

# Development of the Diencephalon in the Rat

## V. THYMIDINE-RADIOGRAPHIC OBSERVATIONS ON INTERNUCLEAR AND INTRANUCLEAR GRADIENTS IN THE THALAMUS

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**ABSTRACT** Groups of pregnant rats were injected with two successive daily doses of  $^3\text{H}$ -thymidine from gestational days 13 and 14 (E13+14) until the day before birth (E21+22). Internuclear and intranuclear cytogenetic gradients were examined in radiograms of the thalamus sectioned in the coronal, sagittal and horizontal planes. There was a precise and segregated lateral-to-medial gradient between and within the habenular nuclei. In the ventral thalamus the reticular nucleus had a lateral-to-medial gradient, the subthalamic nucleus a laterodorsal-to-medioventral gradient. There was a caudal-to-rostral gradient between the medial geniculate and dorsal lateral geniculate nuclei, and between the pars posterior and pars anterior of the lateral nucleus. A clear intranuclear gradient could not be detected in the sensory relay nuclei with the exception of the medial geniculate nucleus. A lateral-to-medial internuclear gradient was seen between the relay nuclei and the intralaminar nuclei, and between the latter and some of the midline nuclei.

On the basis of a consideration of the time of origin and time span of production of neurons of various thalamic nuclei, and taking into account some of the recognizable internuclear and intranuclear gradients, the thalamus was divided into five principal cytogenetic components: the epithalamus, the ventral thalamus, the dorsal thalamus, the medial thalamus, and the posterior thalamus. The epithalamic nuclei form over a protracted period resembling the nuclei of the hypothalamus. The nuclei of the ventral thalamus are generated early and over a relatively long period. The dorsal thalamus consists of the relay nuclei and the intralaminar nuclei; they form rapidly and ahead of the medial thalamus. The medial thalamus was subdivided into the earlier-forming antero-medial nuclei and the latest-forming midline nuclei. The posterior thalamus was not examined in detail.

In the preceding paper of this series (Altman and Bayer, '79a) we determined quantitatively the time of origin of neurons in the nuclei of the epithalamus, thalamus, and ventral thalamus of the albino rat. The data were also used to assess cytogenetic gradients across the thalamus and for the construction of isochronic maps. In this paper we are evaluating qualitatively additional autoradiographic materials in an attempt to obtain further information about intranuclear as well as internuclear gradients in the region of the thalamus. Our purpose is two-fold: (1) to use the intra- and internuclear gradients as "directional arrows" that might reveal the gen-

eration sites and dispersal routes of neurons of various structures and groups of structures, and (2) to use this information, together with the quantitative data about the birth dates of neurons, to identify related cytogenetic systems with presumed shared sources of origin. In the succeeding paper of this series (Altman and Bayer, '79b) we shall re-examine the embryology of the thalamus in the light of the datings accomplished with thymidine-radiography. In particular, we shall attempt to identify formative structures before they acquire some of their mature characteristics and will try to locate in the mosaic pattern of the diencephalic neuroepithelium the ventricular ori-

gins of different thalamic nuclei and nuclear systems.

#### MATERIALS AND METHODS

In addition to the coronally sectioned autoradiograms described in the previous paper (Altman and Bayer, '79a), we also examined a large series of autoradiograms of the forebrain sectioned in the horizontal and sagittal planes (table 1). The animals used were male and female offspring of the dams injected on days E13+14, E14+15 . . . E21+22, as previously described. Survival time, and histological and autoradiographic processing details were unchanged.

#### RESULTS

##### 1. Internuclear gradients in horizontal sections

Figure 1 shows the labelling pattern seen in a rat injected on days E16+17, in a horizontal section at the dorsal level of the epithalamus. Several isochronic zones may be seen which, with one exception, are homogeneous in the rostral-caudal direction. Laterally situated is the unlabelled reticular nucleus, medially the fully labelled medial habenular nucleus. The latter is flanked by the unlabelled lateral habenular nucleus which is followed by a labelled zone of cells that include the anterodorsal, mediodorsal and central lateral nuclei and, curving medially, the pretectal area. But then follows an extensive zone which is usual-

ly subdivided into the lateral nucleus, pars anterior, and the lateral nucleus, pars posterior (König and Klippel, '63; Pellegrino and Cushman, '67). The anterior portion of the lateral nucleus is labelled, its posterior portion is not. This is in conformity with the quantitative data presented in figures 10 and 12 in the previous paper (Altman and Bayer, '79a). The two either represent two separate systems or there is a pronounced caudal-to-rostral gradient in the cytogenesis of the lateral nuclear complex.

More ventrally, as seen in an autoradiogram from a rat injected on days E15+16 (fig. 2), there is a caudal-to-rostral gradient laterally. The neurons of the medial geniculate body are mostly unlabelled, except anteromedially, whereas a large proportion of the neurons of the dorsal nucleus of the lateral geniculate body are labelled. This agrees with the quantitative data presented in figure 12 in the preceding paper (Altman and Bayer, '79a). Many of the reticular nucleus neurons are labelled along its entire rostrocaudal extent.

Returning to the E16+17 injection group, and proceeding ventrally (fig. 3), the unlabelled reticular nucleus is flanked medially by another, essentially unlabelled zone, composed of the ventrolateral complex anteriorly and the ventrobasal complex posteriorly. Perhaps these structures have occasional labelled cells medially at the boundary of the nucleus centralis lateralis and medial lemniscus. The centralis lateralis is composed of both unla-

#### Abbreviations

ac, anterior commissure	me, medial
AD, anterodorsal nucleus	MG, medial geniculate nucleus
AM, anteromedial nucleus	MH, medial habenular nucleus
AV, anteroventral nucleus	ml, medial lemniscus
BS, bed nucleus of stria terminalis	NP, nucleus of posterior commissure
ca, caudal	ot, optic tract
ch, choroid plexus	PF, parafascicular nucleus
CL, central lateral nucleus	PO, posterior nucleus (thalamus)
cp, cerebral peduncle	PR, pretectal area
CP, caudate-putamen	PT, paratenial nucleus
do, dorsal	PV, paraventricular nucleus
fi, fimbria	RE, reuniens nucleus
fx, fornix	RH, rhomboid nucleus
GP, globus pallidus	ro, rostral
hp, habenulopenduncular tract	RT, reticular nucleus
ic, internal capsule	sc, subcommissural organ
la, lateral	sm, stria medullaris
LA, lateral nucleus, pars anterior	st, stria terminalis
LGd, lateral geniculate nucleus, pars dorsalis	ST, subthalamic nucleus
LGv, lateral geniculate nucleus, pars ventralis	VB, ventrobasal complex
LH, lateral habenular nucleus	VC, ventral central gray (midbrain)
LP, lateral nucleus, pars posterior	ve, ventral
lv, lateral ventricle	VE, ventrolateral complex
MB, mammillary body	ZI, zona incerta
MD, mediodorsal nucleus	III, third ventricle

