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# Development of the Precerebellar Nuclei in the Rat: I. The Precerebellar Neuroepithelium of the Rhombencephalon

JOSEPH ALTMAN AND SHIRLEY A. BAYER
Laboratory of Developmental Neurobiology, Department of Biological Sciences, Purdue University, West Lafayette, Indiana 47907 (J.A.) and Department of Biology, Indiana University-Purdue University, Indianapolis, Indiana 46223 (S.A.B.)

ABSTRACT

Short-survival thymidine radiograms from rat embryos aged 13–19 days were analyzed to delineate the precerebellar neuroepithelium of the rhombencephalon. The original definition of the term "rhombencephalon" was modified to refer only to the unique dorsal portion (surface plate) of the medulla and pons where the neural groove fails to fuse and, instead, the medullary velum covers the rhomboid lumen of the fourth ventricle. Initially, the neuroepithelial tissue of the rhombencephalon consists of a pair of rostral and caudal bridgeheads: the former the primary neuroepithelium of the cerebellum and the latter the primary neuroepithelium of the octavoprecerebellar system. The spatial relationship between the cerebellar and precerebellar neuroepithelia soon changes as a result of ongoing morphogenetic events, such that the cerebellar primordium assumes a dorsal position and the precerebellar primordium a ventral position, and the distance between the two decreases. Concurrently the tela choroidea invaginates into the fourth ventricle and a secondary precerebellar neuroepithelium develops. The rostral portion of the secondary precerebellar neuroepithelium grows forward along the choroid plexus and forms the medial recess of the anterior fourth ventricle, while its caudal portion grows in the opposite direction beneath the medullary velum and forms the rostral wall of the posterior fourth ventricle. Evidence will be presented in the succeeding papers that the primary precerebellar neuroepithelium first generates the neurons of the inferior olive that migrate by a circumferential intramural (parenchymal) route to their destination. Next, the neurons of the lateral reticular and external cuneate nuclei are generated. These migrate by a posterior extramural (superficial) route and settle contralaterally. Subsequently, the primary precerebellar neuroepithelium produces the neurons of the nucleus reticularis tegmenti pontis and these form the anterior extramural migratory stream and settle ipsilaterally. Finally, the secondary precerebellar neuroepithelium produces the latest generated neurons of the basal pontine gray that follow the anterior extramural stream and settle ipsilaterally.

**Key words: neuroembryology, neuronal migration, thymidine autoradiography**

The term "rhombencephalon" is widely used by embryologists to designate the region of the neuraxis that surrounds the fourth ventricle and its recesses and is the primordium of the adult hindbrain. Some embryologists subdivide the developing rhombencephalon into two parts, the myelencephalon, which is considered to be the primordium of the medulla, and the metencephalon, which is said to give rise to the cerebellum and the pons (e.g., Patten and Carlson, '74). So conceptualized, the ventral portion of the rhombencephalon, the basal plate, is continuous caudally with the spinal cord and rostrally, by way of the narrowed

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isthmus region, with the tegmentum of the mesencephalon. This continuity with the caudal and rostral neuraxis is absent dorsally. The dorsal (surface or alar) plates fail to fuse medially in this region. Instead, a membrane, the medullary velum, part of which becomes the tela choroidea, spreads over the enlarged rhomboid cavity, the fourth ventricle. This membrane initially forms a simple canopy over the fourth ventricle and interconnects the edges of the caudal and rostral portion of the classical dorsal rhombencephalon. The tela choroidea then invaginates to form the primitive choroid plexus, and neural tissue spreads along the edges of its folding surface. The choroid plexus and the neuroepithelial tissue associated with it give rise to recesses of the fourth ventricle. For reasons that will be justified below, we shall use the term "rhombencephalon" to designate the surface plate neuroepithelium forming the bridgeheads of the tela choroidea rostrally and caudally, and a complex of secondary matrices derived from this unique region of the surface plate between the two bridgeheads. In terms of this scheme, the dorsal rhombencephalon is the source of neurons of the cerebellum, and the ventral rhombencephalon is the source of the octavoprecerebellar system. The continuous basal plate neuroepithelium situated between the spinal cord and the mesencephalon we shall call the "metencephalon." The metencephalon is the source of neurons of the motor, raphe, and reticular nuclei of the medulla and lower tegmentum.

This paper focuses on one component of the rhombencephalon, the neuroepithelium of the precerebellar nuclei. The study of the embryonic development of the precerebellar nuclei, focusing on the inferior olive and the basal pontine gray, was pioneered by His (1891) and followed up by Essick ('12), Harkmark ('54), Taber Pierce ('66), and Ellenberger et al. ('69). In our earlier studies with long-survival thymidine autoradiography (Altman and Bayer, '78a,b, '80; summarized in Altman, '82: Fig. 3) we have established that the neurons of five suprasegmental precerebellar nuclei are produced in a sequential order. The neurons of the inferior olivary complex are generated first with peak production on embryonic day 13 (E13), followed by the lateral reticular nucleus (day E14), the external cuneate nucleus (day E15), the nucleus reticularis tegmenti pontis (day E16), and ending with the neurons of the basal pontine gray (peak on day E17 and extending to day E19). In the present series of studies (Altman and Bayer, '87a–c), utilizing short-survival and sequential-survival thymidine radiography, we shall present evidence that the neurons of these five precerebellar nuclei originate from a single neuroepithelial source in the ventral portion of the rhombencephalon. The precerebellar neurons are generated in successive waves, first from the primary precerebellar neuroepithelium, then from the secondary precerebellar neuroepithelium, and they follow different extended migratory routes to reach their settling sites, far apart from each other, some ipsilaterally, others contralaterally. This paper of the series, based on short-survival thymidine radiography, deals with the structure and developmental transformations of the precerebellar neuroepithelium in relation to the rest of the rhombencephalon.

## MATERIALS AND METHODS

Three collections of thymidine radiograms were used in this series of studies. All were derived from the offspring of laboratory-bred Purdue-Wistar rats that were injected with a single dose of $^3$H-thymidine at daily intervals from day E12 to E21. The breeding females were placed with males in the evening and examined for sperm in the morning. The day of sperm positivity was counted as day E1; the specific activity of the radiochemical was 6.0 Ci/mM; injections of 5 $\mu$Ci/g body weight were made between 9:00 and 9:30 A.M. The dams were anesthetized before their offspring were removed and the specimens were blocked immediately coronally, sagittally, or horizontally and immersed in Bouin's fluid. After 24 hours, the material was transferred for storage into 10% neutral formalin. Subsequently the blocks were embedded either in paraffin or methacrylate. The paraffin blocks were serially sectioned at 6 $\mu$m and the methacrylate blocks at 3 $\mu$m, and every tenth section was saved. Successive sections were either stained with cresyl violet or hematoxylin-eosin for examination without nuclear emulsion or were prepared for autoradiography. The latter were coated with Kodak NTB-3 emulsion in the dark, exposed for 90 days with a desiccant, developed in Kodak D-19, and stained with cresyl violet or hematoxylin-eosin.

The first collection is referred to as *short-survival radiograms*. In this series the embryos or fetuses were removed 2 hours after injection in order to visualize the sites and magnitude of neuroepithelial cell proliferation as a function of embryonic age at injection. This collection consists of 94 paraffin- or methacrylate-embedded specimens. The second series is referred to as *sequential radiograms*. This consists of 254 paraffin- or methacrylate-embedded embryos, fetuses, or young pups that were removed at daily intervals after injection in order to trace cell migration. The third series is referred to as *perinatal long-survival radiograms*. This series consists of 231 paraffin- and methacrylate-embedded old fetuses or young pups and is used to study the settling patterns and cytogenetic organization of neurons of the precerebellar nuclei. In the first paper concerned with the organization of the precerebellar neuroepithelium we have used primarily short-survival radiograms.

