15. If the human hypothalamus has a similar nuclear structure at the base of the anterior third ventricle behind the optic chiasma, these neurons are estimated to be generated during the 5th and 6th weeks and migrate and settle from the late 5th through the 7th weeks.

The *arcuate nucleus*, also called the infundibular nucleus, is an elongated structure in the mediobasal hypothalamus, extending all the way from the anterobasal nucleus to the mammillary body. It is composed of small neurons that are believed to be part of the tubero-hypophyseal neurosecretory system, the final common pathway for the regulation of secretions from the anterior lobe of the pituitary gland (reviewed in Altman and Bayer, 1986). In rats, neurons in the arcuate nucleus are generated over a long period from E13 to E19, with the majority of the cells originating between E15 and E18 (Altman and Bayer, 1978c). The neuroepithelium generating the arcuate nucleus forms the base and ventrolateral wall of the third ventricle. Neurons migrate away one day after they are generated and initially settle in a lateral (older) to medial (younger) neurogenetic gradient; this gradient becomes less prominent after cytodifferentiation. The final products of the arcuate neuroepithelium are the tanycytes, specialized ependymal cells that line the base of the third ventricle adjacent to the arcuate nucleus (Altman and Bayer, 1978e). In man, we estimate that neurons in the arcuate nucleus are generated, migrate, and settle from the late 6th through the 15th weeks of development.

The *suprachiasmatic nucleus* is a distinct cluster of small neurons above the optic chiasma that originates from E14 to E17 (Fig. 33; Altman and Bayer, 1978c). Suprachiasmatic neurons originate in a discrete neuroepithelial site that forms a shallow midline recess in the floor of the optic evagination. Intense proliferative activity at that site coincides with the time span of suprachiasmatic neurogenesis that declines earlier ventrally than dorsally in accordance with the intranuclear neurogenetic gradient.

The neurons in the *dorsal and ventral premammillary nuclei* are generated from E13 to E15 in rats (Fig. 33) in a ventral (older) to dorsal (younger) neurogenetic gradient (see Fig. 8 in Altman and Bayer, 1978c). Their site of origin appears to be above the germinal source of the arcuate nucleus and in front of the neuroepithelium in the mammillary recess. Neurons settle in the presumptive ventral and dorsal premammillary nuclei on E17 and E18, older neurons ventrally, younger neurons dorsally. In man, we estimate that the neurons in the premammillary nuclei are generated from the early 5th through the 6th weeks, are migrating and settling from the late 5th through the 7th weeks, with the youngest neurons settling during the 8th week.

Supramammillary neurons are generated in rats on E14 through E17, with a peak on E16 (Fig. 33; Altman and Bayer, 1978c). These neurons settle in a medial (older) to lateral (younger) neurogenetic gradient (Altman and Bayer, 1986). The supramammillary neurons appear to be generated in the neuroepithelium at the base of the posterior third ventricle as it curves upward toward the mesencephalon (see Fig. 13 in Altman and Bayer, 1978d). At that site, the midline neuroepithelium becomes thinner earlier than the paired lateral neuroepithelia adjacent to it. That pattern of proliferative activity could produce older neurons in the midline and younger neurons on either side. By E17 in rats, many of the neurons in the midline part of the supramammillary nucleus have settled, and young neurons are migrating into the nucleus from the two lateral sides. In man, we estimate that supramammillary neurons are generated from the late 5th through the 8th weeks, migrate soon after their generation, and many are settling in the 9th week.

The *tuberomammillary nucleus*, also called the tuberal magnocellular nucleus (Altman and Bayer, 1986), is situated in the ventrolateral hypothalamus rostral to the lateral mammillary nucleus. In rats, tuberomammillary neurons are generated between E15 and E18, with most originating on E16 and E17 (Fig. 33) (Altman and Bayer, 1978c). In man, we estimate that these neurons originate from the late 6th through the 9th weeks of development. The tuberomammillary neurons appear to be generated in the dorsal neuroepithelium of the mammillary recess and migrate in a straight mediolateral direction (Altman and Bayer, 1978d, 1986). They settle approximately two to three days later in a random pattern without a neurogenetic gradient. In man, we estimate that most of these neurons are settled by the end of the 14th week.

There are several schemes that subdivide the *mammillary body* into various nuclei (see reviews in Altman and Bayer, 1978c, 1986). There is agreement about the parcellation of the lateral mammillary nucleus, but midline nuclei are variously divided and named. Because of the labeling patterns seen after [^{3}H]thymidine injections, our earlier quantitative study of mammillary body development (Altman and Bayer, 1978c) delineated two nuclei in the midline, the dorsal medial mammillary nucleus, and the ventral principal mammillary nucleus. The neurogenetic

timetables in Figure 33 are from that study. We examined the embryonic development of the mammillary body again (Altman and Bayer, 1986) and delineated several more subdivisions in a single large medial mammillary nucleus in the midline.

The *lateral mammillary nucleus* is composed of large neurons that are generated from E12 to E15 with a peak on E13 (graph 3rd from bottom, Fig. 33). The *dorsal* part of the *medial mammillary nucleus* in rats contains predominantly medium-sized neurons that are generated mainly on E15 (Fig. 33). The *ventral* part of the *medial mammillary nucleus* in rats contains predominantly small neurons in two large clusters on either side of the midline that are generated mainly on E16 with lateral (older) to medial (younger) neurogenetic gradients in each cluster (Fig. 33). In man, we estimate that most neurons in the lateral mammillary nucleus are generated from the 4th through the 6th weeks, while those in the medial mammillary nucleus are generated from the late 5th through the 8th weeks. The neurons of the mammillary body originate in the neuroepithelium of the mammillary recess, which is a clearly recognizable subdivision of the third ventricle by E13 in rats, coinciding with peak neurogenesis in the lateral mammillary nucleus (Altman and Bayer, 1986). The neurons of the lateral mammillary nucleus are presumably generated in the lateral walls and migrate straight laterally one day later. Many of the neurons generated on E13 have already settled by E15 in the dorsolateral part of the nucleus; younger neurons settle in the next few days in the ventromedial part. The first fibers of the presumptive mammillotegmental tract are visible on E15 in the area where the lateral mammillary nuclear neurons are settling. Neurons destined for the large medial mammillary nucleus appear to be generated from all parts of the neuroepithelium in the mammillary recess and migrate away in dorsal and lateral radial patterns. The neuroepithelium in the dorsal mammillary recess becomes thinner earlier than in the ventral recess, correlating with the predominant dorsal (older) to ventral (younger) neurogenetic gradient seen in the medial mammillary nucleus. Nearly all of the medial mammillary neurons settle two days after they are generated. In man, we estimate that lateral mammillary neurons are migrating and settling from the late 5th through the 7th weeks of development, medial mammillary neurons from the 7th through the 14th weeks.

The Basal Telencephalon

The Pallidum. The pallidum contains a diffuse collection of large neurons, many of which are cholinergic, scattered throughout the basal telencephalon in several nuclei: the entopeduncular, globus pallidus, substantia innominata, horizontal limb of the diagonal band of Broca, and large polymorph neurons in the olfactory tubercle. The magnocellular neurons get major input from either the caudate/putamen complex (striatum) or the ventral striatum (olfactory tubercle and the nucleus accumbens), and they project topographically to the cerebral cortex. The degeneration of their axons may be associated with senile dementia of Alzheimer's type (reviewed in Bayer, 1985b).

In rats, the *entopeduncular nucleus* is embedded in the posteroventral part of the internal capsule and is the homolog of the internal segment of the primate globus pallidus. It contains the oldest neurons in the pallidum (top graph, Fig. 34) that originate mainly between E12 and E14 (Bayer, 1985b). These neurons appear to originate in the neuroepithelium of the third ventricle rather than the basal telencephalon at a site where the two neuroepithelia are apposed (Altman and Bayer, 1986). The germinal source of the entopeduncular nucleus is close to the source of the zona incerta and the lateral hypothalamus. Neurons migrate rapidly away from this site soon after their generation, and the entopeduncular nucleus is recognizable in rat brains as early as E13, presumably containing the neurons that were generated on E12 (Altman and Bayer, 1986). In man, we estimate that neurons in the internal segment of the globus pallidus are generated from the early 4th through the middle of the 6th week, migrate soon thereafter, and settle during the early 7th week.

The *globus pallidus* in rats is a mass of large neurons sandwiched between the lateral border of the internal capsule and the ventromedial border of the striatum. Most neurons originate between E13 and E16 (Fig. 34). The oldest neurons (birthdays on E13) are located in the posteroventral globus pallidus; the youngest neurons (birthdays on E16) are located anteromedially (Bayer, 1985b). The germinal source of the globus pallidus is likely to be the neuroepithelium in the ventromedial basal telencephalon where it is apposed to the neuroepithelium of the third ventricle that is the source of the entopeduncular nucleus. Posterior and ventral globus pallidus neurons settle within two days after their generation, (see Figs. 29-30 in Altman and Bayer, 1986). In man, we estimate that globus pallidus neurons are generated from the early 5th week up to the middle of the 7th week and settle by the end of the 9th week.

In rats, the *substantia innominata* contains medium- to large-sized neurons lying beneath the striatum and the globus pallidus. These neurons are generated from E13 to E17 (Fig. 34) in a two-way posterior and lateral (older) to anterior and medial (younger) neurogenetic gradient (Bayer, 1985b). We estimate that these neurons originate in the human brain from the early 5th week through the 7th week.

The *nucleus of the horizontal limb of the diagonal band of Broca*, also called the magnocellular nucleus of the preoptic area, is identical to the basal nucleus of Meynert in primates (reviewed in Bayer, 1985b). In rats, the nucleus extends from the medial edge of the anterior piriform cortex and sweeps forward through the lateral preoptic area to blend in with the large polymorph neurons scattered in layer III of the olfactory tubercle. Medially, the horizontal limb is continuous with the vertical limb of the diagonal band of Broca. In rats, neurons in the horizontal limb are generated mainly from E13 to E16 (Fig. 34) in a

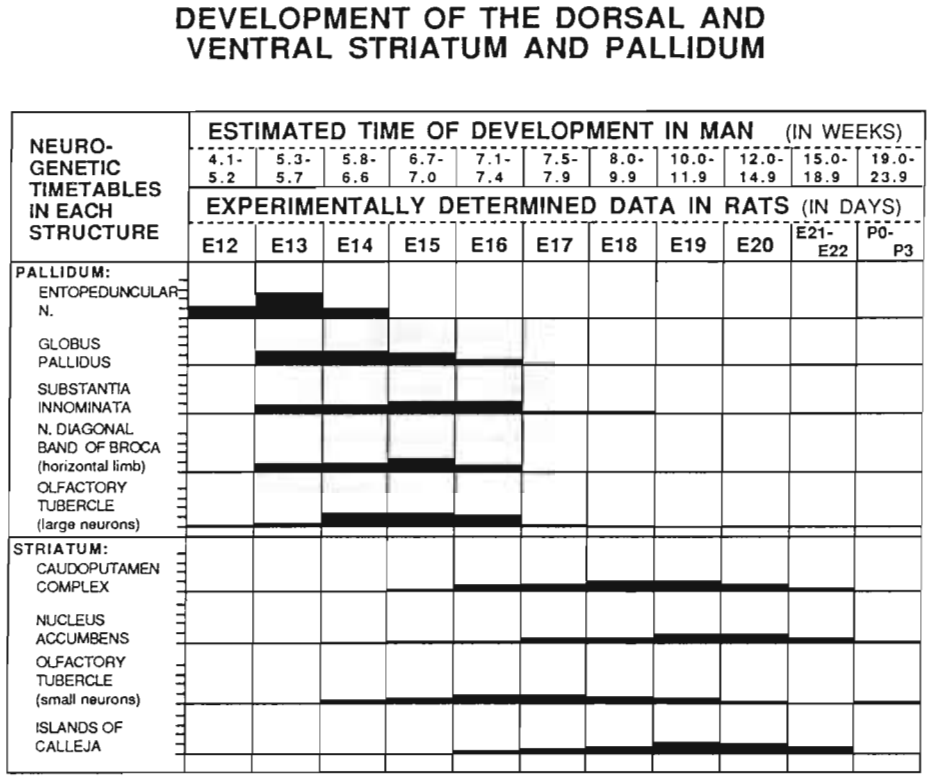


FIG. 34. As in Figure 19 for the striatum and pallidum. (From Bayer *et al.*, in press.)

two-way posterior and lateral (older) to anterior and medial (younger) neurogenetic gradient (Bayer, 1985b). In man, we estimate that these neurons are generated from the early 5th week up to the middle 7th week.