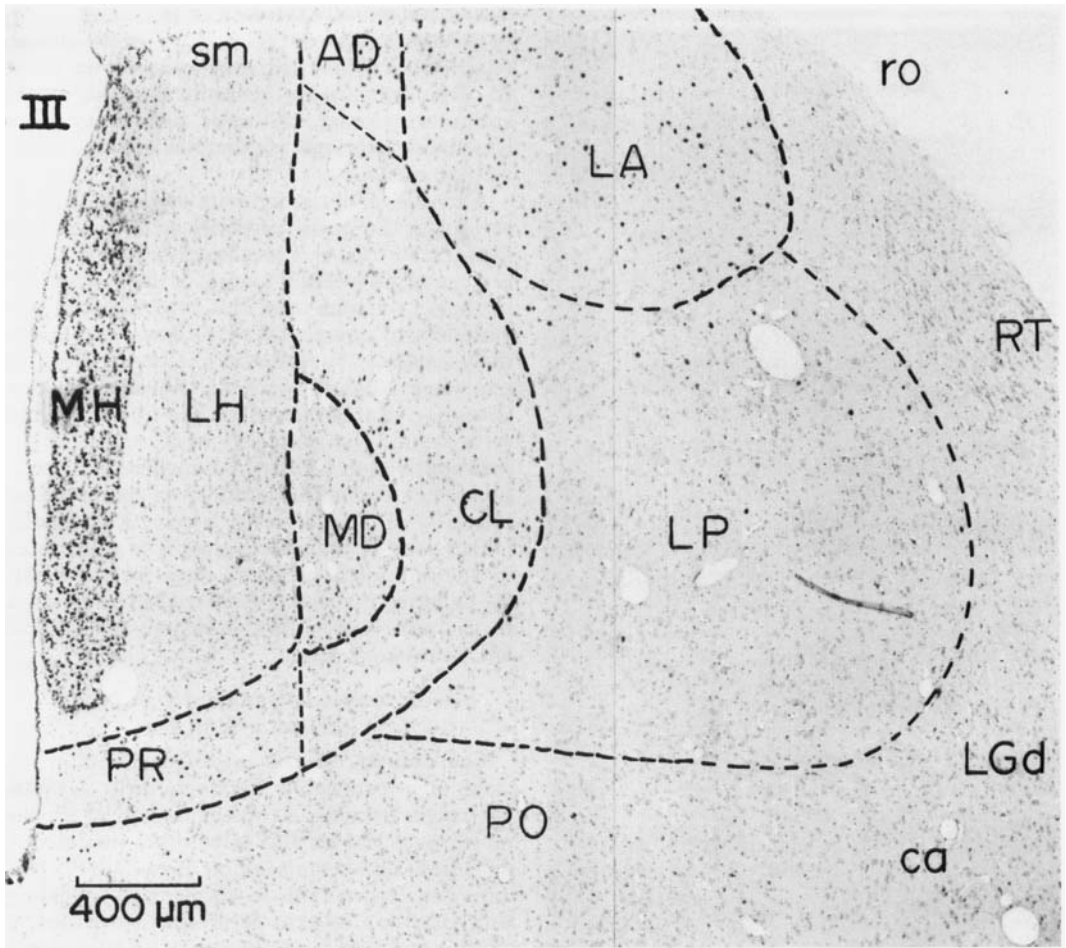


Fig. 1 Dorsal horizontal thymidine-radiogram from a rat injected on days E16+17. There is no gradient in the anteroposterior direction in MH but a pronounced discontinuity in labelling between LA and LP.

TABLE 1

*Number of animals examined. Age, 60 days*

Age at injection	Plane of sectioning			Subtotal
	Coronal	Horizontal	Sagittal	
E13+14	8	8	13	29
E14+15	6	6	6	18
E15+16	6	4	8	18
E16+17	10	9	10	29
E17+18	6	5	4	15
E18+19	6	4	6	16
E19+20	6	6	5	17
E20+21	7	9	8	24
E21+22	6	5	10	21
Subtotal	61	56	70	
Total				187

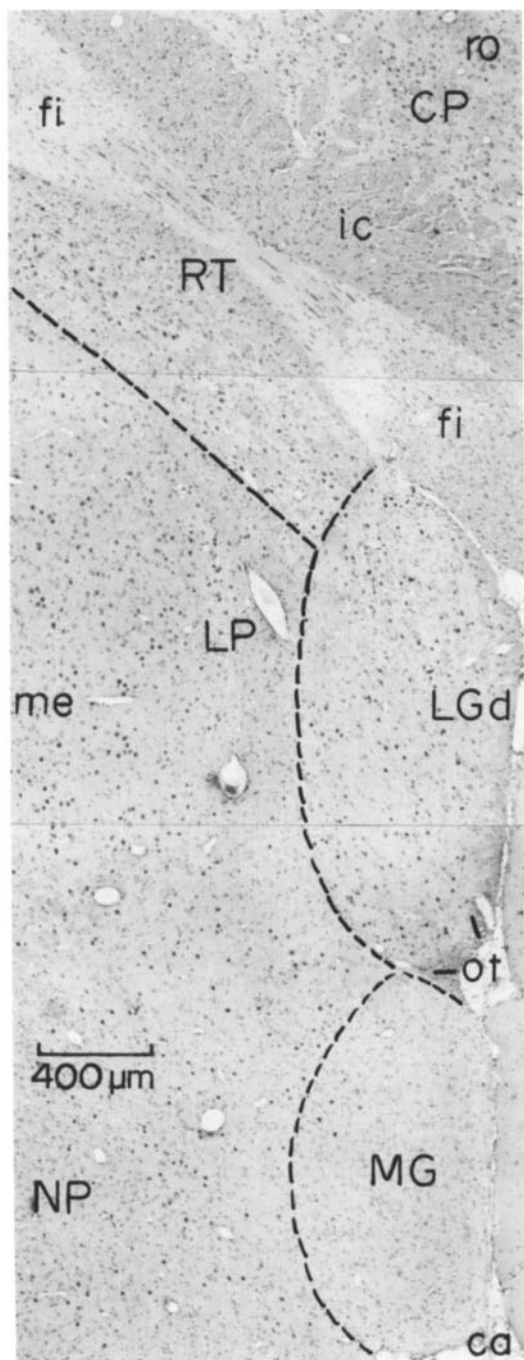


Fig. 2 Rat injected on days E15+16. Labelling pattern in a horizontal section situated ventral to that shown in figure 1. Note labelling difference between MG and LGd.

belled and heavily labelled cells. More medially there is an extensive field in which virtually all cells are labelled, either lightly or heavily. The components include the anteroventral, anterodorsal, thalamic paraventricular, rhomboid, reuniens, mediodorsal, and parafascicular nuclei.

At the level of the anterior commissure, representing the most ventrally situated section illustrated (fig. 4), there is an extensive lateral zone of unlabelled nuclei. It consists of the reticular nucleus, and the ventrolateral and ventrobasal complexes. This zone is flanked more medially by the centralis lateralis which has some labelled cells. At the anterior continuation of this belt is the bed nucleus of the stria terminalis (probably of telecephalic derivation) which is full of labelled cells. The extensive core of midline nuclei is composed essentially of labelled cells. By day E17 this labelled zone is contracting, as it is illustrated in the animal injected on days E17+18 (fig. 5). Labelled neurons are restricted by this age to the paraventricular, paratenial, rhomboid and reuniens nuclei.

## 2. Intranuclear gradients in the epithalamus

The neurons of the lateral habenular nucleus are generated between days E13-16, with peak formation time on days E14-15; the neurons of the medial habenular nucleus on days E15-19, with a peak on days E16-17 (Altman and Bayer, '78). In addition to this clear internuclear lateral-to-medial gradient, a similar gradient is easily identified in horizontal sections within the lateral habenular nucleus (fig. 6). While in animals injected on days E14+15 the labelled cells tend to be scattered throughout the nucleus (fig. 6A) in animals injected on days E16+17, the labelled cells (those forming on day E16) tend to be concentrated in the medial boundary of the nucleus (fig. 6B). No gradient could be detected in the ventrodorsal direction, or in the caudorostral plane (fig. 6).

An even more rigid lateral-to-medial intranuclear gradient exists in the medial habenular nucleus, as illustrated in coronal sections in figures 7 and 8. The lateral disposition of the earliest arising neurons (those that form on day E15) is suggested by their intense labelling in the animal tagged on days E14+15 (fig. 8A) and their lack of labelling in the E16+17 animals (fig. 8B). Figures 7 and 8 illustrate the medial shift of the cells that can