## RESULTS

The configuration of the rhombencephalon (RH; a list of abbreviations used in this paper—and their meanings—precedes Fig. 1) on day E14 is shown in a midsagittal short-survival radiogram in Figure 1A. It has three parts: (1) a rostral neuroepithelial field, the primordium of the cerebellum (ce); (2) an interconnecting, as yet uninvaginated, membranous cover over the fourth ventricle, the tela choroidea (tc); and (3) a caudal, mitotically active neuroepithelial field, designated as the primary precerebellar neuroepithelium (pcp). The basal boundaries of the rhombencephalon are partly represented by an imaginary line through the ventricular system that divides throughout the neuraxis the surface plate (sp) of the embryonic nervous system, the source of afferent neurons, from the base plate (bp), the source of efferent neurons. In the upper medulla the boundary is uncertain (broken lines in Fig. 1A,B) because the rhombencephalic vestibular neuroepithelium (ve?) has yet to be delineated from the metencephalon (MET) generating the neurons of the motor, raphe, and reticular nuclei of the medulla (ME), pons (PO), and lower tegmentum (TEl).

The changing spatial relationship between the cerebellar and precerebellar primordia is illustrated in midsagittal thymidine radiograms from days E15 (Fig. 1B), E16 (Fig. 2A), and E17 (Fig. 2B) rats. The two most important features are (1) that the cerebellar and precerebellar primordia

progressively approximate each other and (2) that the cerebellum assumes a dorsal position in relation to the precerebellar primordium. This change is associated with three morphogenetic events. First, the flexure of the neuraxis in the pontine region (PO) becomes more acute (upward arrows in Figs. 1A,B, 2A) so that the primordium of the inferior colliculus (ic) becomes displaced caudally over and beyond the cerebellum, which, in turn, is moved closer and closer to the caudal rhombencephalon (note the shortening of the rhombencephalon, RH, in Figs. 1B, 2A,B). Second, partly influenced by this process, the tela choroidea folds into the fourth ventricle and the rostrally expanding choroid plexus (cp and horizontal arrow in Fig. 1B) produces the medial recess of the fourth ventricle (mr in Fig. 2A). Third, the cavity of the fourth ventricle shrinks progressively, seemingly because the differentiating neurons of the rhombencephalon and metencephalon fill the available internal space of the fourth ventricle.

In short-survival thymidine radiograms of the primary precerebellar neuroepithelium (Figs. 1B, 3) three zones can be distinguished: (1) a periventricular layer with labeled cells (pcp); (2) a layer of darkly staining, circular (transversely cut) unlabeled cells (iop); and (3) a population of obliquely oriented, spindle-shaped, unlabeled cells (iom). On the basis of observations to be presented in the succeeding paper (Altman and Bayer, '87a), the zone of darkly staining cells is identified as the premigratory differentiating neurons of the inferior olive and the spindle-shaped cells as migrating young olivary neurons that follow a circumferential course within the parenchyma. Since the neurons of the inferior olive are generated on the preceding days (days E13 and E14), the labeled cells of the primary precerebellar neuroepithelium can no longer be producing neurons for this structure. We shall present evidence (Altman and Bayer, '87b) that the neurons generated on days E15 and E16 (and some that are produced on the preceding days) take a different migratory route than do the inferior olivary neurons. One group of cells follows a posterior migratory route over the surface of the medulla, crosses ventrally to the opposite side, and forms the lateral reticular and external cuneate nuclei. Another group of cells follows an anterior route over the surface of the medulla and pons and terminates ipsilaterally to form the nucleus reticularis tegmenti pontis.

From day E16 onward (Figs. 2, 4, 5), the shape of the precerebellar neuroepithelium changes substantially as it expands caudally, to form a wall between the anterior and posterior fourth ventricles (v4a and v4p in Figs. 4, 9A), and rostrally beneath the choroid plexus, to form the medial recess of the anterior fourth ventricle (mr in Figs. 4, 5, 9A). These two regions are designated as the rostral (pcsr) and caudal (pcsc) secondary precerebellar neuroepithelia. We shall present evidence (Altman and Bayer, '87c) that this late-forming germinal field generates the neurons of the basal pontine gray that migrate by way of the rostral extramural stream to the pons, where they settle ipsilaterally.

The three-dimensional configuration of the secondary precerebellar neuroepithelium is revealed in a comparison of a series of parasagittal (Figs. 4, 5) and coronal (Figs. 6–8) thymidine radiograms from rats labeled on day E18 and killed 2 hours later. Midsagittally (Fig. 4), the entire precerebellar secondary neuroepithelium forms a continuous, elaborately folded sheet of proliferating cells. More laterally (Figs. 5, 6), the rostral and caudal secondary precerebellar neuroepithelia appear as separate germinal zones. Coronal short-survival thymidine radiograms (Figs. 6–8) show the relationship of components of the secondary precerebellar neuroepithelium to each other, to the secondary auditory neuroepithelium (aus in Fig. 6A,B), and to the rhombencephalon as a whole (outlines in Figs. 6B, 7A). By this age (day E18), mitotically active germinal fields are limited in the hindbrain to the rhombencephalon (as we define it). The unlabeled floor of the fourth ventricle (v4f) shifts from ventral to dorsal as one proceeds from caudal (Fig. 8B) to rostral (Fig. 6A). The regressive basal plate (bp) of the metencephalon shifts from a ventral position caudally (Fig. 8) to a dorsomedial position rostrally (Figs. 6, 7). The basal plate has few labeled cells at any level. The regressive surface plate (sp) shifts from a dorsal position caudally (Fig. 8) to a dorsolateral position rostrally (Figs. 6, 7A). Rostrally, the alar and basal plates are separated from

*Abbreviations*

| | |
|---|---|
| aes | anterior extramural stream |
| AQi | aqueduct inferior |
| aus | auditory secondary neuroepithelium |
| bp | basal plate neuroepithelium |
| ce | cerebellar primary neuroepithelium |
| CE | cerebellum |
| CEa | anterior cerebellum |
| CEp | posterior cerebellum |
| cmf | cerebellomesencephalic flexure |
| cp | primordium of the fourth ventricle choroid plexus |
| cpl | lateral portion of the fourth ventricle choroid plexus |
| cpm | medial portion of the fourth ventricle choroid plexus |
| egl | external germinal layer |
| gt | germinal trigone |
| ic | inferior collicular neuroepithelium |
| IC | inferior colliculus |
| IO | inferior olive |
| iom | inferior olivary intramural migratory stream |
| iop | inferior olivary premigratory zone |
| is | isthmal canal |
| IST | isthmus |
| lrl | lower rhombic lip |
| lr | lateral recess of fourth ventricle |
| me | primary medullary neuroepithelium |
| ME | medulla |
| MET | metencephalon |
| mr | medial recess of the fourth ventricle |
| MS | mesencephalon |
| nt | neural tube |
| pcp | precerebellar primary neuroepithelium |
| pcs | precerebellar secondary neuroepithelium |
| pcsc | caudal precerebellar secondary neuroepithelium |
| pcsr | rostral precerebellar secondary neuroepithelium |
| pes | posterior extramural migratory stream |
| pi | postisthmal (cerebellar) recess of fourth ventricle |
| pms | pontine migratory stream |
| PO | pontine region |
| RH | rhombencephalon |
| SC | spinal cord |
| sl | sulcus limitans |
| sp | surface plate neuroepithelium |
| sz | synthetic zone of neuroepithelium |
| tc | tela choroidea |
| tel | lower tegmental neuroepithelium |
| TEl | lower tegmentum |
| tem | middle tegmental neuroepithelium |
| TEm | middle tegmentum |
| url | upper rhombic lip |
| ve | vestibular neuroepithelium |
| vm | medullary velum |
| v4a | anterior fourth ventricle |
| v4f | floor of the fourth ventricle |
| v4p | posterior fourth ventricle |
| VS | principal sensory nucleus of the trigeminal |
| XII | hypoglossal nucleus |