The *large olfactory tubercle neurons* are the most anterior pallidal neurons and resemble those that are in the globus pallidus, substantia innominata, horizontal limb of the diagonal band. In rats, these neurons are generated mainly from E14 to E16 (Fig. 34) in a lateral (older) to medial (younger) neurogenetic gradient (Bayer, 1985a). We estimate that these neurons are generated from the late 5th week up to the middle of the 7th week during human development.

With the exception of the entopeduncular nucleus, the remaining magnocellular basal telencephalic nuclei have linked neurogenetic gradients. The oldest neurons are in the caudal globus pallidus; the youngest neurons are in the most rostral olfactory tubercle, and neurons in intermediate levels (substantia innominata and the horizontal limb of the diagonal band) are intermediate in age. When two or more of the magnocellular basal nuclei are at the same level, ventrally situated ones, such as the horizontal limb of the diagonal band contain older neurons than dorsally situated ones, such as the substantia innominata and the globus pallidus. Also, lateral nuclei (substantia innominata or horizontal limb of the diagonal band) have older neurons than medial nuclei (vertical limb of the diagonal band, medial septal nucleus); neurogenetic timetables of the medial magnocellular neurons will be presented with the septal region. That linkage in neurogenetic gradients suggests that these nuclei represent a single large system of magnocellular neurons that are widely scattered throughout the basal telencephalon. It further implies that these neurons are generated sequentially from a common neuroepithelial source; studies are planned that will investigate the embryonic development of the basal telencephalon in rats (Bayer and Altman, in preparation).

The Striatum. The caudoputamen complex is the most prominent component of the striatum in the rat brain. This structure is the focus of intense neurochemical research due to evidence that in man, damage to dopamine terminals in the striatum from source neurons in the substantia nigra may be the cause of such degenerative neurological disorders as Parkinson's disease and Huntington's chorea. Developmental studies in the rat striato-nigral system indicate that the rich anatomical interconnections between the striatum and the substantia nigra in adults are likely to be the outcome of precisely timed developmental events because the patterns of axonal terminations and neurogenetic gradients between them are correlated (see Fig. 9 in Bayer, 1984). The large population of medium-spiny neurons in the rat caudoputamen complex are generated mainly from E16 to E21-E22 (Fig. 34). There are several neurogenetic gradients between these neurons (Bayer, 1984). The most prominent one is that ventrolateral neurons are older than dorsomedial neurons. But there are divergent neurogenetic gradients between anterior and posterior parts of the striatum. In the anterior part, older neurons are in superficial and posterior positions, younger

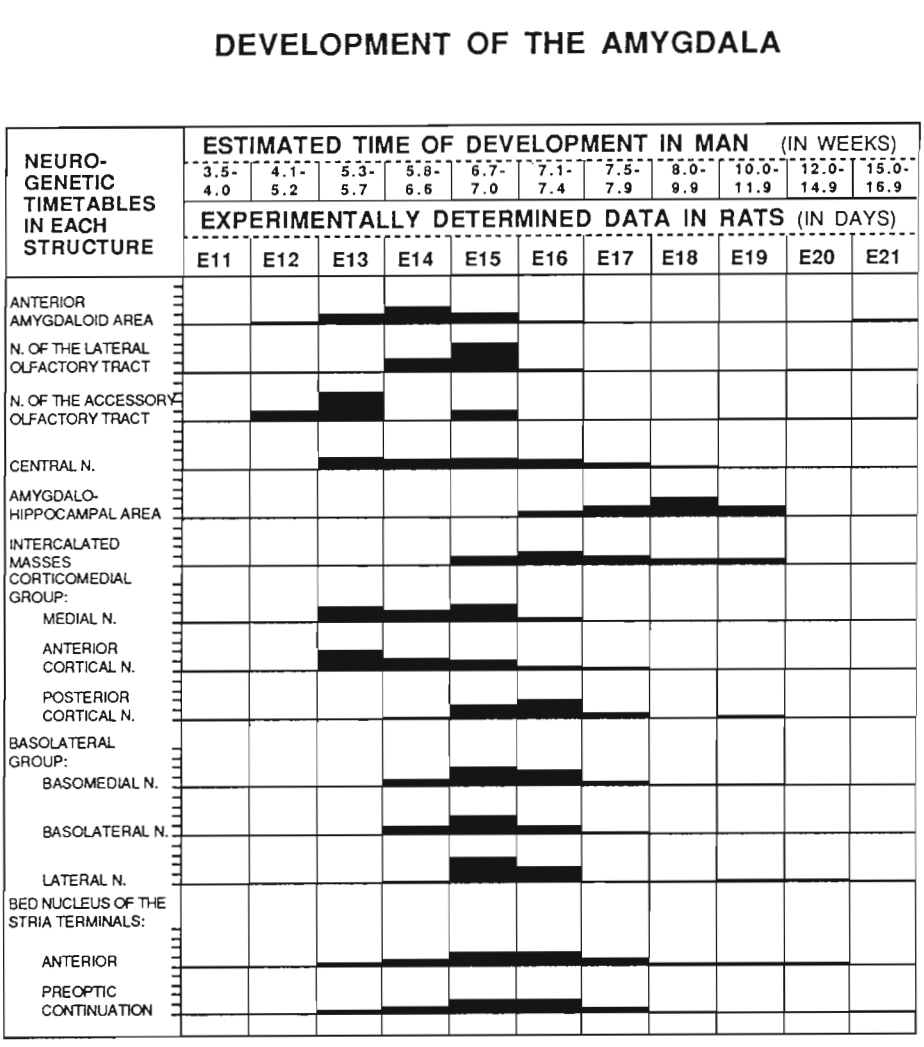


FIG. 35. As in Figure 19 for the amygdala. (From Bayer *et al.*, in press.)

neurons are deep and anterior. In the posterior part, the reverse is true; older neurons are in deep and anterior positions, younger neurons are superficial and posterior. In man, we estimate that striatal neurons in the caudate and putamen nuclei are generated from the early 7th week through the 18th week.

The *nucleus accumbens* surrounds the inferior horn of the lateral ventricle and extends forward to the olfactory peduncle. It has been included in the septal region, but the structure of its neurons and its developmental patterns place it within the striatum (Bayer, 1981). The fiber bundles of the internal capsule do not traverse the nucleus accumbens, rather, the anterior commissure passes through its medial part. In rats, nucleus accumbens neurons are generated over a protracted period, from E15 through P3 (Fig. 34). Neurogenetic gradients within the nucleus are similar to those in the caudoputamen complex, lateral and ventral neurons are older than medial and dorsal neurons. In man, we estimate that nucleus accumbens neurons are generated from the late 6th week through the 24th week. The germinal source of the nucleus accumbens is postulated to be a secondary germinal matrix derived from the neuroepithelium in the inferior horn of the lateral ventricle. A high level of mitotic activity in this zone coincides with the period of neurogenesis in the nucleus accumbens. Neurons rapidly migrate away from this source and settle in an orderly fashion, with the oldest neurons outside, youngest neurons inside. In man, we estimate that nucleus accumbens neurons are migrating and settling from the 10th week through the 24th week.

The *small olfactory tubercle neurons* are similar in size and dendritic structure to the medium spiny neurons in the caudoputamen complex and have a similarly long period of neurogenesis. In rats, these neurons are generated from E14 to E20, a few are generated from P0-P3 (Fig. 34). The neurons settle in a lateral (older) to medial (younger) gradient (Bayer, 1985a), a similar pattern but at an earlier time than those in the caudoputamen complex (compare the two graphs in Fig. 34). Throughout the striatum, ventral neurons are older than dorsal neurons (see above), and the early time of origin of the neurons in the olfactory tubercle may be related to their position ventral to the caudoputamen complex. In man, we estimate that small neurons in the olfactory tubercle are generated mainly from the late 5th week through the 24th week.

The *islands of Calleja* are dense clusters of small granule

cells in the olfactory tubercle and bordering the nucleus accumbens. In rats, neurons are generated in the islands from E16 to E22 (Fig. 34) in a two-way neurogenetic gradient (Bayer, 1985a); ventral and lateral neurons are older than dorsal and medial neurons. In the large island on the medial border of the nucleus accumbens, anterior neurons are older than posterior neurons. We estimate that neurons in the islands of Calleja in man are generated from the early 7th week through the 19th week after fertilization.

The Amygdala. The amygdala forms the floor of the telencephalon from the olfactory tubercle to the ventral part of the hippocampal region. It is a prominent structure in the rat brain and contains several areas and nuclei (listed in Fig. 35). With the exception of the bed nucleus of the stria terminalis, our studies of development in the rat amygdala are limited to neurogenetic timetables.

The *anterior amygdaloid area* in the rat is a diffuse collection of variably-sized neurons lying lateral to the preoptic area and deep to the nucleus of the lateral olfactory tract and the anterior cortical nucleus. Anteromedially, there are scattered large cells resembling those in the horizontal limb of the diagonal band. Neurogenesis occurs mainly from E13 to E15 (top graph, Fig. 35), but a few neurons originate as early as E12, and some are not generated until E21 (Bayer, 1980c). The long span is due to the spatial overlap of several distinct neuronal populations. Medium sized neurons are generated mainly between E13 and E15, with a peak on E14; large neurons are generated on E14 and E15, with a peak on E14; small neurons are generated from E18 to E21. In man, we estimate that most anterior amygdaloid area neurons are generated from the early 5th through the 7th weeks, with some originating as late as the end of the 16th week.