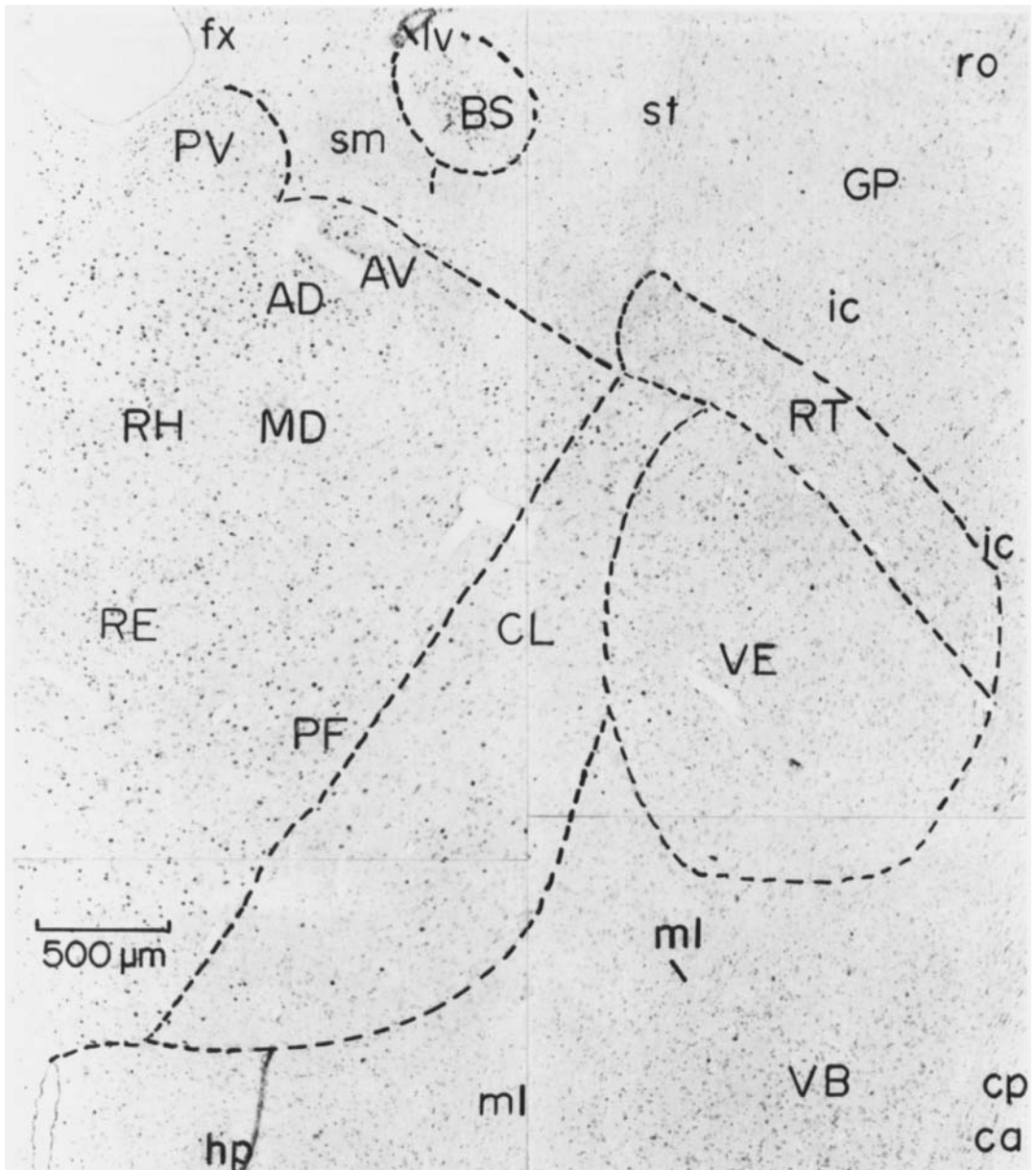


Fig. 3 Rat injected on days E16+17. Mid-horizontal section through the thalamus. Note limited labelling in VE and VB; more labelled cells in CL; and the labelling of most cells in the midline nuclei.

be labelled with progressive delay of injections. In addition to this gradient a slight caudal-to-rostral gradient is visible; but, as shown in horizontal sections (fig. 9), there is no gradient in the caudal-to-rostral plane.

These observations indicate that the neu-

rons of the epithalamus are generated concurrently along the entire length of the dorsal aspect of the third ventricle, and that the early-forming neurons are displaced laterally by the later-forming neurons with minimal spatial disarrangements taking place during the

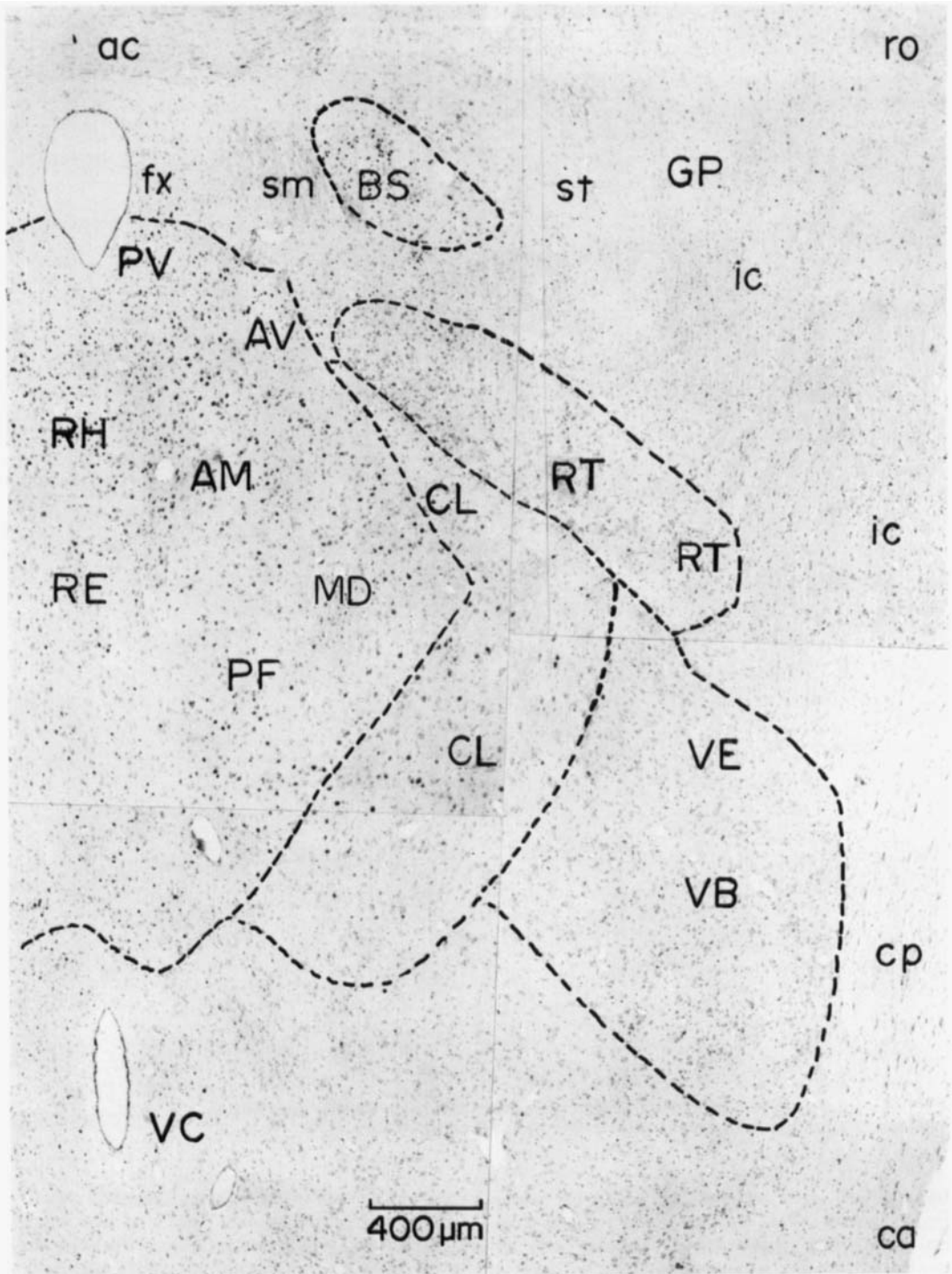


Fig. 4 Rat injected on days E16+17. Labelling pattern in a horizontal section at the ventral level of the anterior commissure.