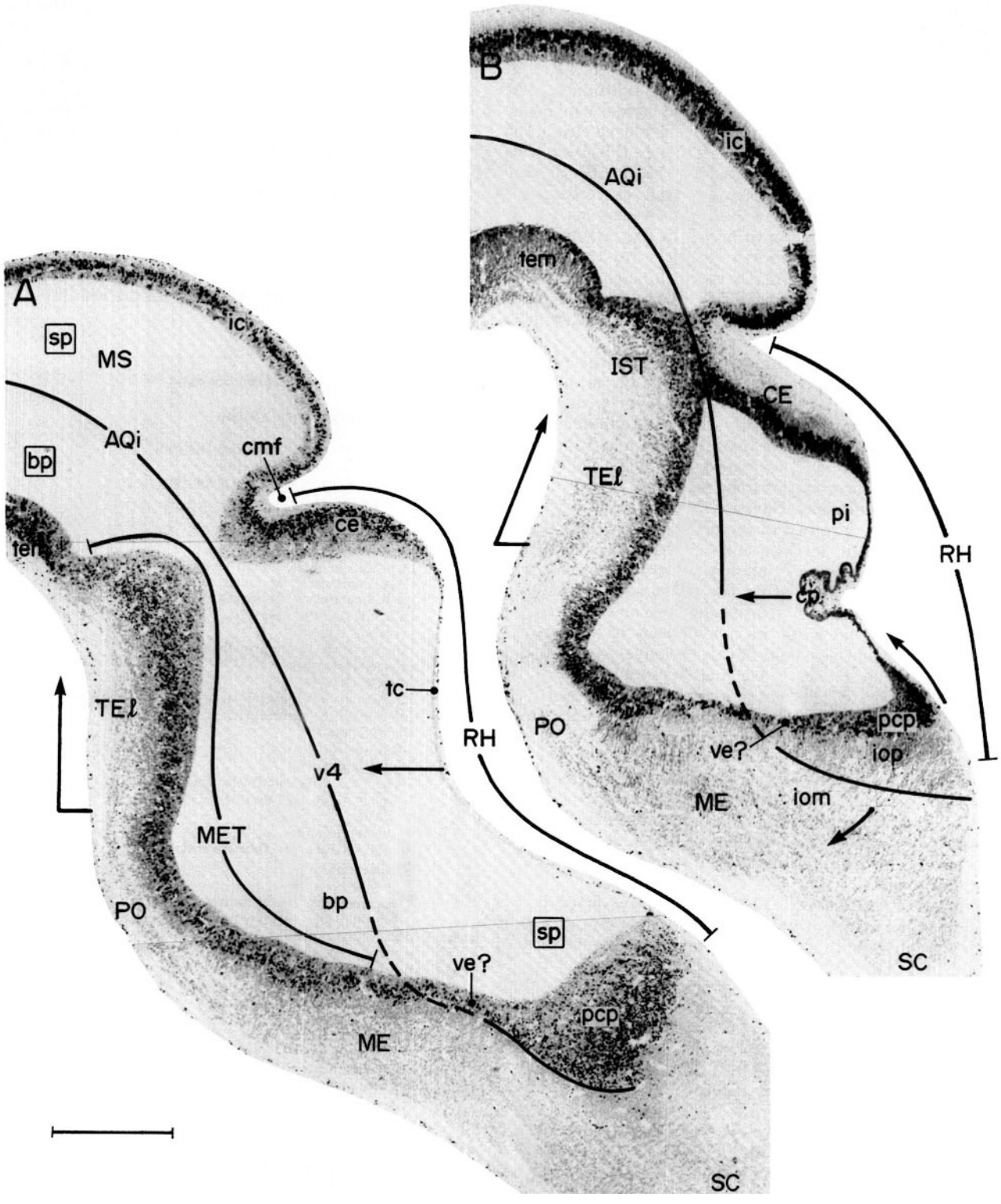


Fig. 1. **A:** Sagittal radiogram from a rat labeled on day E14 and killed 2 hours later. The rhombencephalic neuroepithelium (RH) is separated from the metencephalic neuroepithelium (MET) by a line drawn through the middle of the embryonic ventricular system that separates the surface plate neuroepithelium (sp) from the basal plate neuroepithelium (bp). **B:** Sagittal radiogram from a rat labeled on day E15 and killed 2 hours later. Due to the progressive pontine flexure (vertical and oblique arrows on the left in Figs. 1A,B, 2A) and the invagination of the choroid plexus into the fourth ventricle (horizontal arrows) the cerebellar anlage (ce) and the primary precerebellar anlage (pcp) approximate each other and the rhombencephalon becomes shorter (compare with Figs. 1A, 2A,B). A. Methacrylate. B. Paraffin. Scale: 500 $\mu$m.