In the rat brain, the *nucleus of the lateral olfactory tract* is a distinct spherical cluster of densely packed medium-sized neurons in the anteromedial amygdala. Its neurons are generated mainly on E14 and E15 (Fig. 35) and settle in a medial (older) to lateral (younger) order. The *nucleus of the accessory olfactory tract* contains diffusely packed smaller cells posteromedial to the nucleus of the lateral olfactory tract. Its neurons are generated in a biphasic pattern, most on E12 and E13, and a few on E15. These nuclei are not distinct in primate brains (reviewed in Bayer, 1980c), but we estimate that the existing neurons are generated from the early 4th week through the 6th week after fertilization.

In the rat, the central nucleus lies in the dorsal part of the amygdala, just beneath the striatum and medial to nuclei in the basolateral group. Its neurons are generated from E13 to E18 (Fig. 35) and settle in an anteromedial (older) to posterolateral (younger) order (Bayer, 1980c). In man, we estimate that neurons in the central nucleus are generated from the early 5th week through the 9th week.

The *amygdalo-hippocampal area* in rats is a small region in the posteromedial amygdala where the medial nucleus blends with the ventral hippocampus. Some of the youngest neurons in the amygdala are located here; neurogenesis occurs from E16 through E19 (Fig. 35) and the cells settle in a superficial (older) to deep (younger) gradient (Bayer, 1980c). In man, we estimate that these neurons are generated during the 7th through the 11th weeks of development.

The *intercalated masses* are clumps of densely packed small cells interspersed between other nuclei in the amygdala. Anteriorly, they are clustered around the temporal limb of the anterior commissure; posteriorly, they are clustered amongst the fibers in the core of the amygdala between nuclei in the corticomedial and basolateral groups. In rats, these neurons are generated late (E15 to E19, Fig. 35), and settle in an anterior (older) to posterior (younger) order (Bayer, 1980c). In man, we estimate that neurons in the intercalated masses arise from the late 6th week through the 11th week of development.

The *medial nucleus* forms the medial wall of the amygdala from the anterior amygdaloid area to the ventral tip of the hippocampus. In rats these neurons are generated from E13 to E16 (Fig. 35) in an anteroventral (older) to posterodorsal (younger) neurogenetic gradient (Bayer, 1980c). In man, we estimate that neurons in the medial nucleus are generated from the early 5th week through the middle 7th week of development.

The *cortical nuclei* are subdivided into anterior and posterior parts. In rats, there is a strong anterior (older) to posterior (younger) neurogenetic gradient between the parts (Fig. 35). Both nuclei have superficial (older) to deep (younger) neurogenetic gradients, and the posterior nucleus has a medial (older) to lateral (younger) gradient (Bayer, 1980c). In man, we estimate that most neurons in the cortical nuclei are generated from the early 5th week through the 7th week.

In rats, the *basomedial nucleus* lies in the core of the amygdala throughout much of its rostrocaudal extent, while the *basolateral* and *lateral nuclei* form a pyramid-like structure apposed to the white matter that borders the piriform cortex. Neurons in the basomedial, basolateral, and lateral nuclei are generated from E14 through E17 (Fig. 35). All nuclei have anterior (older) to posterior (younger) neurogenetic gradients (Bayer, 1980c). In man, we estimate that most neurons in the basolateral complex are generated from the late 5th week through the 7th week.

The stria terminalis is a major fiber tract that leaves the amygdala and reaches various targets in the basal forebrain. Neurons that are scattered within this fiber tract collectively form the *bed nucleus of the stria terminalis*. The anterior part of the nucleus encircles the interbulbar part of the anterior commissure, extending from the nucleus accumbens to just behind the decussation of the anterior commissure. In rats, neurons in the anterior part are generated from E13 to E20 (Fig. 35), and settle in a posterior (older) to anterior (younger) gradient (Bayer, 1979a, 1987). The preoptic continuation extends ventromedially into the posterior preoptic area. These neurons are generated mainly from E13 through E16 (Fig. 35) and settle in a ventrolateral (older) to dorsomedial (younger) order (Bayer, 1987). In man, we estimate that neurons in both parts of the

DEVELOPMENT OF THE SEPTUM

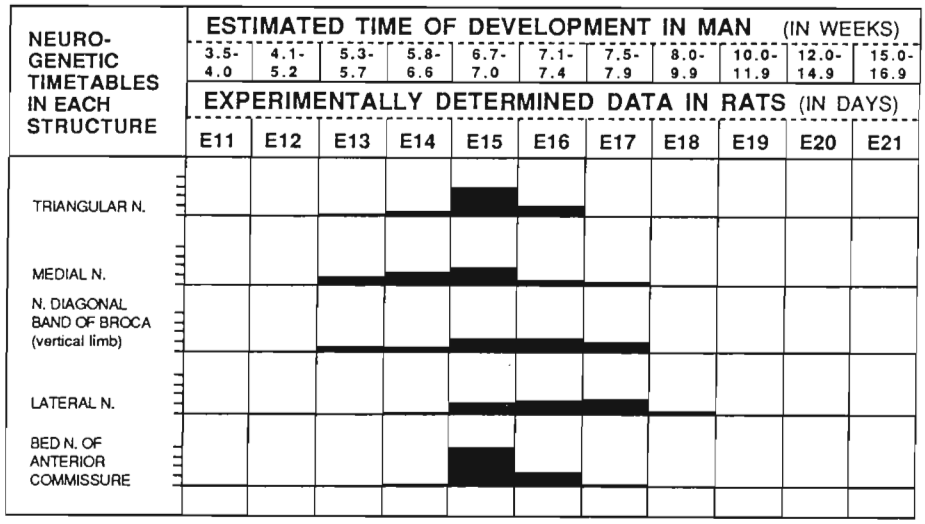


FIG. 36. As in Figure 19 for the septum. (From Bayer *et al.*, in press.)

bed nucleus of the stria terminalis are generated mainly from the early 5th week through the 7th week; a few neurons may be generated in the anterior part as late as the 15th week. Morphogenetic studies of the strial bed nucleus indicate that the two parts arise from distinct neuroepithelial sources. The anterior strial bed nucleus is generated at the base of the inferior horn of the lateral ventricle, extending from the decussation of the anterior commissure forward to the primordium of the nucleus accumbens. Neurons migrate radially from that source so that older neurons settle ventromedially, and younger neurons settle dorsolaterally, closest to the inferior horn. The preoptic continuation of the strial bed nucleus is generated in the neuroepithelium at the base of the transient medial horn of the lateral ventricle, lateral to the area of fusion with the anterior thalamic neuroepithelium. Neurons migrate radially from that source and settle in a downward curving pattern, reflecting the curvature of the medial horn. Younger neurons accumulate adjacent to the older lateral neurons. Throughout the strial bed nucleus, neurons begin to migrate within one day after their generation and usually settle one or two days later (Bayer, 1987). In man, we estimate the strial bed nucleus neurons are migrating and settling from the late 5th week through the 17th week of development.

The Septum. Beginning with the midline septal nuclei, neurons in the *triangular nucleus* (top graph, Fig. 36) are generated from E13 to E17 (less than 5%), with a peak on E15; those in the lateral part are generated slightly earlier than those in the midline (Bayer, 1979a). Neurons in the *medial septal nucleus* are generated from E13 to E17 (Fig. 36) and settle in a posterior (older) to anterior (younger) order. Indeed, the oldest neurons in the septal complex lie in the medial septal nucleus above the decussation of the anterior commissure (Bayer, 1979a). Neurons in the *nucleus of the diagonal band of Broca* (vertical limb) are also generated from E13-E17 (Fig. 36) and settle in a posterior (older) to anterior (younger) order, continuing the gradient in the medial septal nucleus. Neurons in the *lateral septal nucleus* are generated from E14 to E19 and settle in a medial (older) to lateral (younger) order. The youngest neurons in the septal complex lie in this nucleus adjacent to the ependymal lining of the lateral ventricle. Neurons in the *bed nucleus of the anterior commissure* are generated from E14 to E17, and settle mainly on E15 and E16 (Fig. 36) following a similar timetable to neurons in the triangular septal nucleus. In man, we estimate that neurons in the septal complex are generated from the early 5th week through the 9th week, probably with medial neurons originating earlier than lateral neurons.

The source of most neurons in the septal complex is the neuroepithelium lining the medial wall of the lateral ventricle (Bayer, 1979b). Already by E15 in rat embryos, a thick band of young neurons has accumulated outside of that neuroepithelium. The young neurons are presumably those that will form the medial septal and diagonal band nuclei. By E17, The neuroepithelium is less prominent, and more young neurons, presumably those of the lateral septal nucleus, accumulate just outside it. By now, the vertical limb of the diagonal band is recognizable. More neurons accumulate on E19, and the septal neuroepithelium becomes very thin. At posterior levels, there is some indication of differentiation in the medial septal nucleus. By E21, the septal neuroepithelium has changed to the primitive ependyma, and the zone of differentiating cells has greatly enlarged. In man, we estimate that septal neurons migrate one day after their generation and many will settle on the second day. Thus, the times of production, migration, and settling of neurons are largely overlapping during septal development.

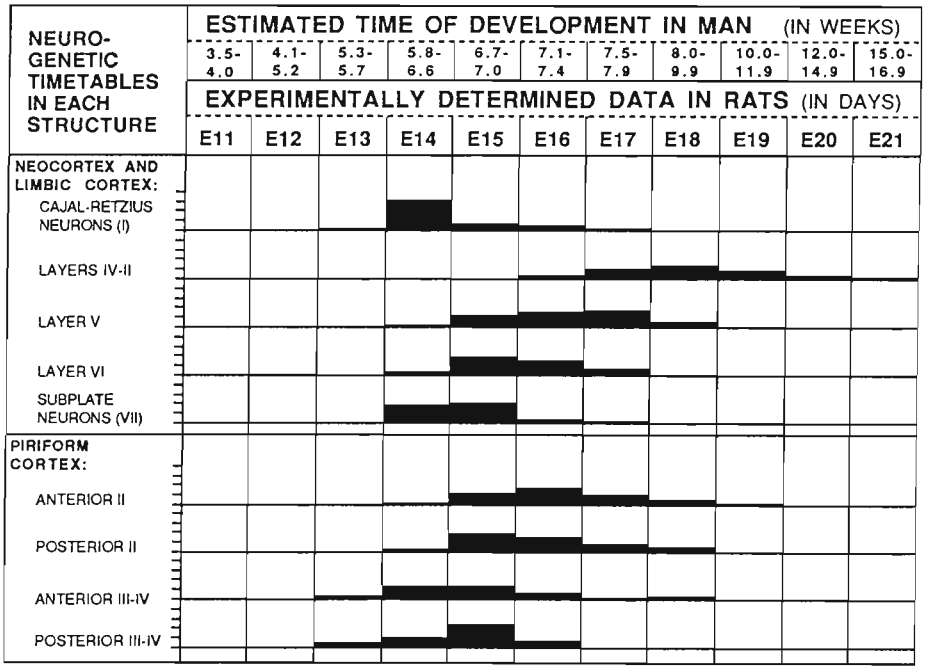


FIG. 37. As in Figure 19 for the neocortex, limbic cortex, and piriform cortex. (From Bayer *et al.*, in press.)