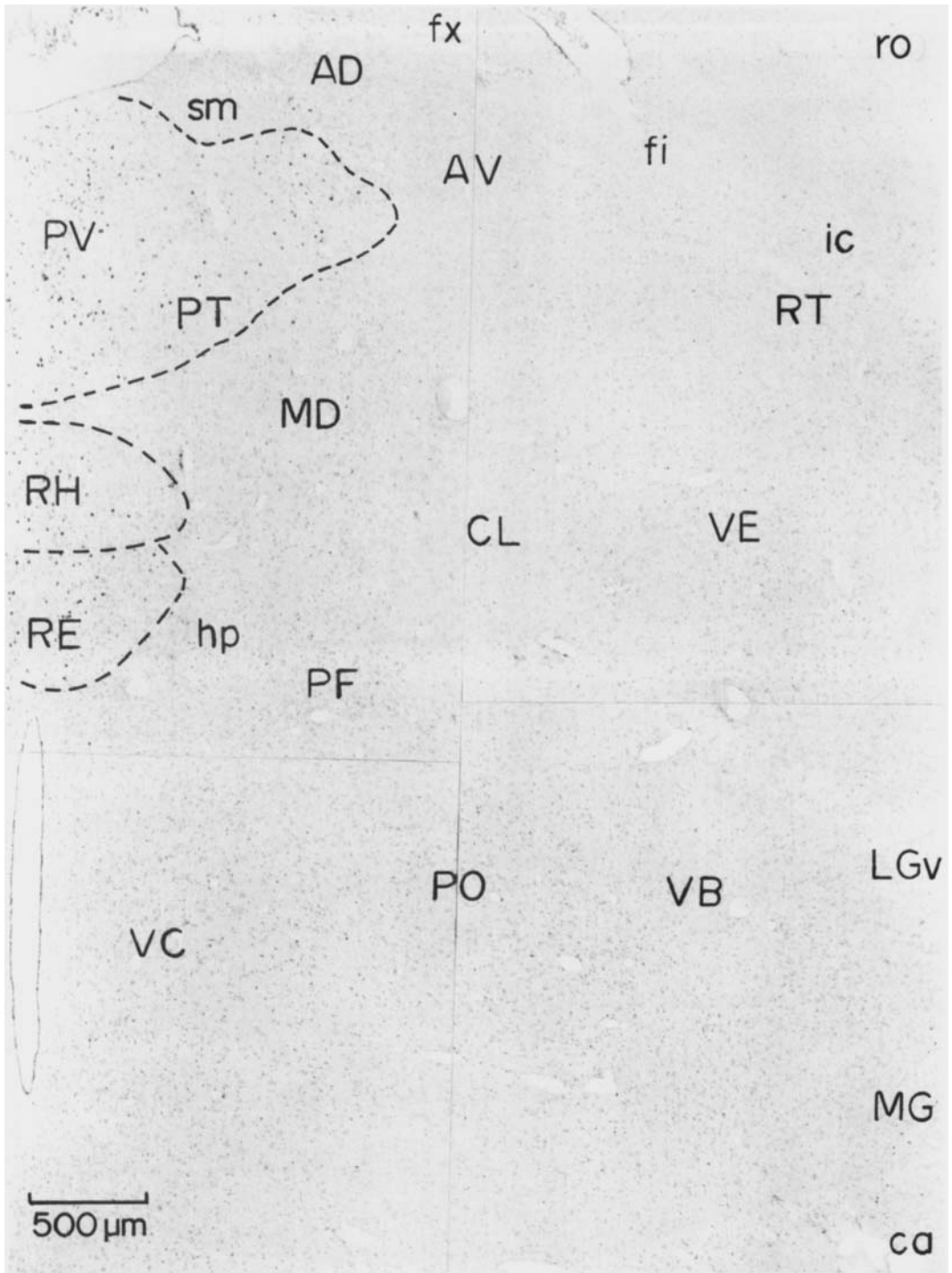


Fig. 5 Rat injected on days E17+18. Mid-horizontal section through the thalamus. Labelled cells restricted to PV, PT, RH and RE.



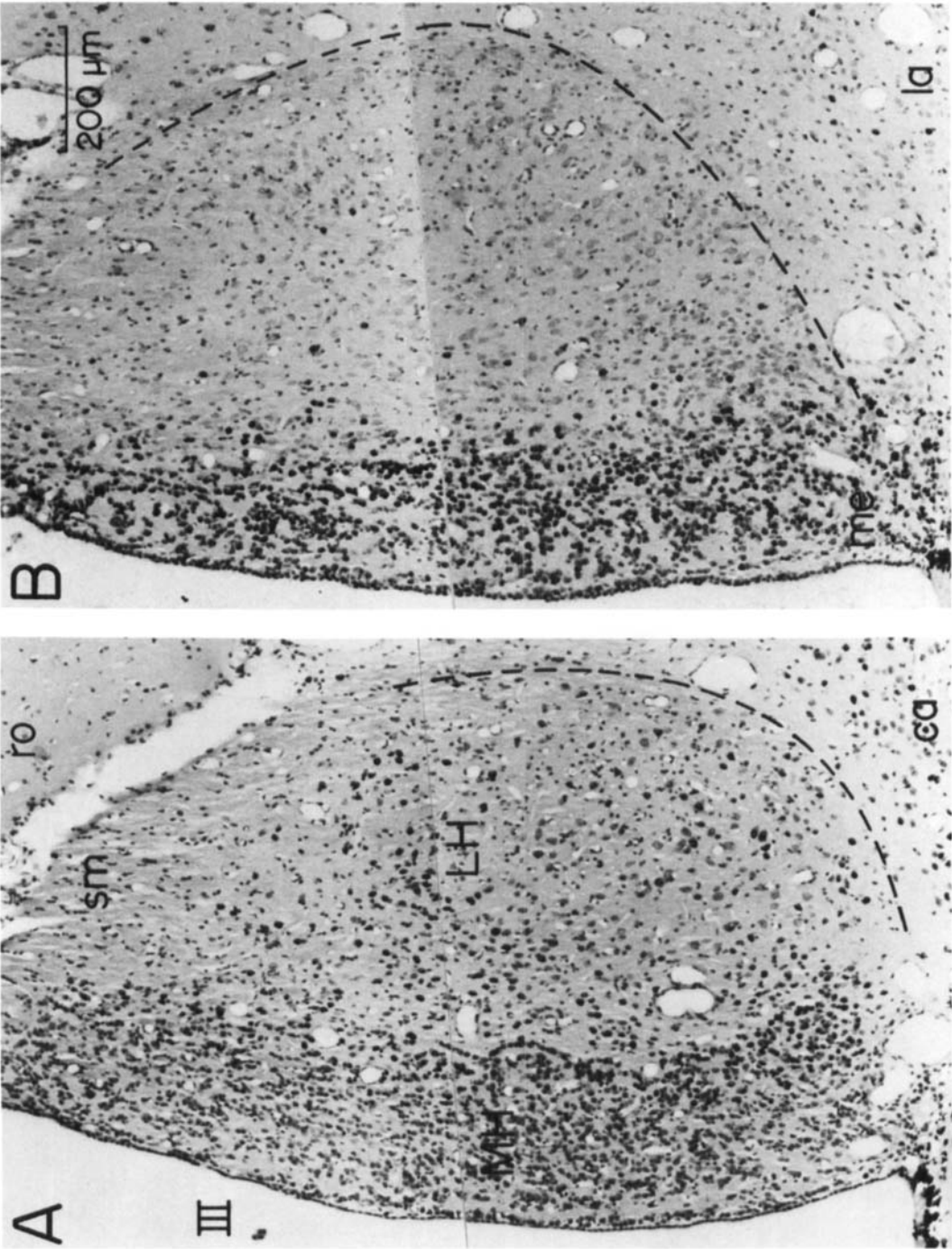


Fig. 6 Lateral-to-medial intranuclear gradient in LH. A, E14 + 15; B, E16 + 17. Horizontal sections.



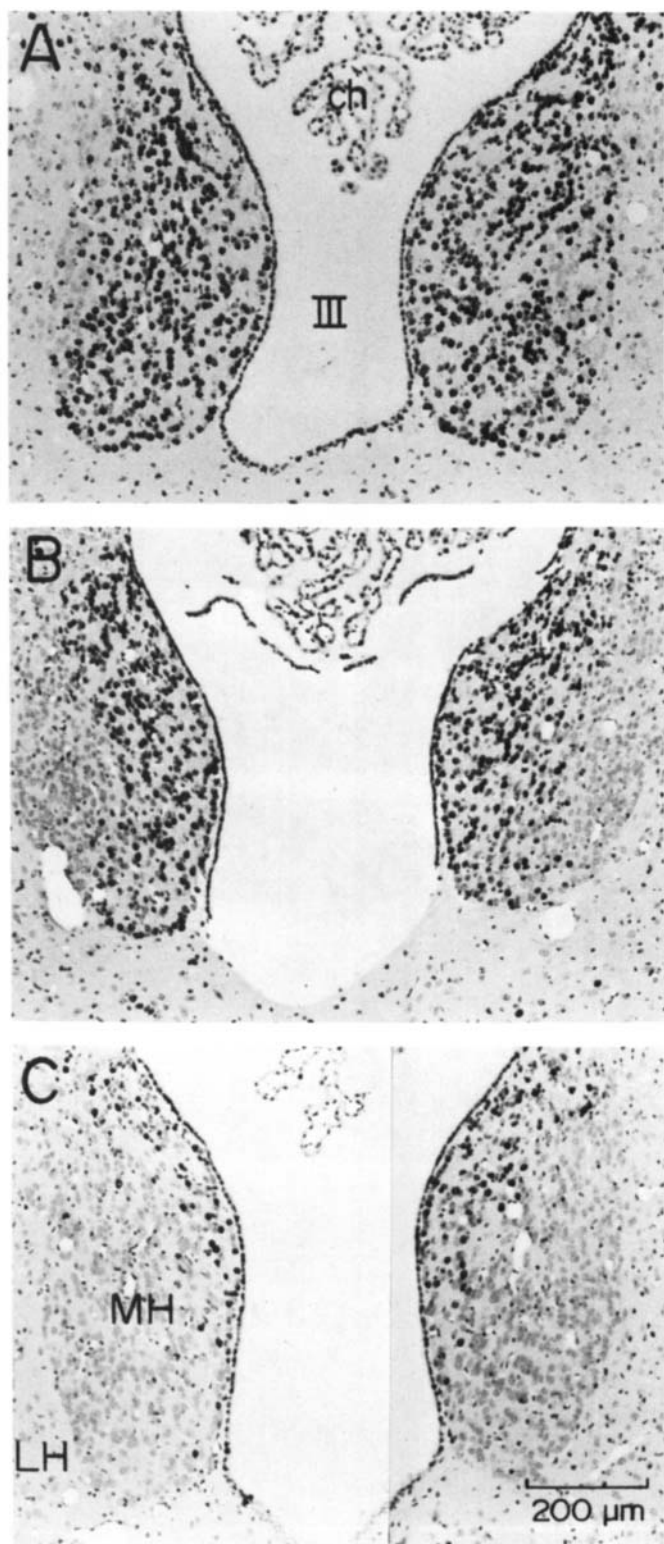


Fig. 7 Lateral-to-medial intranuclear gradient in MH. A, E16+17; B, E17+18; C, E18+19. Coronal sections.