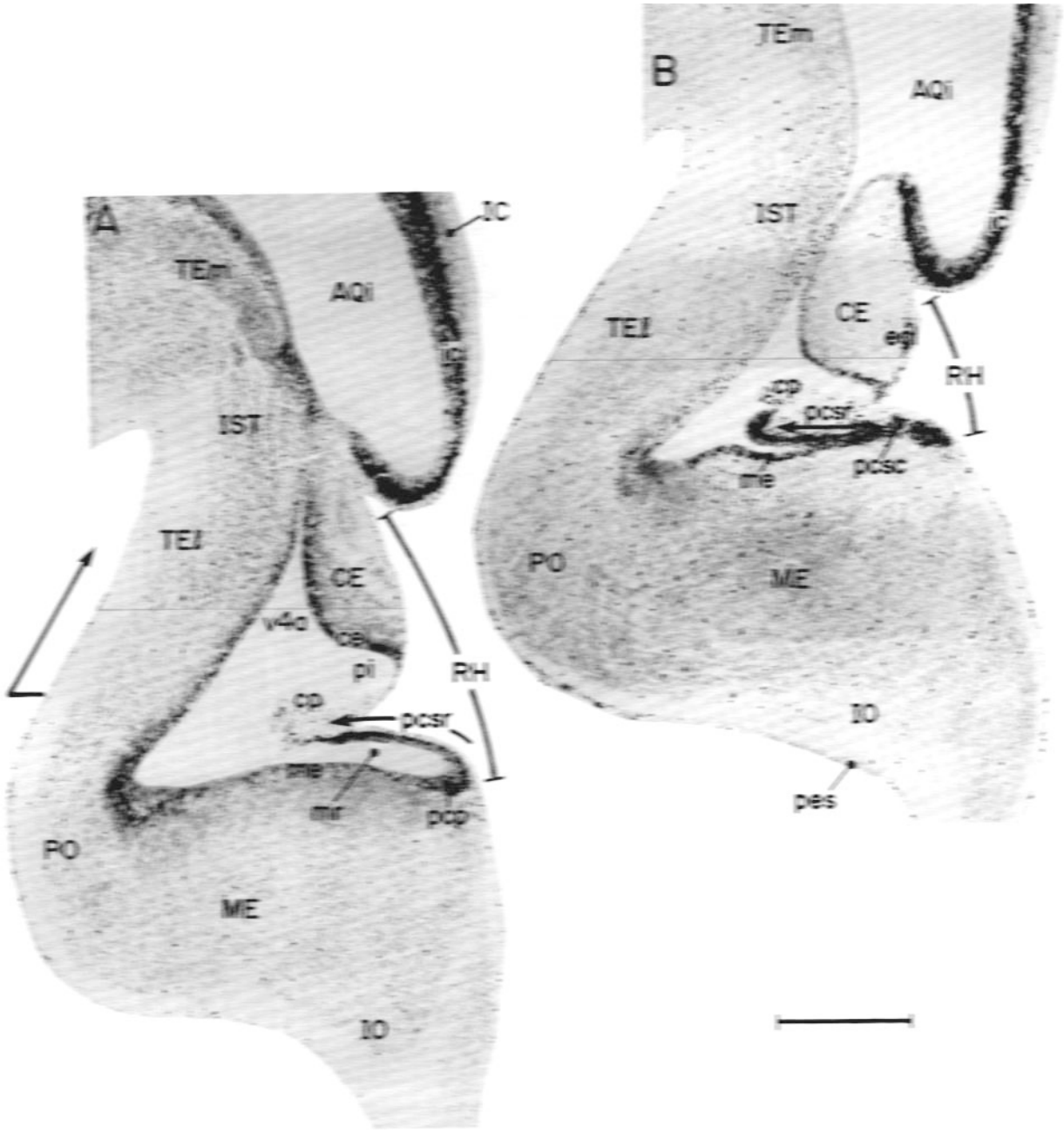


Fig. 2. **A:** Sagittal radiogram from a rat labeled on day E16 and killed 2 hours later. **B:** Sagittal radiogram from a rat labeled on day E17 and killed 2 hours later. Note the formation of the rostral (pcsr) and caudal (pcsc) secondary precerebellar neuroepithelia. Paraffin. Scale: 500 $\mu$m.

each other by the sulcus limitans (*sl* in Figs. 6, 7). The surface plate is largely devoid of labeled cells caudally (Figs. 7, 8) but rostrally (Fig. 6) some labeled cells are present in the transition area to the precerebellar secondary neuroepithelium, which itself is composed entirely of labeled cells. Apparently, the germinal matrix of the metencephalon has become transformed into a postmitotic ependymal layer.

The area within which the rhombencephalic neuroepithelium (primary or secondary) is situated is outlined in Figures 6B and 7A. At these rostral levels, the lateral recess of the fourth ventricle (lr) divides the rhombencephalon into a larger dorsal component and a smaller ventral component. The dorsal rhombencephalon is the primordium of the cerebellum, and it has three germinal fields: the external germinal layer (egl), the germinal trigone (gt), and the

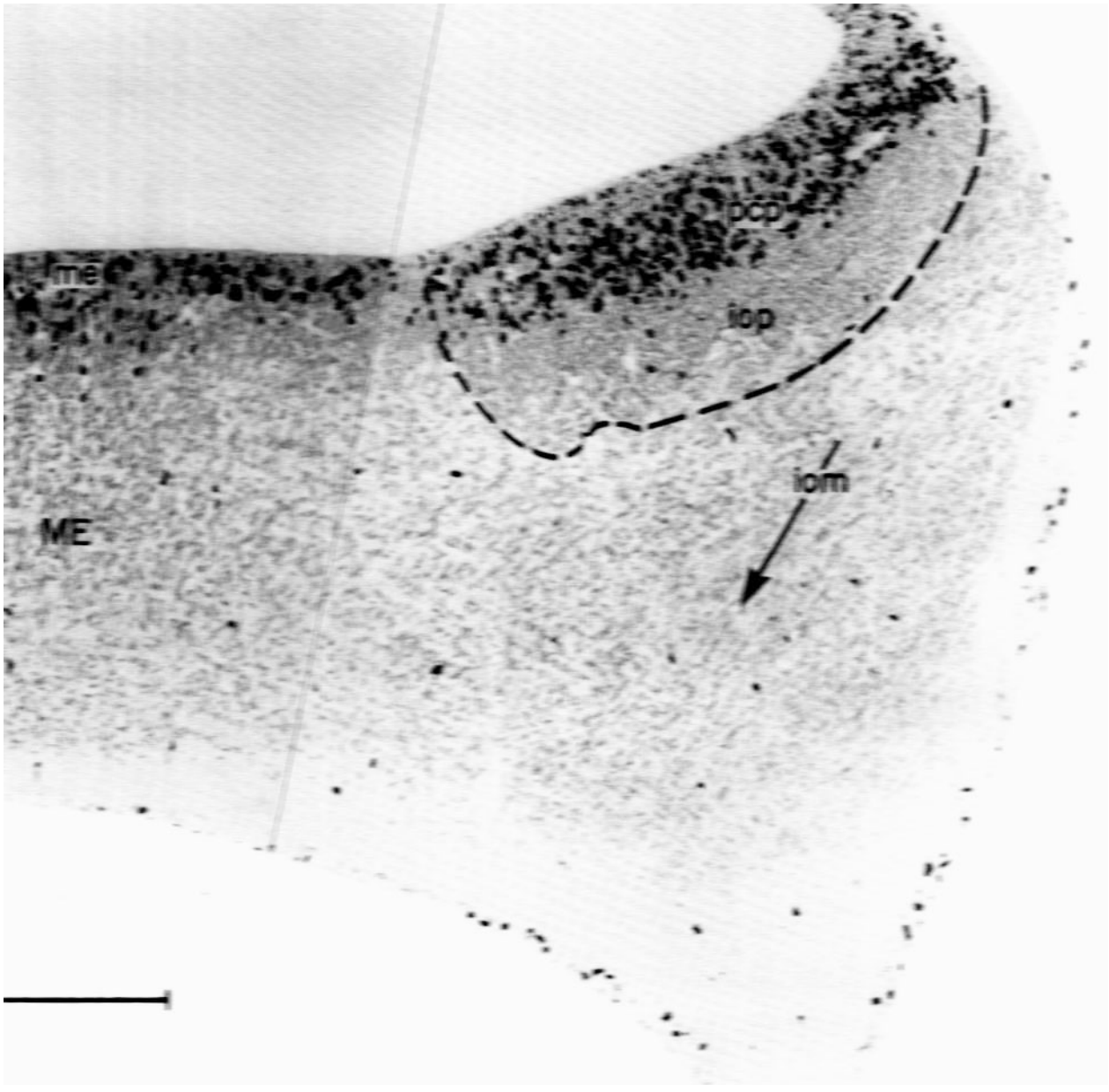


Fig. 3. Sagittal section at higher magnification from a rat labeled on day E15 and killed 2 hours later. It shows the labeled cells of the primary precerebellar neuroepithelium (pcp), the unlabeled round cells of the inferior olivary premigratory zone (iop), and the unlabeled spindle-shaped cells of the inferior olivary intramural migratory stream (iom). Paraffin. Scale: 200 $\mu$m.