The Cerebral Cortex

The cerebral cortex is the largest structure in the mammalian telencephalon. It can be subdivided into the neocortex and limbic cortex, the piriform cortex, and the hippocampal region. The timetables of neurogenesis of all the parts of the cerebral cortex in rats have been determined with long-survival [^{3}H]thymidine autoradiography, and short-survival [^{3}H]thymidine autoradiography has been used to follow neuronal migration in the limbic cortex and neocortex.

Neocortex and Limbic Cortex. The neocortex in both man and rats has five cell-dense layers (II-VI), large Cajal-Retzius neurons sparsely distributed in layer I, and scattered neurons in the deep white matter (layer VII or the subplate). In rats. the superficial layers (II-IV) are much smaller than those in the human neocortex but layers VI and V are quite well developed, each taking up one-third of the total cortical depth (Bayer and Altman, 1991a). In the limbic neocortex of rats, five cell-dense layers are also present. Generally, layers V and VI are easily distinguished from each other, but they tend to be thinner than the same layers in the neocortex. The superficial layers (IV-II) are quite reduced and are often grouped together in a single layer. The limbic neocortex in man is also transitional in form, with modifications to layers II-VI in the neocortex (Sidman and Rakic, 1982).

Timetables of Neurogenesis and Neurogenetic Gradients. In spite of the fact that the rat *neocortex* has thinner layers than those in the human neocortex, the pattern of development is comparable in the two species. In rats, most neocortical and limbic cortical neurons are generated between E14 and E20 (Fig. 37) and settle in a very strict gradient between the layers (Bayer and Altman, 1991a) that can be separated into three major epochs. During the first epoch, the Cajal-Retzius neurons in layer I and subplate neurons (layer VII) are sequentially generated and settle in a superficial (older) to deep (younger) gradient. The peak time of origin of Cajal-Retzius neurons occurs on E14, while subplate neurons are generated on E14 and E15. Neurons in layers VI-II are generated during the second and third epochs and settle in a deep (older) to superficial (younger) radial gradient, one of the most prominent neurogenetic gradients in the entire brain (Fig. 37; Bayer and Altman, 1991a). Layers VI-V are sequentially generated from E15 to E17 (second epoch); layers IV-II are sequentially generated from E17 to E20 (third epoch). Only a few of the most superficial neurons in layer II are generated on E21, the last day of cortical neurogenesis in rats. There is evidence that neurons in the primate neocortex are generated in exactly the same pattern. The Cajal-Retzius cells are first, followed by those in layer VII. The radial gradient between layers VI and II is even more pronounced in primates than the one found in rats (Sidman and Rakic, 1982). In man, we estimate that Cajal-Retzius and subplate

neurons are generated mainly from the late 5th through the 6th weeks, while neurons in layers VI-II are generated from the late 6th through the 15th weeks. After examining drawings of the human neocortex (Sidman and Rakic, 1982), we estimate that neurogenesis is completed by the end of the 16th week because the cortical neuroepithelium is extremely thin, similar in appearance to that in the rat on E21.

The *limbic cortex* surrounds the neocortex. Although there is the same stacking of older to younger cells in the radial dimension, the medial limbic cortex (cingulate and retrosplenial areas) reverses the neocortical transverse gradient and the lateral limbic cortex (insular areas) has a different longitudinal gradient than the one in the neocortex (Bayer and Altman, 1991a). The lateral limbic cortex in man appears to have the same maturational gradient as it does in the rat (Sidman and Rakic, 1982). These findings lend support to the argument that the limbic and neocortical parts of the cerebrum have different phylogenetic roots; the limbic neocortex may be partially linked to neurogenetic gradients in the paleocortex (Bayer and Altman, 1991a).

Neuronal Migration and Settling in the Cortical Plate. The neurons destined to settle in layers VI-II move out of the neuroepithelium within 1 day after their generation and first sojourn in narrow bands (zones) in the wider subventricular and intermediate zones for approximately one day; they sort themselves out according to cell type during this time (see Bayer and Altman, 1991a). Next, the young neurons continue their migration to the cortical plate (diagrammed in Fig. 38). Those bound for the dorsal neocortex migrate for 1 day in the radial direction and settle on the next day; the entire sequence from birth to settling takes only 2 days. Neurons bound for the lateral neocortex do not follow a radial path because the growth of the basal ganglia causes the cortical neuroepithelium to be displaced medially and these neurons are generated as much as 0.5 mm to 1.0 mm medial to the points where they will penetrate the cortical plate. Consequently, these neurons migrate laterally for at least 1 day in the lateral cortical stream then turn radially to enter the cortical plate 3 days after their generation. Neurons bound for the far lateral neocortex, such as the insular area, migrate laterally for 2 days and take 4 or more days to reach their destinations in the cortical plate. An interesting finding is that the cortical neuroepithelium also gives rise to neurons that are destined to settle in the piriform cortex and in other sites in the basal telencephalon, such as the intercalated masses of the amygdala. (For implications of these data, see Bayer and Altman, 1991a.)

It is important to note here that the human neocortical neuroepithelium also shows a medial shift due to growth of the ganglionic eminence. Consequently, it is likely that many neurons in the developing human neocortex are also migrating in a lateral direction through the intermediate zone. This calls into doubt the very popular hypothesis of the guidance of cortical neurons by radial glia (Sidman and Rakic, 1982). (For a critique of this hypothesis, see Bayer and Altman, 1991a.)

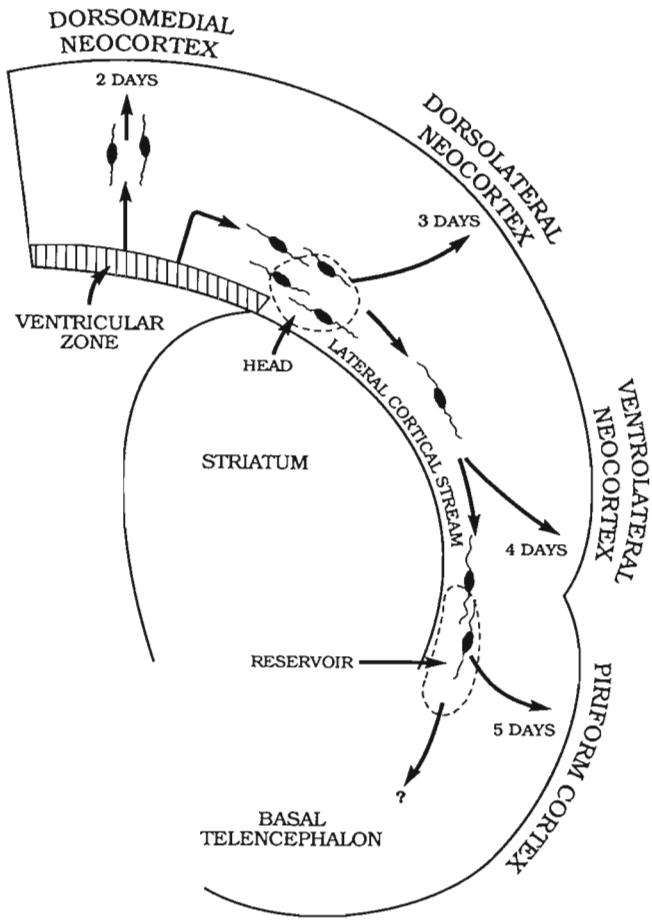


FIG. 38. A diagram of the various trajectories taken by migrating neocortical neurons that are cogenerated on the same embryonic day (E17 for example) but are destined to settle in various parts of the cortical plate and even outside of the neocortex. All of these neurons are produced by committed precursor cells in the cortical neuroepithelium (striped region, ventricular zone) and migrate out within 24 hrs to sojourn for approximately one day in specific bands in the subventricular and intermediate zones (not illustrated). Those neurons that will settle in the dorsal cortex resume their migration on the second day and penetrate the cortical plate, those that will settle in the dorsolateral neocortex migrate in the lateral cortical stream for 1 day, then turn radially on the next day to reach the cortical plate 3 days after their generation. Those bound for the ventrolateral neocortex migrate laterally for 3 days and penetrate the cortical plate 4 days after their generation. Some cells generated in the neocortical neuroepithelium migrate in the lateral cortical stream for 4 or more days and accumulate in a reservoir. From there some penetrate the piriform cortex or as yet unidentified areas in the basal telencephalon 5 or more days later. (From Bayer and Altman, 1991a)

Piriform Cortex. The rat piriform cortex is located below the rhinal sulcus and forms the ventrolateral edge of the cerebral hemispheres. It extends nearly 7.4 mm in the rostrocaudal direction, from the anterior olfactory nucleus to the lateral entorhinal cortex. The enormous expansion of the neocortex in man pushes the piriform cortex into the ventromedial part of the temporal lobe. Comparative neuroanatomists consider the piriform cortex to be

"paleocortex" because it is represented in the cortical structures of fish, amphibians, and reptiles. Another characteristic that distinguishes piriform cortex from neocortex is that it receives monosynaptic input from the main olfactory bulb throughout its entire length and breadth (reviewed in Bayer, 1986b), while all sensory input to the neocortex is through a relay in the thalamus. Most anatomists consider the piriform cortex to have three cell layers in addition to the cell sparse external plexiform layer (I). Layer II contains densely packed small pyramidal cells, layer III sparsely packed medium-sized pyramidal cells, and layer IV very sparse large-sized pyramidal cells and polymorph cells.

Neurogenesis in the rat piriform cortex proceeds in two gradients: deep neurons are older than superficial neurons, and posterior neurons are older than anterior neurons (Fig. 37). Deep neurons in layers III and IV are generated mainly from E13 to E16, 80% of the posterior deep neurons on or before E15, while over 30% of the anterior deep neurons on or after E16. The superficial neurons are generated mainly from E15 through E18, 75% of the posterior ones on or before E16, 37% of the anterior ones on or after E17. We estimate that neurons in the piriform cortex of man are generated from the early 5th week through the 12th week of development. In the anterior piriform cortex of rats, layer II is quite thick, and the small pyramidal cells are stacked 2-3 deep rather than in a monolayer. Here, the superficial neurons are generated slightly earlier than the deep ones (see Fig. 6 in Bayer, 1986b). These data indicate that the piriform cortex does not have the same type of radial gradient as the neocortex where younger neurons are always superficial to older deep neurons.

Although we have not studied the embryonic development of the piriform cortex, others (reviewed in Bayer, 1986b) have shown that the posterior part matures earlier than the anterior part, in accordance with the posterior to anterior neurogenetic gradient. At least some of the neurons in the piriform cortex are generated in the neocortical neuroepithelium and migrate laterally and ventrally for several days before settling (Bayer and Altman, 1991a). Other neurons may be generated in the palliostriatal ventricular angle where the neuroepithelia of the neocortex and the basal ganglia meet (Bayer and Altman, 1991b). The significance of these findings awaits further research. If these same events occur in the human brain, neurons ought to be migrating into the piriform cortex from the 7th week to the 19th week.