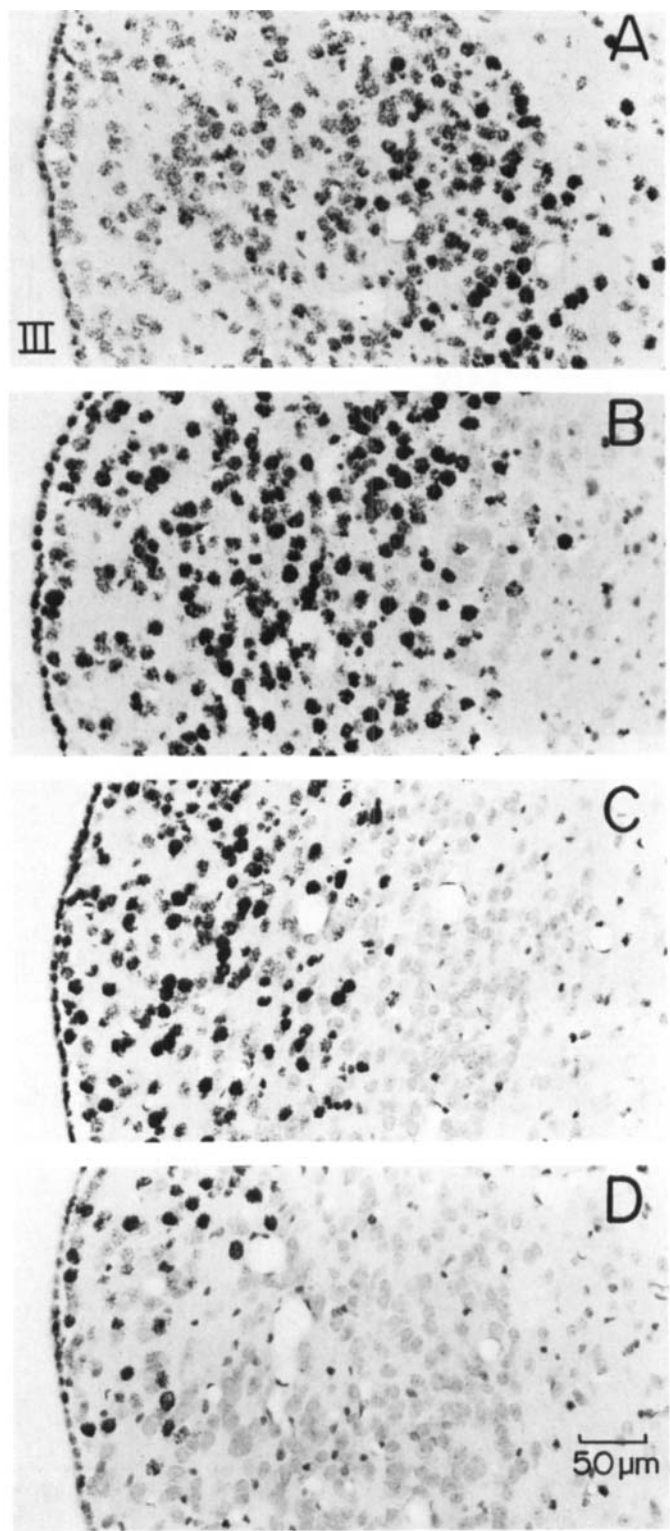


Fig. 8 Lateral-to-medial gradient in MH. A, E14+15; B, E16+17; C, E17+18; D, E18+19. Coronal sections. Note label dilution in all but lateral aspect of MH in A. In C and D only glial cells are labelled laterally. Coronal sections.

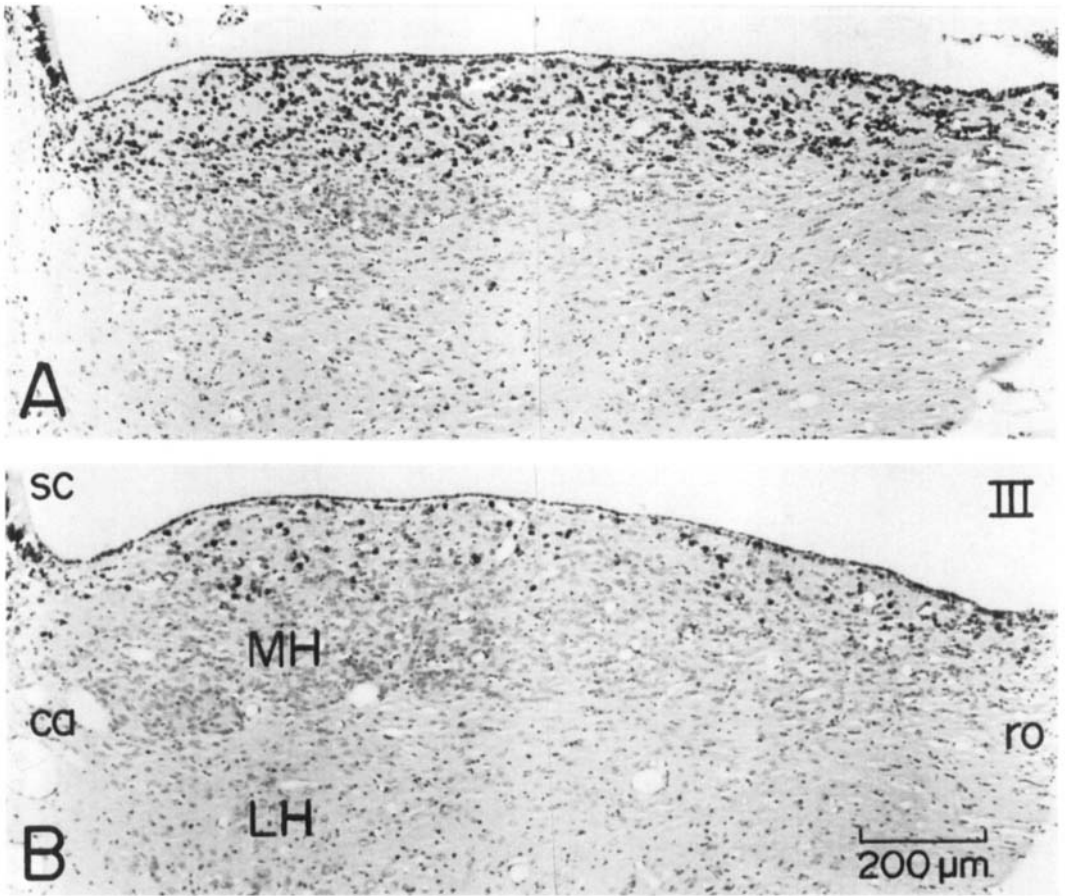


Fig. 9 Absence of a cytogenetic gradient in MH in the anteroposterior plane. A, E17+18; B, E18+19. Horizontal sections.

maturation of the lateral and medial habenular nuclei.

### 3. Intranuclear gradients in the ventral thalamus

The first arising component of this region is the *zona incerta*. Because its boundaries are so undefined, the presence or absence of a cytogenetic gradient could not be determined (fig. 10). However, there was a clear laterodorsal-to-medioventral gradient in the subthalamic nucleus (figs. 10-12). If cell disposition follows here, as in the epithalamus, an "outside-in" pattern (Angevine, '70), then the neurons of the subthalamic nucleus must be generated in the ventrocaudal aspect of the diencephalic neuroepithelium and move laterodorsally over the descending fibers of the cerebral peduncle.