regressive cerebellar neuroepithelium (ce). If we are to retain His's (1891) use of the term "rhombic lip," the germinal trigone is the upper rhombic lip (url in Figs. 6B, 7A). The ventral rhombencephalon beneath the lateral recess constitutes the octavoprecerebellar neuroepithelial field. Far laterally, corresponding to the lower rhombic lip (lrl in Figs. 6B, 7A) is the secondary auditory neuroepithelium (aus on the right side in Fig. 6A,B). Extending from this region medially is the rostral secondary precerebellar neuroepithelium (pcsr), which covers a tonguelike structure (inverted with respect to the "rhombic lip"). The rostral secondary precerebellar neuroepithelium is inconspicuous in the most anterior section (Fig. 6A) and is continuous here with the surface plate (sp) of the medulla. More posteriorly (Fig. 6B) the rostral secondary precerebellar neuroepithelium becomes more prominent in terms of labeled cell concentration, and here it forms a tonsillike structure above the medial recess of the anterior fourth ventricle (mr in Fig. 6B). The rostral secondary precerebellar neuroepithelium is associated here with the medial portion of the choroid plexus (cpm in Fig. 7A). Proceeding farther caudally, the vertically oriented matrix of the caudal secondary precerebellar neuroepithelium (pcsc in Fig. 7A) becomes conspicuous. This region separates the anterior and poste-

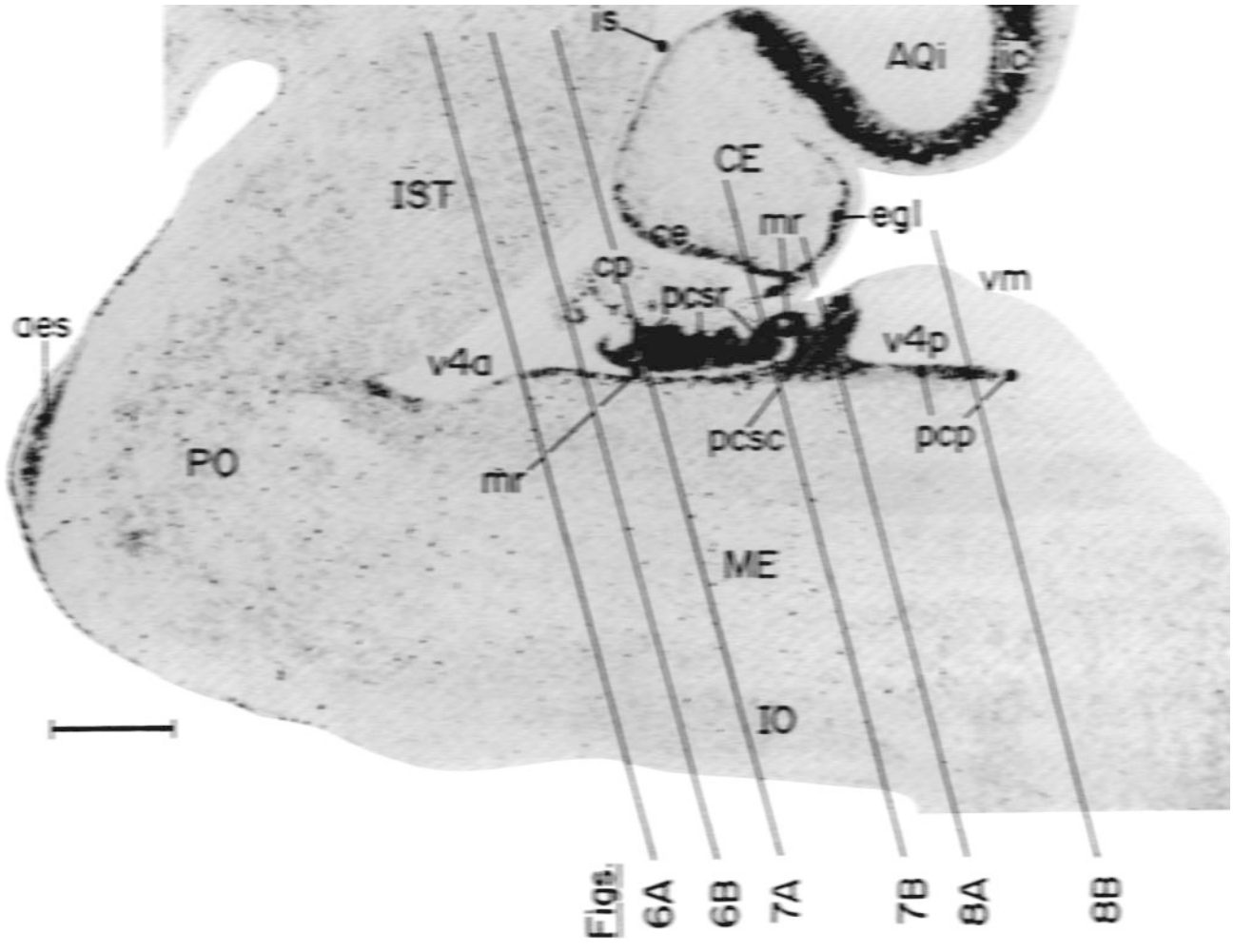


Fig. 4. Parasagittal radiogram from a rat labeled on day E18 and killed 2 hours later. Note the continuing high level of cell proliferation in the rostral (pcsr) and caudal (pscs) secondary precerebellar neuroepithelia. Oblique lines indicate the approximate position of coronal sections shown in the corresponding figures. Paraffin. Scale: 300 $\mu$m.

rior parts of the fourth ventricle (v4a and v4p in Fig. 7A,B). The mitotically active matrix then progressively tapers off (Figs. 7B, 8A,B). In these short-survival radiograms both the rostral and the caudal precerebellar neuroepithelia are flanked by a layer of unlabeled (postmitotic) cells, the anterior extramural migratory stream (aes in Figs. 6B, 7A,B). Rostrally (Fig. 6B), this stream is comma-shaped; caudally (Figs. 7A,B) it forms a thin band over the dorsal surface of the medulla and is distinguished from another band designated as the posterior extramural migratory stream (pes in Figs. 7B, 8A,B).

The components of the secondary precerebellar neuroepithelium are illustrated at higher magnification in a series of sagittal, short-survival thymidine radiograms from a day E19 rat (Fig. 9) representing the last day of precerebellar (pontine gray) neurogenesis. The dorsal, tonsillike portion of the rostral region (pcsr) and the vertical portion of the caudal region (pcsc) are still thick and mitotically active. Medially (Fig. 9A,B), the anterior extramural migratory stream (aes) is interdigitated with the secondary neuroepithelium. More laterally (Fig. 9C) the anterior migratory stream assumes a ventral position with respect to the neuroepithelium.

## DISCUSSION

We propose to restrict the term "rhombencephalon" to the unique dorsal, or surface plate, region of the fourth ventricle rather than apply it to the entire primordium of the hindbrain. The uniqueness of this region begins during neurulation and continues throughout the embryonic and fetal period. At the outset, the neural groove fails to close here and, instead, a nonneural membrane, the medullary velum, covers the rhomboid fluid space of the fourth ventricle. The basal plate neuroepithelium, the metencephalon, is not affected by this anomaly, as the continuity between the primordia of the medulla, pons, and tegmentum is nowhere severed. However, the surface plate neuroepithelium is interrupted between the lower medulla caudally and the isthmus region of the midbrain rostrally. Two bridgeheads form here behind and in front of the medullary velum, the former representing the primordium of the octavoprecere-