The Hippocampal Region. The hippocampal region is a prominent component of the rat cerebral cortex, containing five contiguous structures. The entorhinal cortex, presubiculum, parasubiculum, and subiculum take up most of the ventroposterior cortical wall. The hippocampus proper extends forward beneath the corpus callosum and the deep white matter of the neocortex and lateral limbic cortex. The human hippocampal region has all the parts found in the rat except that it is buried in the depths of the temporal lobe due to the expansive growth of the neocortex. The hippocampal region is one of the best known neuroanatomical structures due to intense study with a variety of descriptive and experimental anatomical methods (reviewed in Bayer, 1980a). Our studies in the rat include quantitative determinations of the timetables of neurogenesis (Altman, 1966; Bayer, 1980a, 1982; Bayer and Altman, 1974; Bayer et al., 1982), cell migration and settling (Altman and Bayer, 1990a,b,c; Bayer, 1980b), and response to X-irradiation (Bayer and Altman, 1975a,b).

The Entorhinal Cortex. The entorhinal cortex contains five layers that, with the exception of layer I, are substantially different from those found in the neocortex. Layer II contains the cell bodies of large stellate cells, grouped into islands laterally and separated from layer III by a cell-sparse zone. Layer III contains medium-sized pyramidal cells. Layer IV is a cell-sparse zone (lamina dessicans) with a few scattered large pyramidal cells. Layer V-VI contains relatively densely packed medium and small-sized neurons. The neurogenetic timetables shown in Figure 39 indicate a modified deep (older) to superficial (younger) neurogenetic gradient. Neurons in layer V-VI are generated mainly on E15, those in layers II and IV mainly on E15 and E16, and the youngest neurons in layer III mainly on E17. All layers have lateral (older) to medial (younger) neurogenetic gradients (Bayer, 1980a). In man, we estimate that neurogenesis in the entorhinal cortex extends from the late 5th week through the 9th week after fertilization.

The neuroepithelium in the posterolateral cortical primordium is the presumed source of neurons in the entorhinal cortex (Bayer, 1980b). In rat embryos on E16, this thick neuroepithelium is bordered by an equally thick zone of young neurons that migrate outwards in the lateral part of the primordium. The entorhinal neuroepithelium is still prominent on E17, and there are layers resembling the cortical intermediate zone and a cortical plate; both of these are thicker laterally than medially. Between E17 and E18, the entorhinal neuroepithelium becomes much thinner, coinciding with reduced neurogenesis on that day (Fig. 39), while the cortical plate becomes thicker, again more so laterally than medially. Also on E18, a cell sparse region develops beneath the cortical plate. This is similar to the upper intermediate zone in the neocortex, and will eventually become the white matter at the base of the entorhinal cortex. On E19, there is a split in the entorhinal cortical plate, possibly representing the lamina dessicans in layer IV. That morphological feature distinguishes the entorhinal primordium from the limbic and neocortical primordia, where the cortical plate has no cell-sparse zones. The splitting of the cortical plate proceeds in a lateral to medial direction, and is quite prominent throughout the entorhinal cortex by E22 (the day before birth in rats). Although the lamination of the entorhinal cortex is obvious by E22 in rat embryos, there are still a few spindle-shaped radially oriented cells in the intermediate zone, indicating that neurons may still be migrating. In man, we

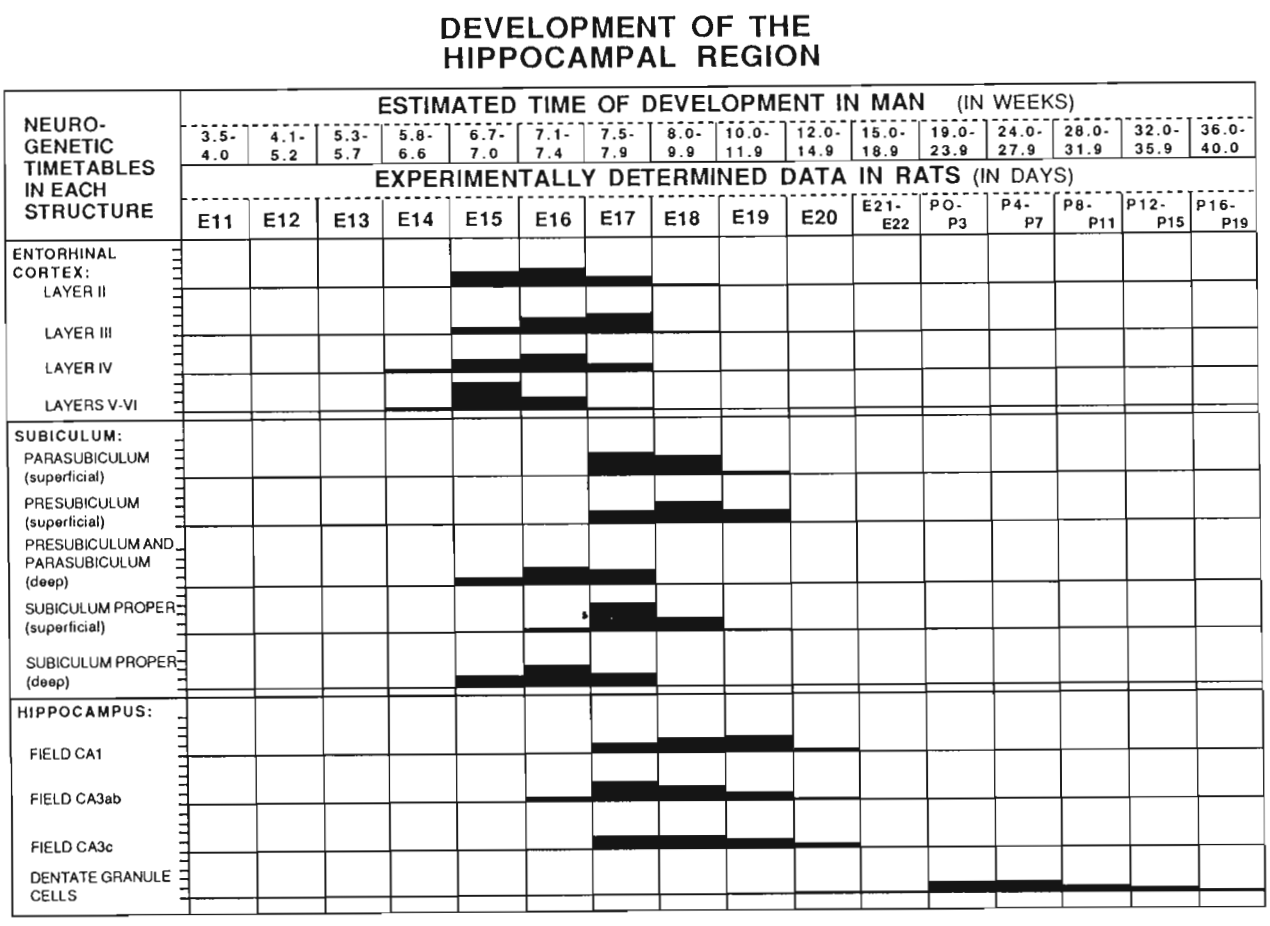


FIG. 39. As in Figure 19 for the hippocampal region. (From Bayer *et al.*, in press.)

estimate that morphogenesis of the entorhinal cortex proceeds in a similar pattern to that in the rat. Older neurons migrate and some may already be settled before the youngest neurons in layer III are generated. It is likely that entorhinal neurons are migrating and settling from the 7th week to the 15th week, but some of the youngest neurons may still be migrating up to the 40th week.

The Subiculum. The structures between the medial edge of the entorhinal cortex and the hippocampus are the parasubiculum, presubiculum, and the subiculum proper. The parasubiculum and presubiculum form a wedge in the posteromedial angle of the cortical wall. They share a triangular-shaped core of deep neurons that are generated from E15-E17 in rats (Fig. 39), later than the deep neurons in the laterally situated entorhinal cortex. There is a lateral (older) to medial (younger) neurogenetic gradient in the superficial cells of the parasubiculum and the presubiculum. Those in the parasubiculum are generated earlier (mainly on E17 and E18) than the small superficial neurons in the presubiculum (more neurogenesis on E19, Fig. 39). The pyramidal layer in the subiculum proper appears to be an extension of the deep neurons of the para-and presubiculum. Within the layer, deep neurons are generated earlier (peak on E16) than superficial neurons (peak on E17, Fig. 39). When taken as a whole, neurons in the subiculum proper are generated later than the deep neurons in the para- and presubiculum. These patterns indicate that the lateral (older) to medial (younger) neurogenetic gradient in the entorhinal cortex is continued throughout the subiculum (Bayer, 1980a). In man, we estimate that neurons in the subiculum are generated from the late 6th week through the 12th week of development.

In rat embryos on E18 and E19, the cortical plate rapidly invades the hippocampal primordium (Bayer, 1980b). By E20, the bifurcation of the entorhinal cortical plate ceases to progress medially, and the adjacent wedge-shaped non-bifurcated cortex can now be more accurately delineated as the para- and presubiculum. The neurons in this part of the cortical plate arrive there from E18 through E20 and probably represent deep neurons in the para- pre- and subiculum proper. The parasubiculum cannot be distinguished from the presubiculum until E22 because the migration of neurons to the superficial layers, especially in the presubiculum, is exceptionally late. In man, we estimate that deep neurons migrate and settle in the subiculum from the 8th week through the 15th week, while some superficial neurons migrate from the 12th week up to birth at 40 weeks and afterwards.

The Hippocampus Proper. The hippocampus in rats contains two interlocked C-shaped layers of cortex, the

pyramidal cells of Ammon's horn (fields CA1-3) and the granule cells in the dentate gyrus. The dentate granular layer is much longer in the human hippocampus and is characterized by small zig-zag folds that resemble teeth, thus the name "dentate."

In Ammon's horn of the rat, the oldest pyramidal cells are in field CA3ab (peak on E17, Fig. 39) and younger pyramidal cells flank them in fields CA1 (closer to the subiculum) and CA3c (in the hilus of the dentate gyrus). It is remarkable that the lateral (older) to medial (younger) neurogenetic gradient seen throughout the entorhinal cortex and the subiculum is broken by the sandwich gradient seen in the pyramidal cells of Ammon's horn (Bayer, 1980a). In man, we estimate that pyramidal cells in the hippocampus are generated from the 7th week through the 14th week of development.