For reasons justified in the DISCUSSION section, the laterally situated reticular nucleus is included among the components of the ventral thalamus. A clear intranuclear cytogenetic gradient was not discernible within the shell formed by the reticular nucleus but there was evidence of an imprecise lateral-to-medial gradient (figs. 13, 14) combined with a ventral-to-dorsal gradient. The latter could be identified in regularly spaced horizontal sections (fig. 14). In general, reticular cells situated adjacent to or embedded in the internal capsule tend to form earlier than those situated in the neighborhood of neurons of the dorsal thalamic nuclei.

An imprecise lateral-to-medial gradient was noted in the ventral nucleus of the lateral geniculate body (fig. 15). This imprecision was

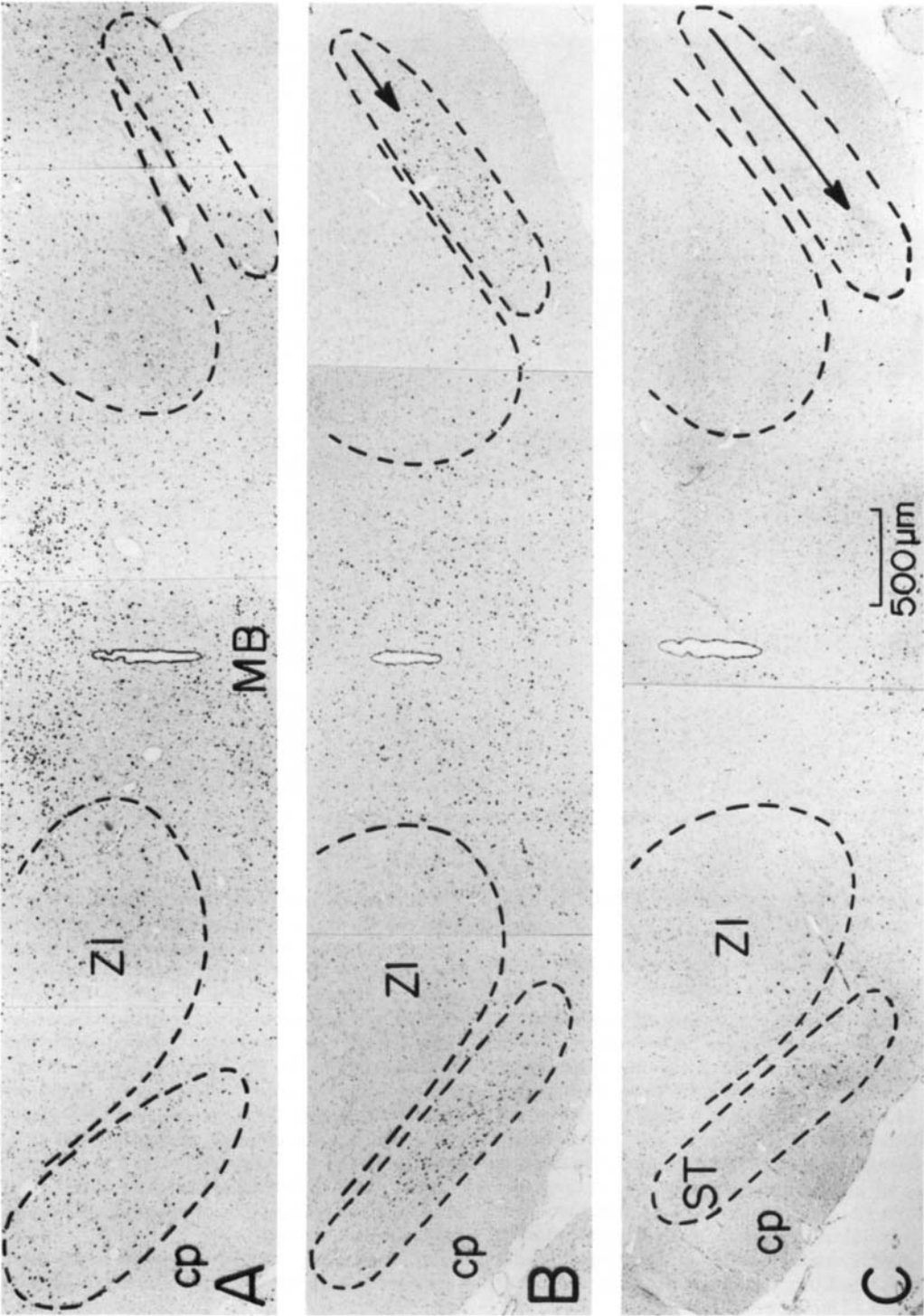


Fig. 10 Ventral thalamus in coronal sections. A, E14 + 15; B, E15 + 16; C, E16 + 17. Note the cytochrome gradient (arrows) in ST.

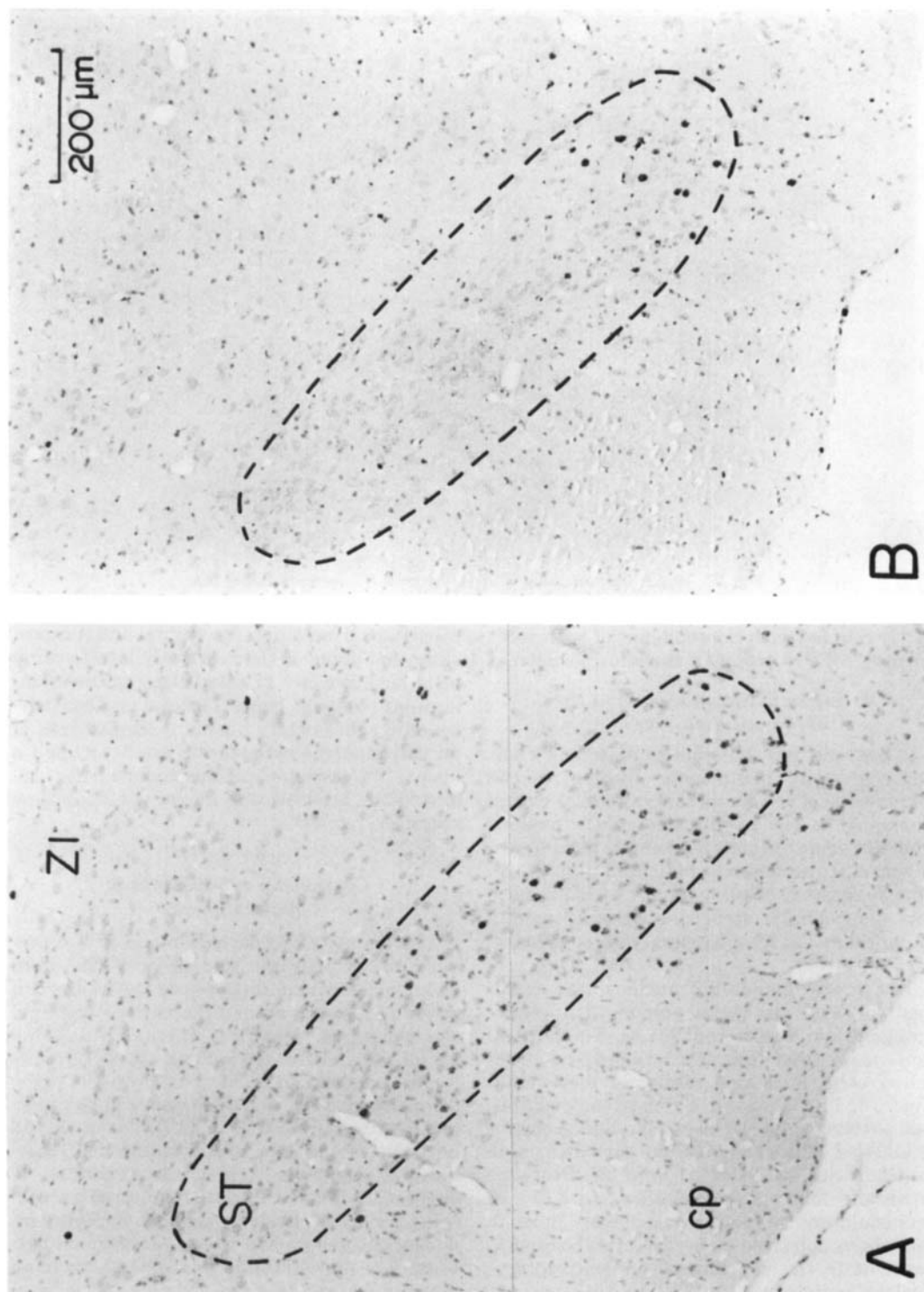


Fig. 11 Cytogenetic gradient in ST. A, E15 + 16; B, E16 + 17. Coronal sections.