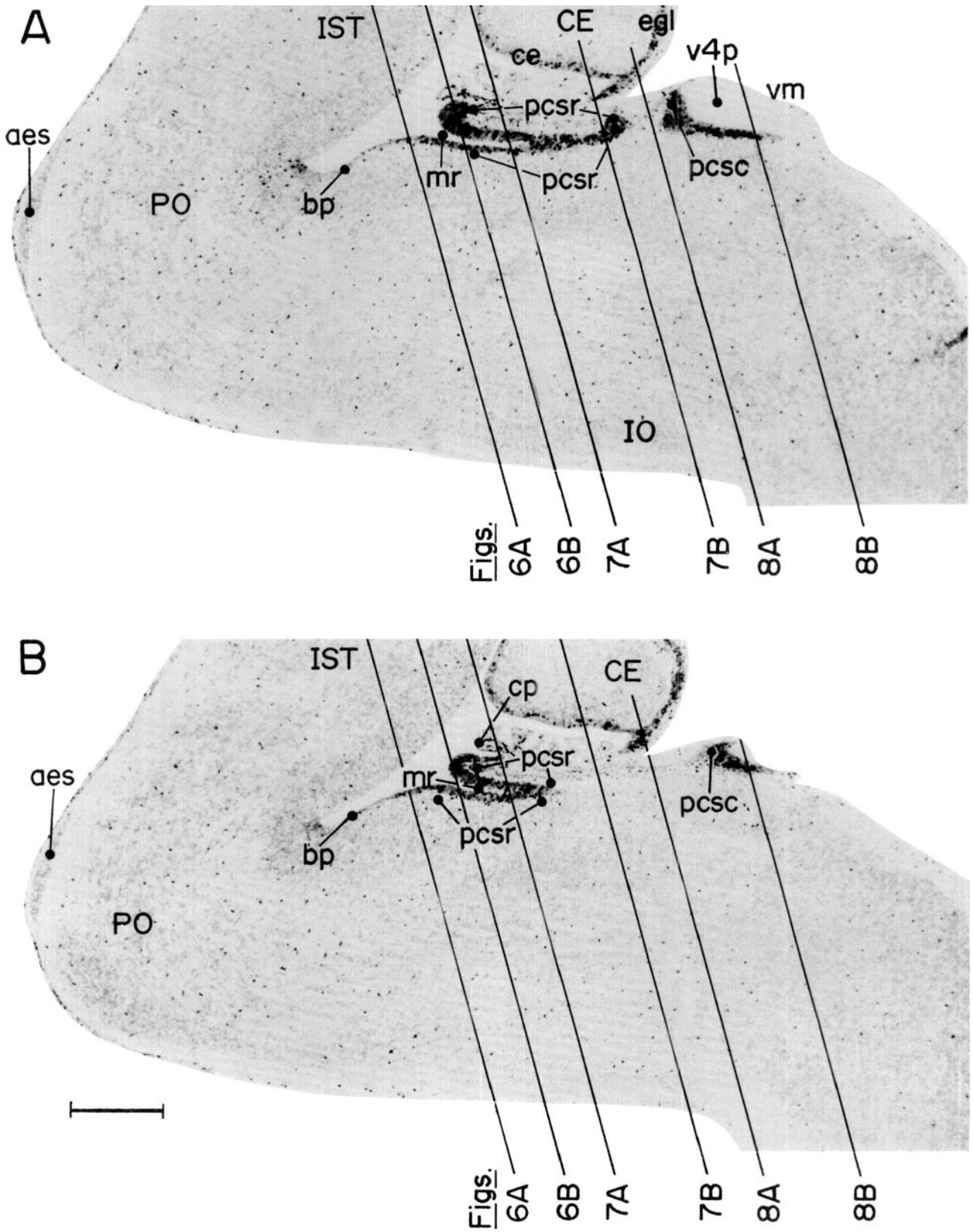


Fig. 5. **A:** Parasagittal section from the same rat shown in Figure 4 but more laterally. **B:** Parasagittal section still more laterally. Paraffin. Scale: 300 $\mu$m.

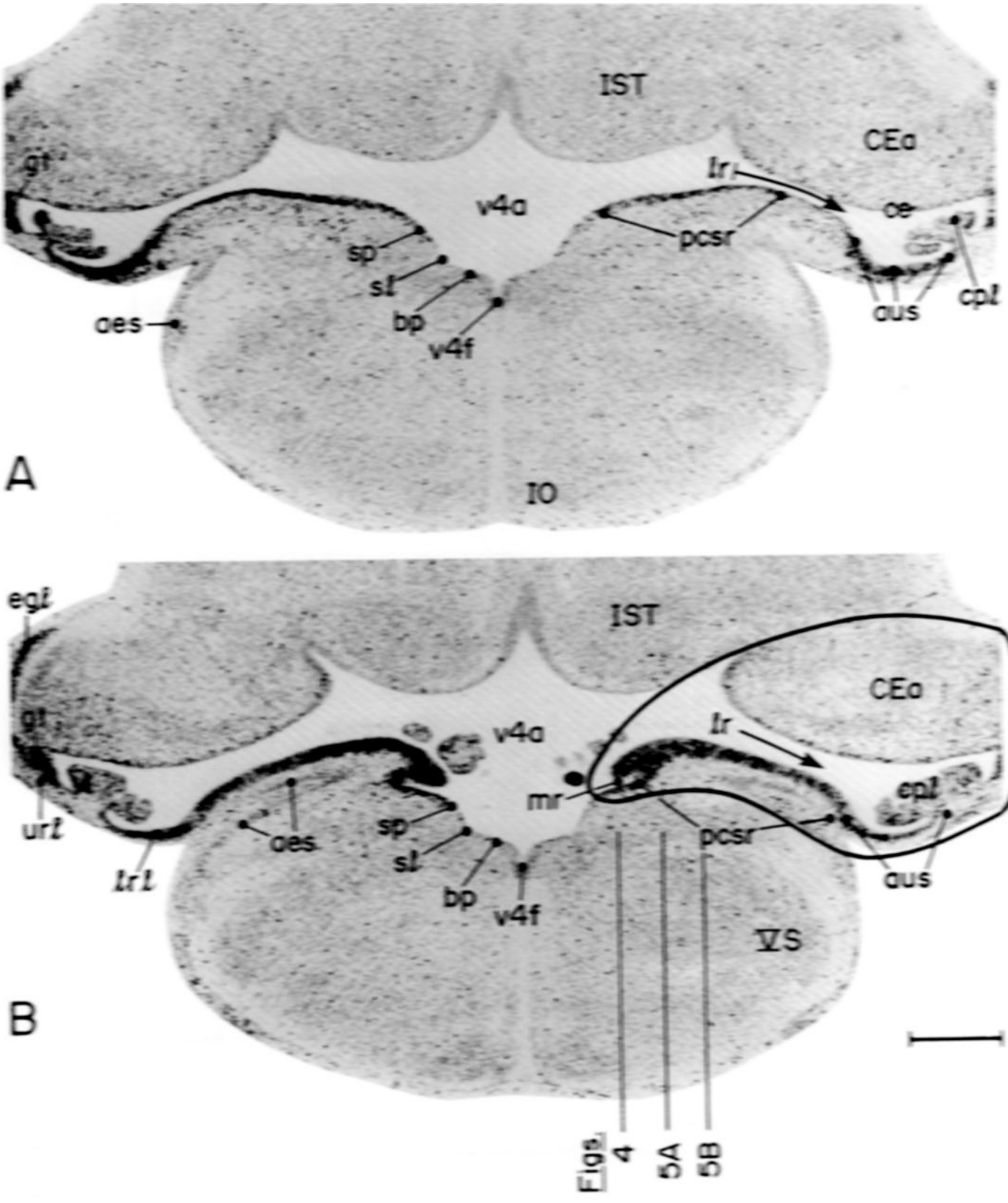


Fig. 6. Coronal sections from a rat labeled on day E18 and killed 2 hours later, from rostral (A) to caudal (B). In B, the outline encloses the region of the secondary neuroepithelia of the rhombencephalon. Horizontal lines indicate the approximate position of sagittal sections in the corresponding figures. Paraffin. Scale: 300 $\mu$m.