The granule cells in the dentate gyrus are noted for their exceptionally late time of origin (Bayer, 1980a). Approximately 85% of these neurons are generated after birth in rats, mainly during the first postnatal week (Fig. 39). Neurogenesis gradually tapers off during the second and third postnatal weeks, so that the dentate gyrus appears mature by the time of weaning (21 days). In man, we estimate that dentate granule cells are generated from the 12th week up to (and possibly beyond) birth. Most of the dentate granular neurons settle in a superficial (older) to deep (younger) gradient, opposite to the gradients between and within layers of the neocortex (Bayer, 1980a). The dentate granular layer is also unusual because there are always a few neurons that can be labeled after [^{3}H]thymidine injections are given to juvenile and adult rats (Altman, 1963; Bayer, 1982; Bayer et al., 1982). It has been established that the neurons produced in adults add to the total population of dentate granule cells. Year old rats have significantly more neurons than month-old rats (Bayer, 1982; Bayer et al., 1982). Adult neurogenesis has not been observed in the dentate gyrus of primates (Rakic, 1985) and may not exist in man.

In rat embryos, [^{3}H]thymidine autoradiographic studies indicate that the neuroepithelium constituting the hippocampal primordium has three components (Altman and Bayer, 1990a). One gives rise to the pyramidal cells of Ammon's horn; a second gives rise to the granule cells in the dentate gyrus; a third gives rise to the glia that will populate the fimbria (a major fiber tract that enters and exits the hippocampus).

The putative source of Ammon's horn pyramidal cells is a characteristic bulge in the medial telencephalic wall that can be seen in rat embryos as early as E14. This neuroepithelium shows a high level of proliferative activity until E19; relatively few pyramidal neurons are generated on E20. After a single [^{3}H]thymidine injection on E18, the migratory routes of the pyramidal cells were tracked by killing animals at daily intervals after the injection (Altman and Bayer, 1990b). All of the pyramidal cells move out of the neuroepithelium one day after their generation and form a band of heavily labeled cells just outside it. On subsequent days, the pyramidal cells leave this band and migrate into the pyramidal layer. CA1 neurons migrate radially and take 4 days to reach their destinations. Although the CA3 neurons are generated earlier than CA1 neurons, they take longer to migrate to the pyramidal layer because part of their migratory trajectory is a curved path around the edge of the accumulating CA1 neurons. Possibly the earlier time of origin of CA3 neurons is related to their longer time of migration. At the time of birth in rats, many pyramidal cells are still migrating into the pyramidal layer. If these events observed in rats apply to man, we estimate that most Ammon's horn pyramidal cells migrate and settle from the 8th week through the 24th week.

The granule cells of the dentate gyrus are derived from the dentate neuroepithelium that indents slightly at the edge of the Ammonic neuroepithelium, a region called the "dentate notch" (Altman and Bayer, 1990a). By E18, an aggregate of proliferative cells, the secondary dentate germinal matrix, accumulates outside of the reduced dentate neuroepithelium (Altman and Bayer, 1990c). From E19 to the time of birth, the proliferative cells migrate into the dentate gyrus, following a curved path between the fimbria and around the edge of Ammon's horn. The secondary matrix produces the older granule neurons that forms the superficial border of the granular layer. It also produces the tertiary dentate germinal matrix that becomes dispersed throughout the hilus of the dentate gyrus during the perinatal period. Over a period of 1-2 weeks, the tertiary matrix produces granule neurons that accumulate according to age beneath the older superficial neurons. Between postnatal days 20 and 30, the tertiary matrix disappears from the hilus, but a remnant remains just beneath the granular layer in the subgranular zone. Granule neurons that arise during juvenile and adult periods are derived from the scattered precursor cells in the subgranular zone. If similar developmental patterns exist in the human dentate gyrus, we estimate that many granule neurons are migrating and settling from the 19th week up to and beyond the time of birth.

The Olfactory Bulb and Peduncle

The rat *olfactory bulb* is a prominent component of the forebrain. In contrast, the human olfactory bulb is small and is dwarfed by the enormous expansion of the frontal lobes in the cerebral cortex. In both species, the internal structure of the olfactory bulb is similar. Olfactory nerve fibers that originate from the olfactory epithelium in the upper part of the nasal cavity penetrate small foramina in the cribriform plate, and terminate in the superficial glomerular layer of the olfactory bulb. In the glomerular layer, olfactory nerve axons synapse with the primary dendritic branches of mitral and tufted neurons. Axons of the mitral and tufted cells leave the olfactory bulb to terminate in various parts of the olfactory peduncle and in the primary olfactory cortex. There are three populations of short-axon interneurons; a large population of granule cells that forms a thick layer beneath the layer of mitral cells, small neurons scattered diffusely in the external plexiform layer, and

DEVELOPMENT OF THE OLFACTORY BULB AND THE ANTERIOR OLFACTORY NUCLEUS

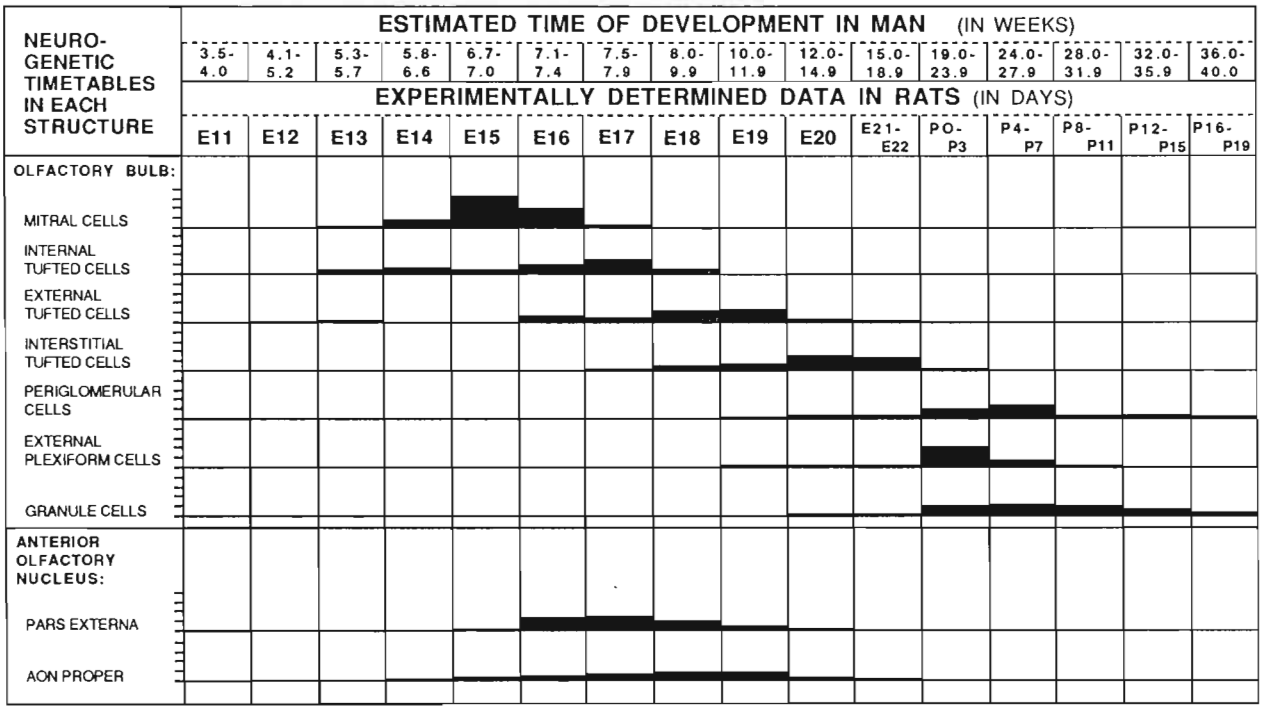


FIG. 40. As in Figure 19 for the olfactory bulb and anterior olfactory nucleus. (From Bayer *et al.*, in press.)

small neurons dispersed between the glomeruli. The external plexiform layer is between the glomerular layer and the mitral cell layer; it is a region where the secondary branches of mitral cell and tufted cell dendrites interact with input from granule cells and the external plexiform interneurons; it also contains the scattered cell bodies of the tufted output neurons.

Neurogenetic timetables in the rat olfactory bulb (Fig. 40) show a highly sequential pattern of generation between different neuronal populations (Bayer, 1983). The oldest neurons are the mitral cells that originate mainly on E14-E16. The internal, external, and interstitial tufted cells follow, with peaks on E16-E17, E18-E19, and E20-E22, respectively. The interneurons in the glomerular, external plexiform, and granular layers are generated mainly after birth in rats. Nearly all of the external plexiform cells and the periglomerular cells are generated by the end of the first postnatal week, but the large population of granule cells continues to be generated up to and beyond P19 (Fig. 40). Granule cells in the olfactory bulb are generated during the adult period since a few are always labeled within a few weeks after [^{3}H]thymidine injections are given to adult rats (reviewed in Bayer, 1983). Unlike the hippocampus, adult neurogenesis in the olfactory granule cells does not result in a numerical increase in the population (Bayer, 1983) and the persistent neurogenesis probably indicates a slow turnover rate in the population. In man, we estimate that neurogenesis of the mitral and tufted neurons proceeds sequentially from the 5th week through the 19th week. Interneurons and granule cells are probably generated mainly from the 19th week up to (and perhaps beyond) the time of birth. However, adult neurogenesis in the human olfactory bulb is not indicated by the studies of Rakic (1985).

The *anterior olfactory nucleus* (AON) in rats is located posteriorly adjacent to the olfactory bulb in the olfactory peduncle. It is one of the major olfactory processing centers; the olfactory bulb is its major afferent input and is also the principal target of its axons. The anterior olfactory nucleus can be divided into a pars externa, an ectopic group of neurons in the anterior dorsolateral part of the peduncle, and the anterior olfactory nucleus proper, which contains the pars dorsalis, pars lateralis, pars ventralis, and pars medialis. The posterior parts of the anterior olfactory nucleus proper form transition areas to the primary olfactory cortex in the piriform lobe.