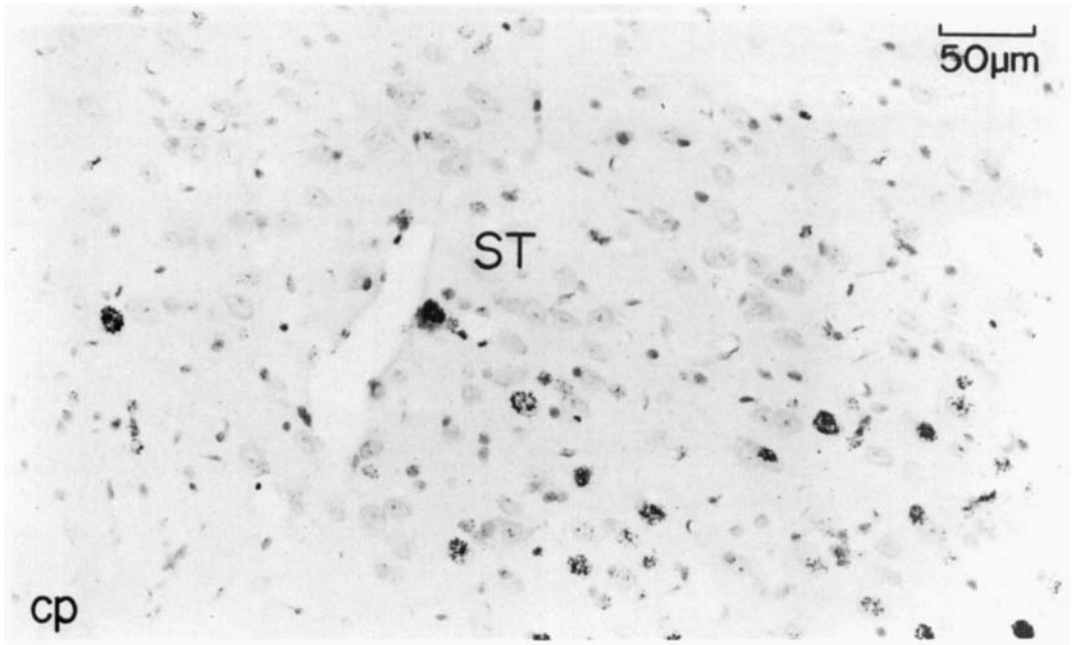


Fig. 12 Higher magnification of upper region of ST shown in figure 11A.

partly coupled with the tendency of some late-forming cells to occupy a capsular position.

#### 4. *Intranuclear gradients in the dorsal thalamus*

It has not been possible to discern a clear and consistent intranuclear gradient in the relay nuclei of the dorsal thalamus. The exception may be the medial geniculate nucleus where in some animals a posterolateral-to-anteromedial gradient was indicated (figs. 2, 16). This suggests a possible supply of neurons to this diencephalic structure situated among midbrain nuclei from a rostral neuroepithelial site.

The lateral geniculate nucleus was examined in detail in three planes with photographs taken at different levels. The impression was gained that the labelled and unlabelled cells were not randomly distributed (figs. 15, 17). However, a consistent distribution pattern could not be established. A core of unlabelled cells was noted but with a variable configuration in different animals. Presence or absence of neuronal labelling in E15 + 16 rats could not be related to cell size. In some rats there appeared to be a lateral-to-medial gradient in the ventrobasal or ventrolateral nuclear complexes (fig. 3). But this was not

consistent from animal to animal and it is possible that some of the relatively late-forming cells seen in E16 + 17 rats belong to the intralaminar belt (e.g., central lateral nucleus) surrounding these relay nuclei. A similar lack of an intranuclear cytogenetic gradient applies also to the anterior nuclear complex (fig. 18) and to the late-forming nuclei of the midline region.

#### DISCUSSION

##### *Cytogenetic subdivisions of the thalamus*

The quantitative datings made in the previous study (Altman and Bayer, '79a) indicated considerable differences in the time of origin of neurons among the various nuclei of the thalamus. Matched, coronal autoradiograms were evaluated in terms of differences in onset and cessation of cytogenesis (ranging from E13 to E19), and differences in peak formation time (from E13 to E17). The study did not support the idea of an ubiquitous cytogenetic gradient throughout the thalamus. It suggested, instead, a multiplicity of subsystems, each with its own gradient; implying independent generation sites and dispersal patterns. The present study was undertaken in an attempt to identify the cytogenetic subsys-

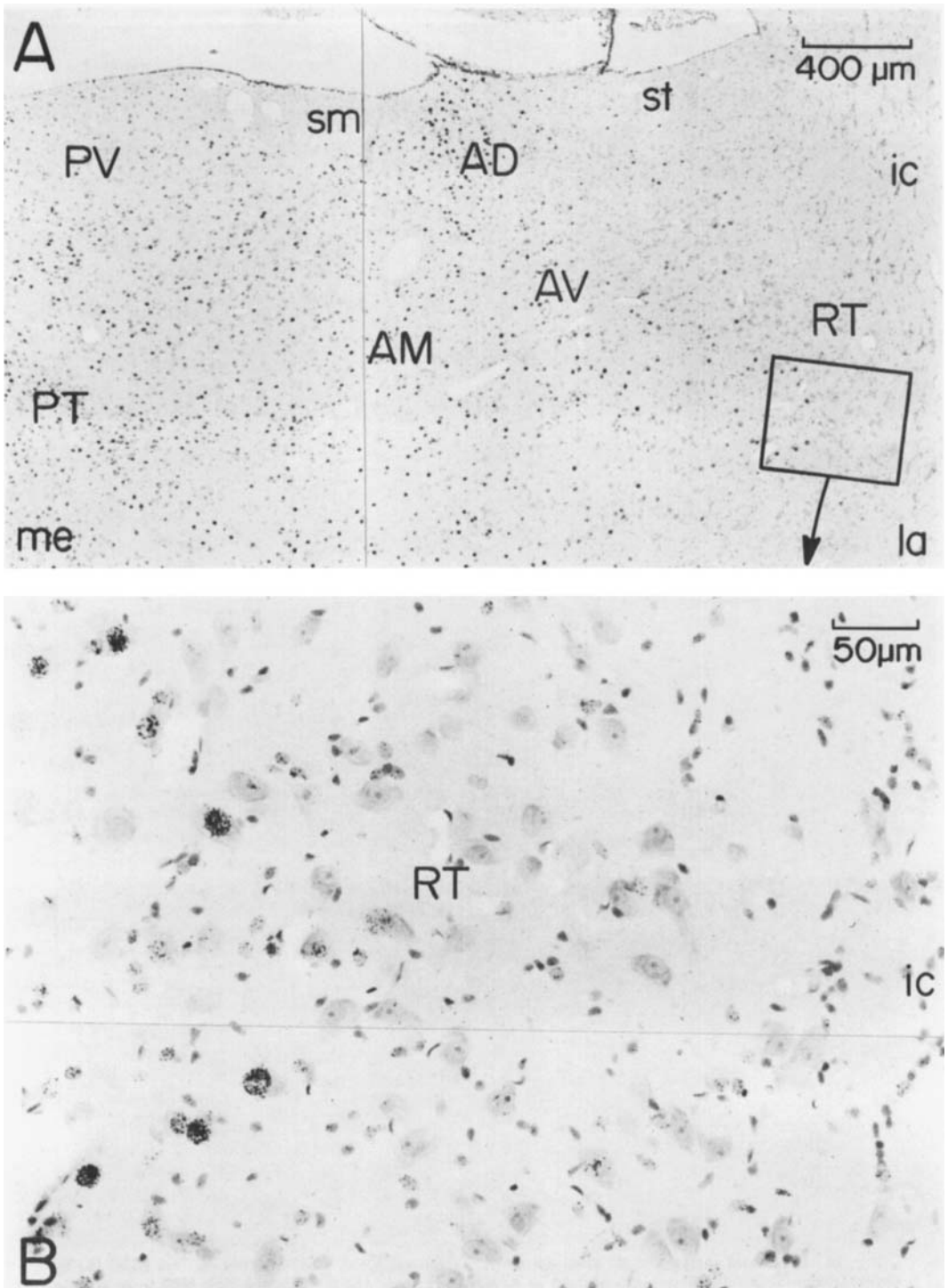


Fig. 13 A. Coronal section through the anterior thalamus in a E15+16 rat. B. Higher magnification of the area enclosed in A, showing the lateral-to-medial gradient in RT.