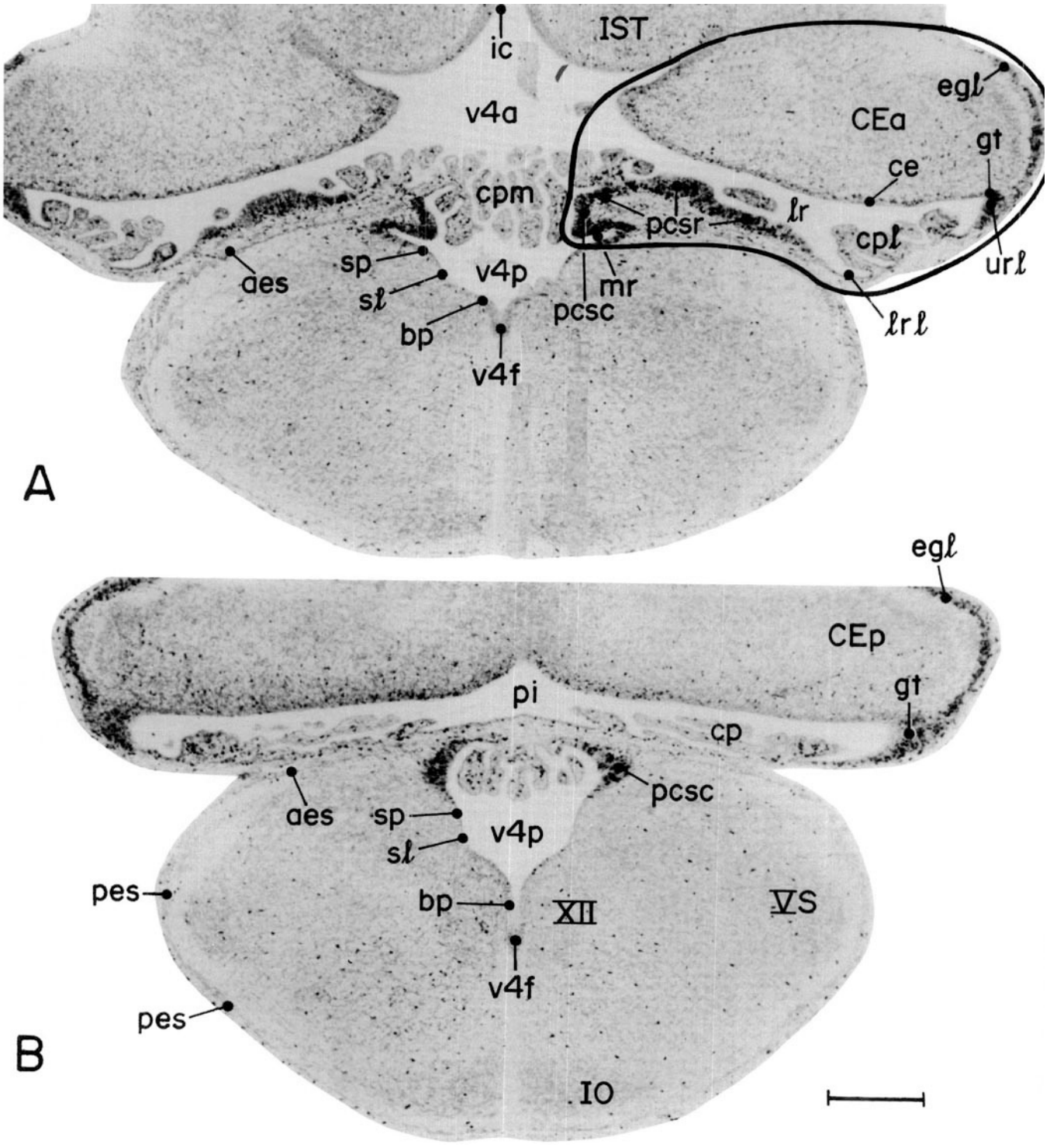


Fig. 7. Continuation of coronal series shown in Figure 6. Scale: 300 $\mu$m.

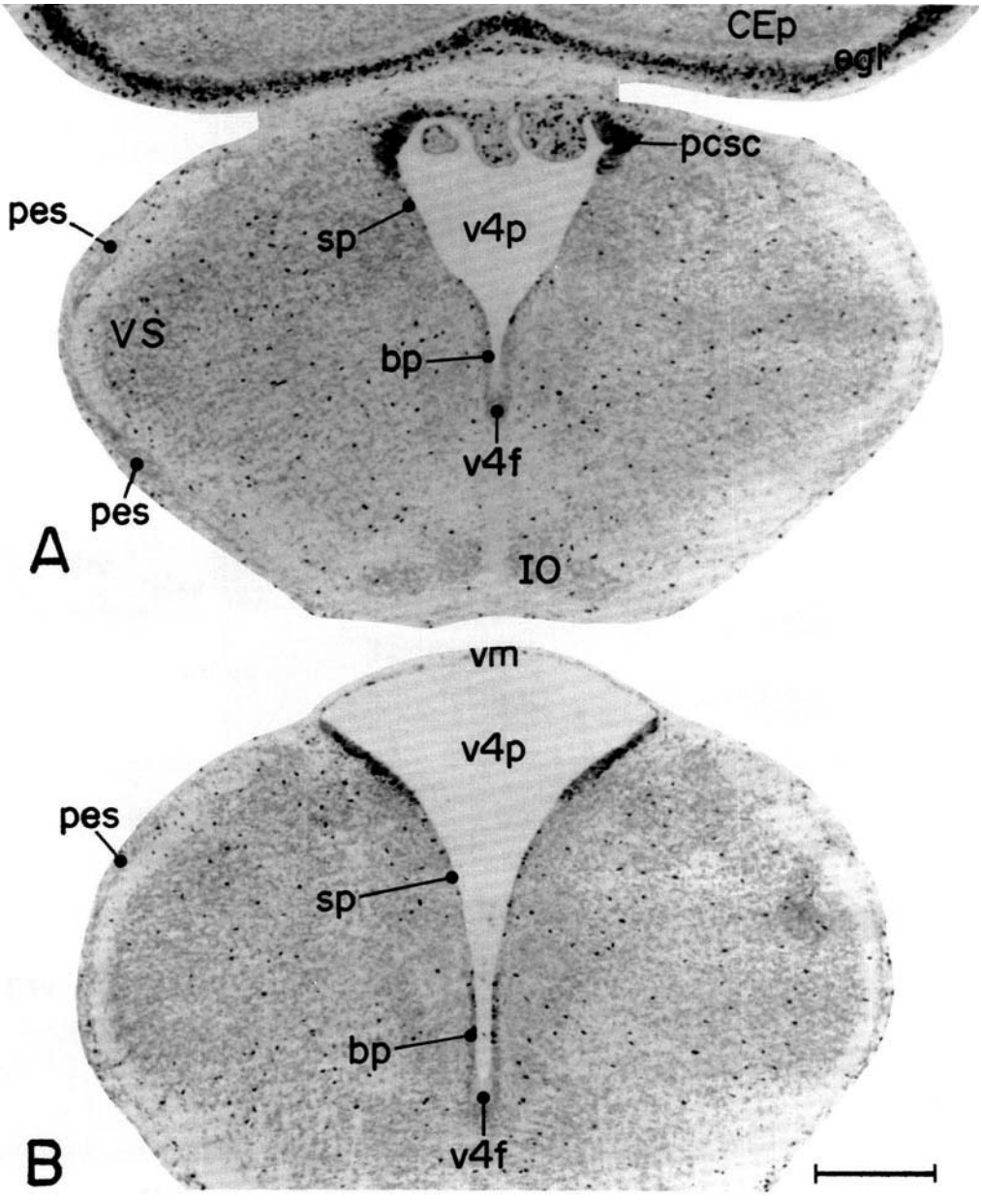


Fig. 8. Continuation of coronal series shown in Figures 5 and 6. B is most caudal section. Scale: 300 μm.

bellar system, the latter that of the cerebellum. Then two morphogenetic events occur that affect the development of the rhombencephalon. First, as a result of the ongoing flexure of the pons and the progressive shrinkage of the fourth ventricle, the distance decreases between the cerebellar primordium (which becomes displaced from rostral to dorsal) and the precerebellar neuroepithelium (whic assumes a ventral position). Second, the tela choroidea d rived from the rostral part of the medullary velum invag nates into the fourth ventricle. It is the formative choroi plexus of the fourth ventricle with which both the expanc ing cerebellar and precerebellar neuroepithelia become intimately associated.