A posterior (older) to anterior (younger) neurogenetic gradient is found both within and between components of the olfactory peduncle in the rat (Bayer, 1986a). Neurons in the pars externa are generated mainly between E16 and E19 (Fig. 40), those in the AON proper from E15 to E20 (data in Fig. 40 are combined for all subdivisions), those in the posterior transition areas from E14 to E19 (data are not shown in Fig. 40, see Bayer, 1986a). Only 3-4% of the neurons in the most anterior pars lateralis and pars dorsalis originate after birth. All parts of the anterior olfactory nucleus proper have a strong superficial (older) to deep (younger) neurogenetic gradient, while many of the tran-

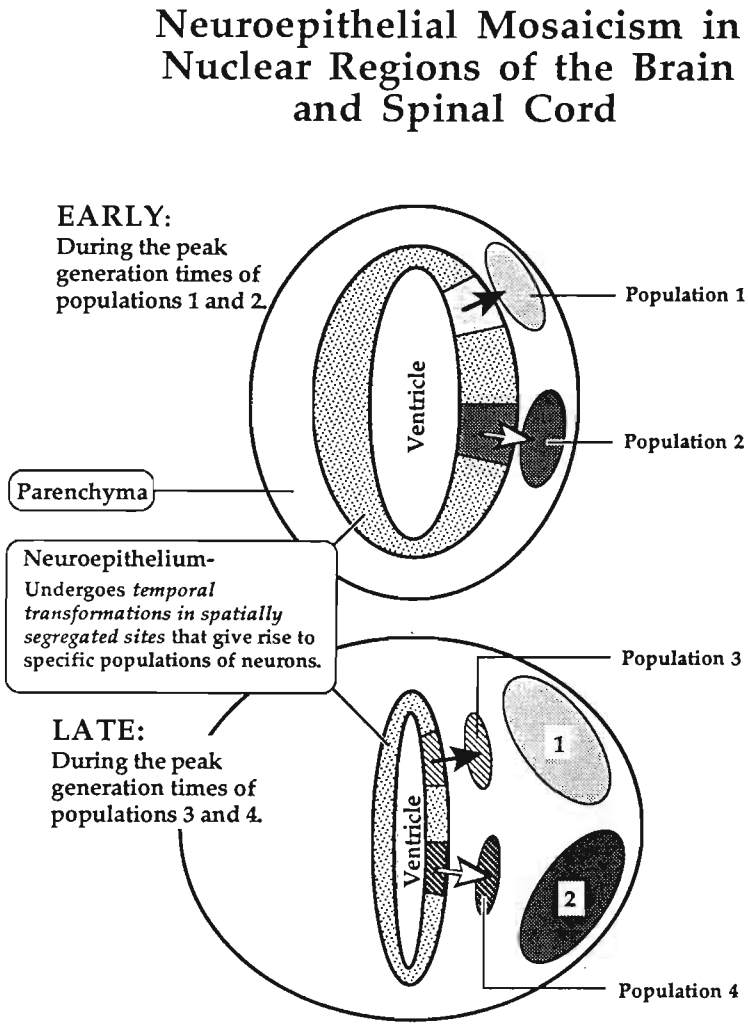


FIG. 41. Postulated mosaicism in the neuroepithelium generating nuclear structures as based on [^{3}H]thymidine autoradiographic developmental studies in rats (From Bayer *et al.*, in press).

sitional areas have a gradient in the opposite direction - deep (older) to superficial (younger). These data suggest that characteristic patterns of neurogenesis, namely the "inside-out" vs the "outside-in" gradients, distinguish nuclear and cortical components of the olfactory processing centers.

Although we have not studied morphogenetic development in the olfactory peduncle, there is evidence that the pattern in which the anterior olfactory nucleus sends axons into the olfactory bulb is related to time of neuron origin: posterior parts project to the bulb first, anterior parts project later. Other anatomical connectons of the anterior olfactory nucleus can also be related to neurogenetic gradients (reviewed in Bayer, 1986a). The olfactory peduncle in man is poorly developed (Truex and Carpenter, 1969; Brodal, 1981). If the neurons there are comparable to those in the olfactory peduncle of the rat, we estimate that posterior neurons would be generated from the late 5th week through the 11th week, anterior neurons from the late 6th week through the 18th week.

DERIVING PRINCIPLES OF CENTRAL NERVOUS SYSTEM DEVELOPMENT FROM EXPERIMENTAL STUDIES IN RATS

Neuroepithelial Organization and Spatiotemporal Mosaic Patterns

Our observations using [^{3}H] thymidine autoradiography and normative histology indicate that before neurons are produced, the neuroepithelium undergoes a series of transformations in shape and composition that are prerequisites for the development of the complex organization of the rat nervous system. In the following discussion we will emphasize that that the general principles governing rat central nervous system development are applicable to man, and the structure of the neuroepithelium in the human fetus is a predictor of the anatomical complexity of the human central nervous system.

Based on our work with [^{3}H] thymidine autoradiog-

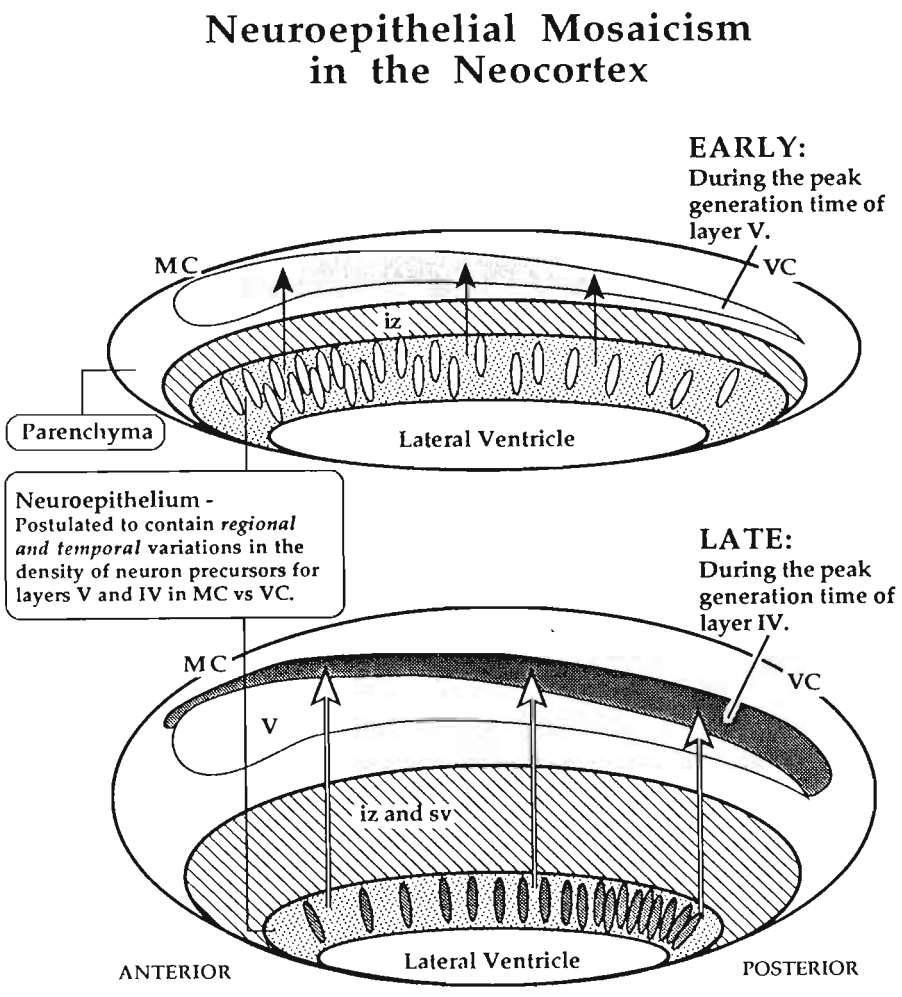


FIG. 42. Postulated mosaicism in the neocortical neuroepithelium based on [^{3}H]thymidine autoradiographic developmental studies in rats. (From Bayer and Altman, in press)

raphy, we postulate that each neuronal populations in the central nervous system has three defining characteristics. (1) Each is generated in a specific site in the neuroepithelium. (2) Each one has a unique timetable of neurogenesis that is (3) linked to developmental patterns in other populations with which it will have strong interconnections. Regarding the neuroepithelium itself, these observations suggest that it contains a spatiotemporal blueprint ("Bauplan") of central nervous system structure. The consistent [^{3}H]thymidine labeling patterns from animal to animal in both embryonic and adult brains suggest that the blueprint is highly conserved within a species and may be encoded in the genes.

The Neuroepithelium Grossly Predicts the Future Shape of the Central Nervous System. The formation of the three primary brain vesicles (prosencephalon, mesencephalon, rhombencephalon) and their later subdivision into five brain vesicles (telencephalon, diencephalon, mesencephalon, metencephalon, myelencephalon) reflects regional differences in the growth of the proliferative neuroepithelium. In turn, differences in the growth dynamics of these vesicles herald the basic morphological organization of the mature central nervous system. For instance, the elongated neural tube, and its division into an alar plate and basal plate, predicts the basic morphology of the spinal cord. Moreover, species differences in neuroepithelial organization herald species differences in adult brain structures. For example, the greater linear expansion of the neuroepithelium in the developing human cerebral cortex predicts a large gyrencephalic structure, while the shorter linear expanse of the neuroepithelium in the developing rat cerebral cortex predicts a smaller lissencephalic structure (compare the sizes of the cortex in Figs. 6-10 and 13-18).

Neuroepithelial Mosaicism. Over time and space, the cells composing the neuroepithelium are a "Bauplan" (blueprint) of all the neuronal populations that will constitute the mature central nervous system. Long-survival [^{3}H] thymidine autoradiography indicates that the regional timetables of neurogenesis are strictly obeyed throughout the central nervous system (Figs. 19-24, 26, 30-37, 39-40). Short-survival [^{3}H] thymidine autoradiography shows that transformations of the neuroepithelium in specific loci are temporally linked to the peak generation of specific popu-

lations of neurons. These observations indicate that the neuroepithelium is a spatiotemporal mosaic, consisting of segments or patches destined to produce neurons for different brain structures at specific times. Our experimental studies with short-survival [^{3}H]thymidine autoradiography indicate that neuroepithelial mosaicism varies in organization between nuclear parts of the central nervous system and laminated parts of the central nervous system.

Nuclear Regions of the Brain and Spinal Cord. Throughout the spinal cord, hindbrain, floor of the midbrain, and the diencephalon, it is possible to subdivide the neuroepithelium into small patches by such landmarks as evaginations or invaginations, thickenings or thinnings, and regional differences in label uptake within 2 hours after an injection of [^{3}H]thymidine. In the above discussion of the spinal cord there are ventral-to-dorsal gradients in proliferative activity which define three neuroepithelial zones (Altman and Bayer, 1984). The ventral zone (base plate) produces the early-generated ventral horn motor neurons. The intermediate zone produces the later-generated relay neurons. The dorsal zone (alar or surface plate) produces the latest-generated dorsal horn interneurons. Moreover, there is evidence for microsegmentation in the spinal cord neuroepithelium that gives rise to the relay neurons.

In the diencephalic neuroepithelium, transformations in the germinal mosaic have been more completely identified with short- and sequential-survival [^{3}H]thymidine autoradiography (Altman and Bayer, 1986, 1988a, b, c, 1989a, b, c; Bayer and Altman, 1987a). The general pattern is diagrammed in Figure 41 and was briefly discussed above. At an early time (top, Fig. 41), spatially discrete sites in the neuroepithelium (shaded bars) give rise to specific populations of neurons (shaded ellipses) that settle in clump-like arrays (nuclei) in the parenchyma of the thalamus, hypothalamus and preoptic area. At a later time (bottom, Fig. 41), the neuroepithelium is transformed so that successive neuronal populations are being generated at the same sites. We have identified evaginations and invaginations (called neuroepithelial lobules and sublobules to be the putative germinal sources of specific thalamic nuclei (Altman and Bayer, 1988a, 1989a). For example, the intermediate lobule in the diencephalic neuroepithelium of the third ventricle contains precursors successively generating neurons bound for specific thalamic nuclei: the ventrobasal on E14/E15, the ventromedial on E16, and more medially situated nuclei on E17 (Altman and Bayer, 1989a). The intermediate lobule is also the source of glial cells that comigrate with the neurons. Other cells that leave the neuroepithelium continue to proliferate locally, producing glia in the brain parenchyma. The final product of the neuroepithelium in the intermediate sublobule is the ependyma that lines a discrete region of the third ventricle. The ependyma itself has spatial variations in composition, especially in the third ventricle (Altman and Bayer, 1978e), presumably a reflection in the adult brain of the germinal mosaic that once existed in the developing brain.

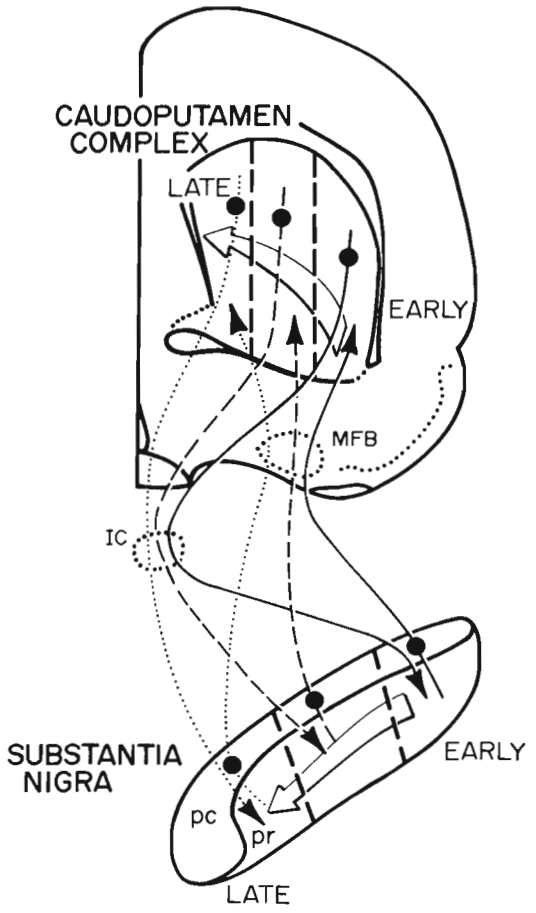


FIG. 43. Correlations between neurogenetic gradients and anatomical connections in the nigro-striatal system. Axons of early originating nigral neurons (solid lines) project via the medial forebrain bundle (MFB) to early-originating cells in the ventrolateral part of the caudoputamen complex. To complete the circuit, axons from superficial neurons in the lateral part of the complex (solid lines) project via the internal capsule (IC) to the dorsolateral substantia nigra. Thus early-originating cells in both structures are interconnected. The same relationship holds for those neurons intermediate in age (axons are represented as dashed lines), and late in age (axons are represented as dotted lines. (From Bayer, 1984)

Laminated Regions of the Brain. In laminated parts of the central nervous system, especially the cerebral cortex, it has been postulated that the precursors of layer-specific neurons have regional variations in their distribution in the neuroepithelium (Bayer and Altman, 1991a). This variation is diagrammed in Figure 42. At an early time (E16-E17), the neuron precursors of the pyramidal cells in layer V (shaded ellipses, upper drawing) are more numerous in the anterior neuroepithelium under the future motor cortex (MC) than in the posterior neuroepithelium under the visual cortex (VC), and more layer V neurons migrate to the motor cortex than to the visual cortex (solid black arrows). At a later time (E18-E19), the precursors of layer IV neurons bound for the visual cortex are more numerous posteriorly than the precursors of layer IV neurons bound for the motor cortex anteriorly (shaded ellipses, lower drawing), and more layer IV neurons migrate to the visual cortex than to the motor cortex (outlined white arrows), Notice that the spatial distribution of layer V and

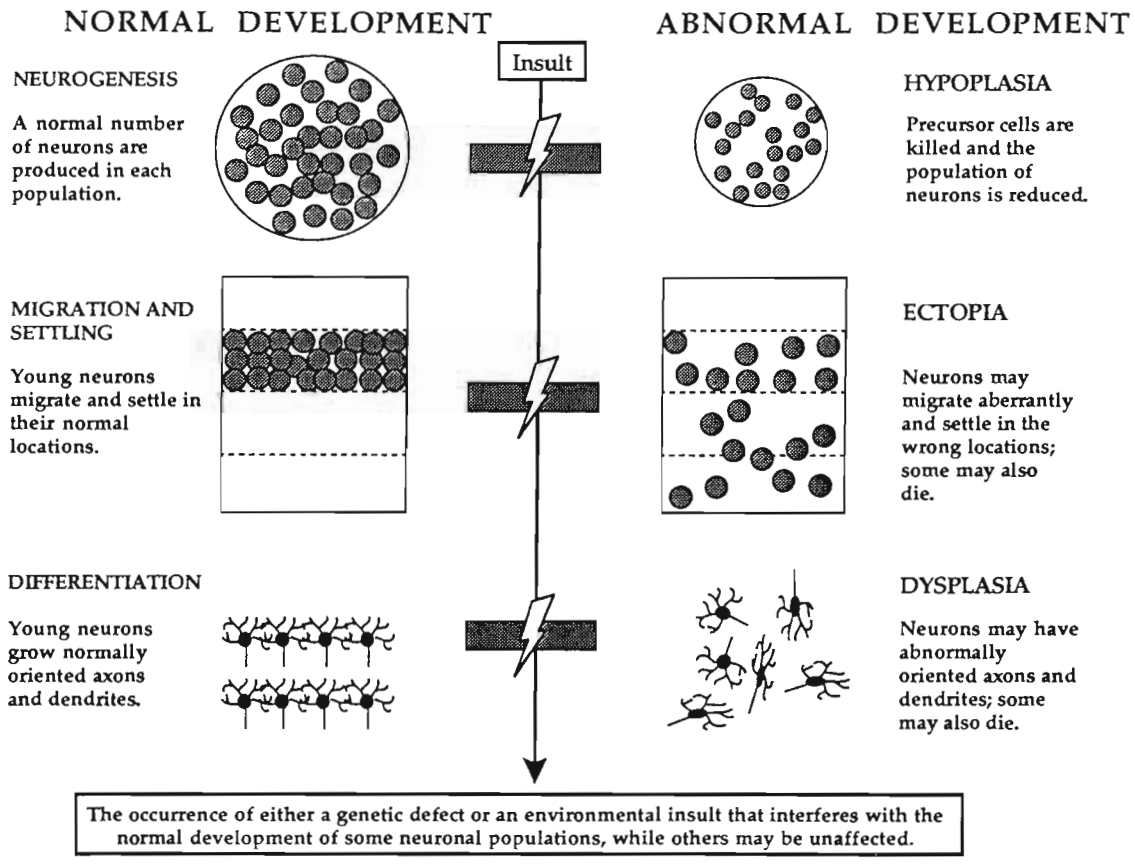


FIG. 44. A diagram showing some of the effects of either genetic defects or environmental insults on the different phases of neuronal development. (From Bayer *et al.*, in press.)

layer IV precursors overlap in the neuroepithelium (compare the upper and lower drawings, Fig. 42). This type of neuroepithelial mosaicism differs from the more spatially segregated pattern in nuclear regions.

The Chronology of Neurogenesis and the Patterns of Neuronal Migration in Relation to the Maturation of Neural Circuits

[^{3}H]thymidine autoradiography indicates that neurogenetic timetables are linked between specific populations to correlate with the pattern of anatomical connections that will later develop. In the thalamocortical system for example, neurons in each specific thalamic relay nucleus and in each cortical target area are produced at just the right time so that the thalamic axons growing into the neocortex can interact with target neurons as they are migrating to the cortical plate (Chapter 16 in Bayer and Altman, 1991a). Synchronized developmental events also occur in other sets of related brain structures, such as those in the limbic system interconnected via the Papez circuit: the hippocampus, anterior thalamic nuclear complex, mammillary bodies of the hypothalamus, and cingulate limbic cortical areas (Bayer, 1980a; Bayer and Altman, 1991a). Throughout the auditory system, there is a general correlation between time of neuron origin and the tonotopic order of axonal interconnections (Altman and Bayer, 1981b). Synchronized patterns are also are also characteristic of the development of the cerebellar cortex and its afferent projections (Altman, 1982). One of the best examples of these correlations is shown in Figure 43. The connections between the substantia nigra and the striatum are age-matched so that older neurons in lateral parts, middle-aged neurons in central parts, and younger neurons in the medial parts are reciprocally interconnected (Bayer, 1984). These correlations, and many others from throughout the neuraxis, form the basis for the hypothesis that the chronology of neurons production is a necessary prerequisite for the proper anatomical and functional development of the central nervous system.

Vulnerability During Central Nervous System Development and Some Possible Consequences

Of special interest to the focus of this article is the question: What happens when either genetic defects or environmental insults interfere with the normal developmental program of the central nervous system? Our experimental studies using X-irradiation of the cerebellum or hippocampus (Altman, 1982; Bayer and Altman, 1975a,b) indicate that when the insult occurs during neurogenesis, the neuron precursors in the germinal matrix are killed in large numbers. Moreover, the surviving precursors do not extend their period of cell proliferation or increase the

number of cells they normally produce to replace the neurons the killed precursors would have generated. Thus the number of neurons in an affected population is moderately to severely reduced, depending on the amount of exposure to the killing agent (Hypoplasia, Fig. 44). In cases where neuronal populations are produced over a short time span, a brief but massive insult may lead to the permanent decimation of the entire population. In addition, the loss of neurons is often the starting point for abnormalities in cell migration, settling, and differentiation of neurons that were already produced or will be produced after the insult has passed.

When X-irradiation occurs during migration, its normal time course is disrupted, and neurons will settle in abnormal locations (Ectopia, Fig. 44). For example, the cerebellar granule cells normally settle below the Purkinje cell layer. After exposure to X-irradiation, the migration of many granule cells is eliminated because their precursors are killed. That results in a break in the normally steady stream of new granule cells that settle in their proper locations. Consequently, the mossy fibers (axons that normally contact granule cell dendrites) do not find the normal complement of granule cell targets and continue to grow upwards into the cerebellar cortex above the layer of Purkinje cells and beyond their normal stopping point. There, they arrest the downward migration of the granule cells that were generated by the few precursor cells surviving X-irradiation. The result is an ectopic layer of granule cells above the Purkinje cells (Altman, 1973a). Ectopia has also been seen after X-irradiation of the cerebral cortex (Jensen and Killackey, 1984). Once ectopia has been produced by abnormal migration, it becomes a permanent anatomical feature of the brain. That situation may generate abnormalities in the circuitry of the nervous system (which neurons are synaptically connected to each other) and often results in abnormal function.

When X-irradiation occurs during differentiation, the axons that normally grow into a field of growing dendrites may either be missing (because their cells of origin have been eliminated by the X-rays) or may arrive at an abnormal time. That disrupts the normal environment that the dendrites grow into and results in abnormally shaped dendritic trees (dysplasia, Fig. 44). As described above, Purkinje cell dendrites become highly dysplastic when X-irradiation changes the axonal environment at critical stages of development (Altman, 1976a,b,c). As with hypoplasia and ectopia, dysplasia is also a permanent phenomenon.

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