We have described elsewhere (Altman and Bayer, '85) the crescent-shaped primary cerebellar neuroepithelium that grows apposed to the tela choroidea dorsolaterally. Also the secondary cerebellar matrix, the external germinal layer, is directly linked to the tela choroidea in that both originate in the germinal trigone (Altman, '82). In the precerebellar germinal system described here it is the secondary neuroepithelium that grows rostrally beneath the choroid plexus. We presume that this nonneuronal substance provides

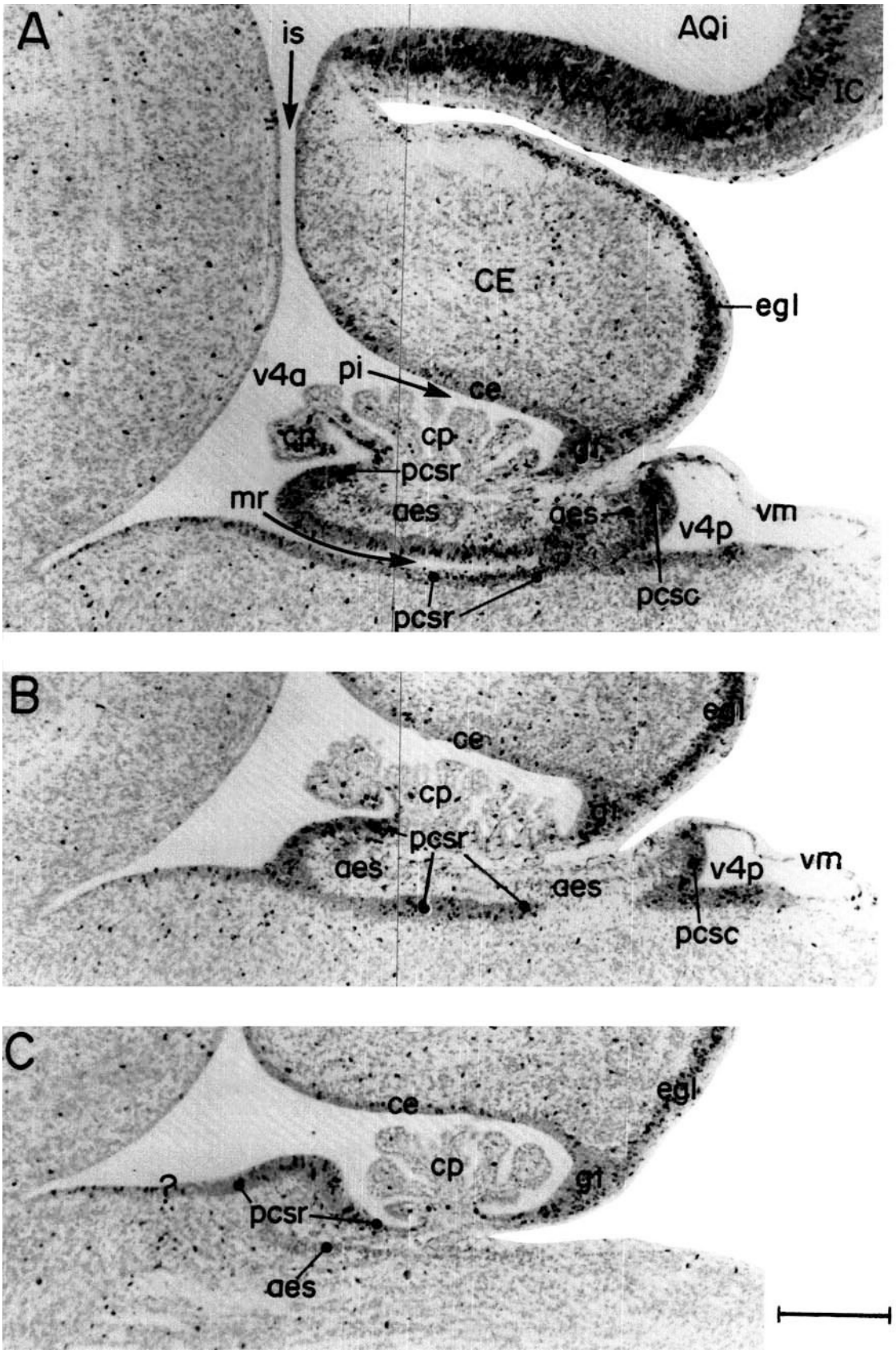


Fig. 9. Parasagittal sections from medial (A) to lateral (B, C) from a rat labeled on day E19 and killed 2 hours later. Scale: 200 $\mu$m.

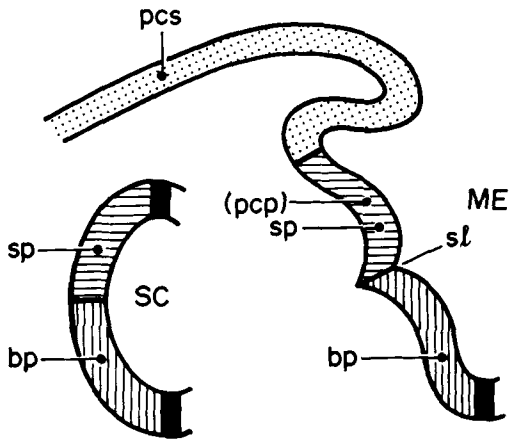


Fig. 10. The neuroepithelial organization of the spinal cord (SC) and the medulla (ME). The precerebellar secondary neuroepithelium is a lateral derivative of the surface plate that fails to fuse in the medulla.

merely an attachment site or supporting substrate for the proliferating cells that soon leave this dorsal site to settle ventrally and anteroventrally. But it may be of some functional significance that both the cerebellar external germinal layer and the precerebellar secondary neuroepithelium have exposed, subpial surfaces. Another similarity between these two rhombencephalic systems is that there is extensive extramural migration in both. This is seen in the dispersion of the proliferative cells of the external germinal layer from the germinal trigone dorsally over the surface of the cerebellum, and, in the case of the precerebellar system, in the various migratory streams that young neurons follow to ventral and anteroventral targets.

Although the secondary precerebellar neuroepithelium is clearly a derivative of the rhombencephalic surface plate, it differs from the latter both temporally and spatially. For several days after mitotic activity has fallen to a low level, or stopped altogether, in the surface plate, it continues briskly in the secondary precerebellar neuroepithelium (Figs. 6–8). The spatial difference is schematically illustrated in Figure 10. The surface plate neuroepithelium occupies a dorsomedial position in the spinal cord (SC). In the medulla (ME), where the neural groove fails to fuse, the surface plate remains in a dorsolateral position, being demarcated from the basal plate by the sulcus limitans (sl). However, the secondary precerebellar neuroepithelium (pcs) is an actively evaginated region, forming the lateral recess of the fourth ventricle.

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