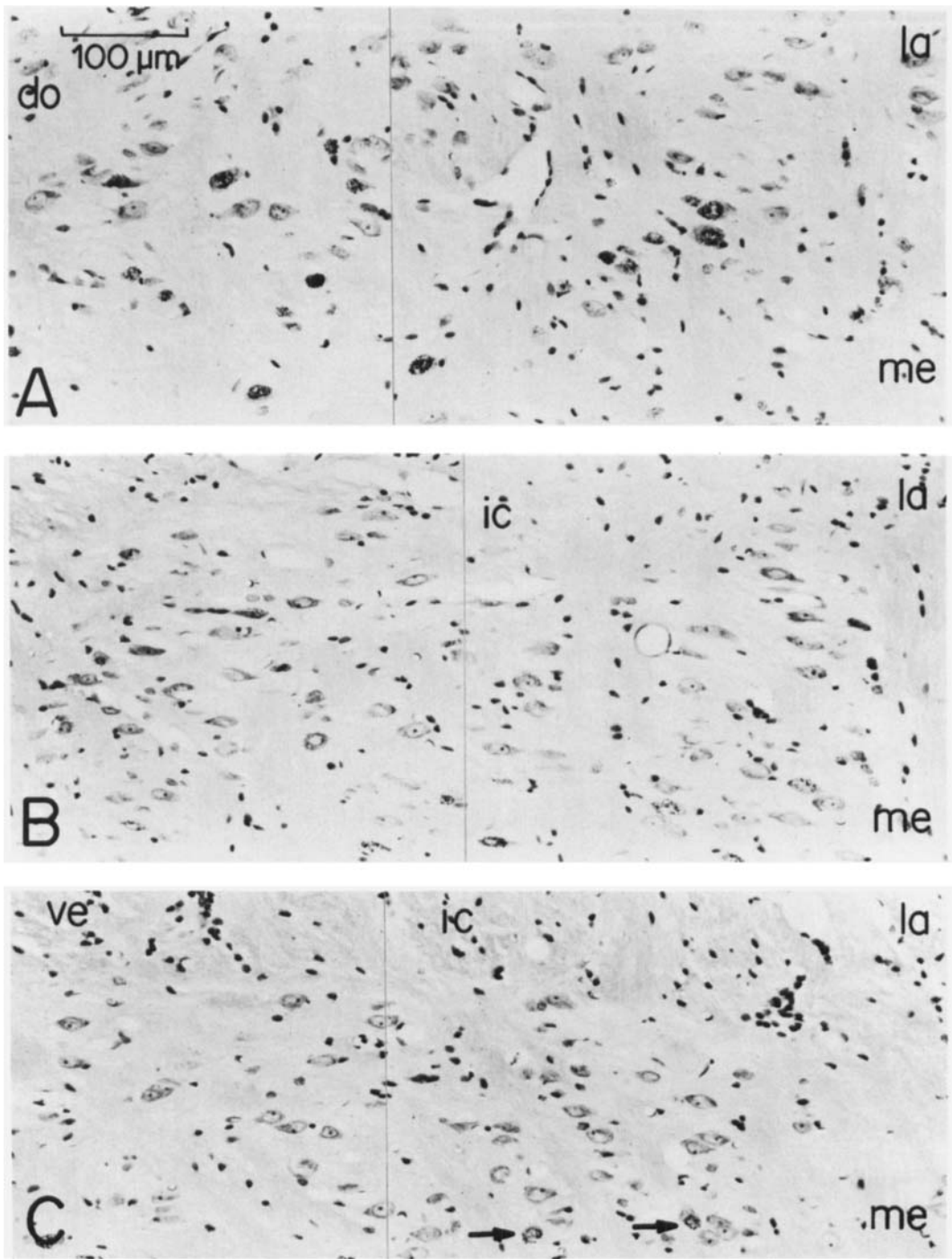


Fig. 14 Horizontal sections of RT from dorsal (A) to ventral (C) in a rat injected on days E15+16. The concentration of labelled neurons is highest in A, and in B and C the few labelled cells tend to be situated medially.

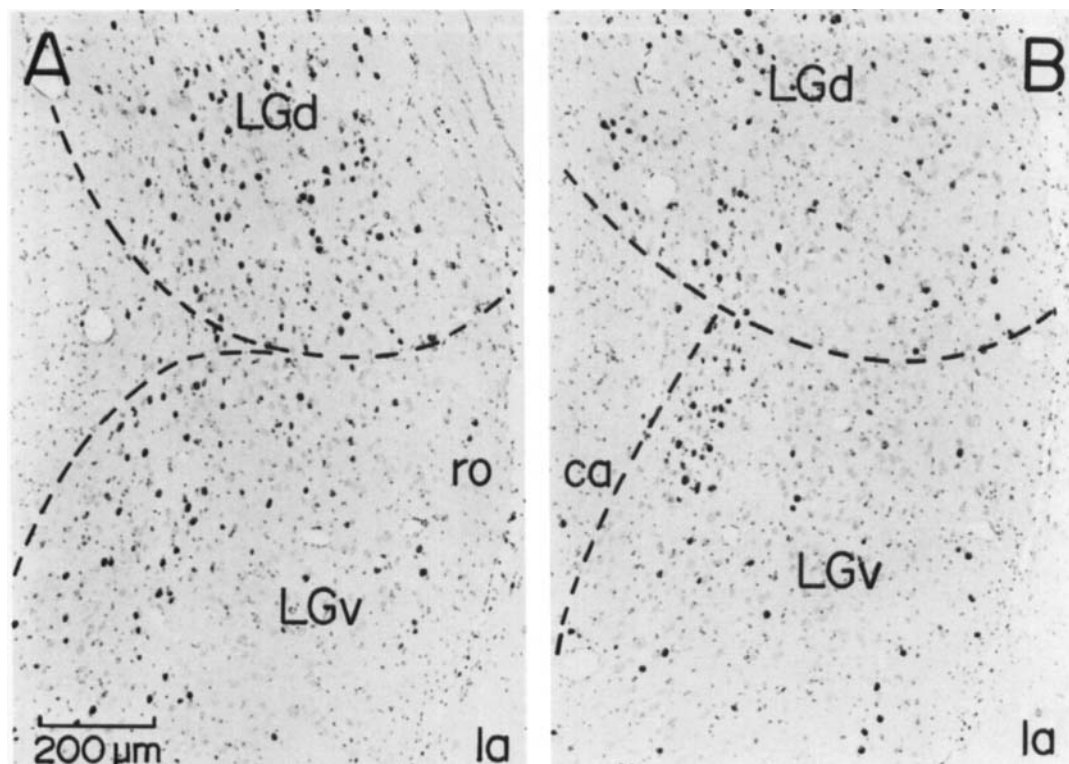


Fig. 15 Coronal sections of the lateral geniculate body (especially pars ventralis) in a rat injected on days E15+16, from rostral (A) to caudal (B).

tems of the thalamic region. In addition to the coronal thymidine-radiograms referred to, we have used sagittally and horizontally cut sections from animals with matched injection schedules.

Traditionally the suprahypothalamic region of the diencephalon is divided into three parts, the epithalamus, the dorsal thalamus, and the ventral thalamus. On the basis of the present and the preceding study, and additional embryological considerations (Altman and Bayer, '79b), we propose a cytogenetic division into five components with several subdivisions. The two most important criteria that we use in identifying these cytogenetic divisions of the thalamus are similarity in time-span of cell production and a consistent internuclear (and intranuclear) gradient within the proposed division. An examination of our quantitative data (Altman and Bayer, '79a: figs. 6, 10, 12) shows that there are thalamic nuclei that form over a protracted period (4-5 days), others that arise faster (3 days), and still

others that are generated very rapidly (2 days, with some forming predominantly in a single day). We take this feature to be an indication that structures with similar generation speeds derive from common or related germinal matrices (Altman and Bayer, '79b). Additional criteria were the data of neuron generation (early or late), and a consideration of the structural and functional affiliations of the different nuclei. The differential germinal origins of these divisions of the thalamus will be dealt with in the subsequent paper (Altman and Bayer, '79b).

The proposed major divisions of the thalamus (table 2) are *epithalamus*, the *dorsal thalamus*, the *medial thalamus*, the *ventral thalamus*, and the *posterior thalamus*. The dorsal thalamus consists of two subdivisions, the laterally situated sensory *relay nuclei* and the intermediate belt of *intralaminar nuclei*. The medial thalamus is considered to be a separate thalamic division; it consists of the *rostromedial nuclei* and the *midline nuclei*. The

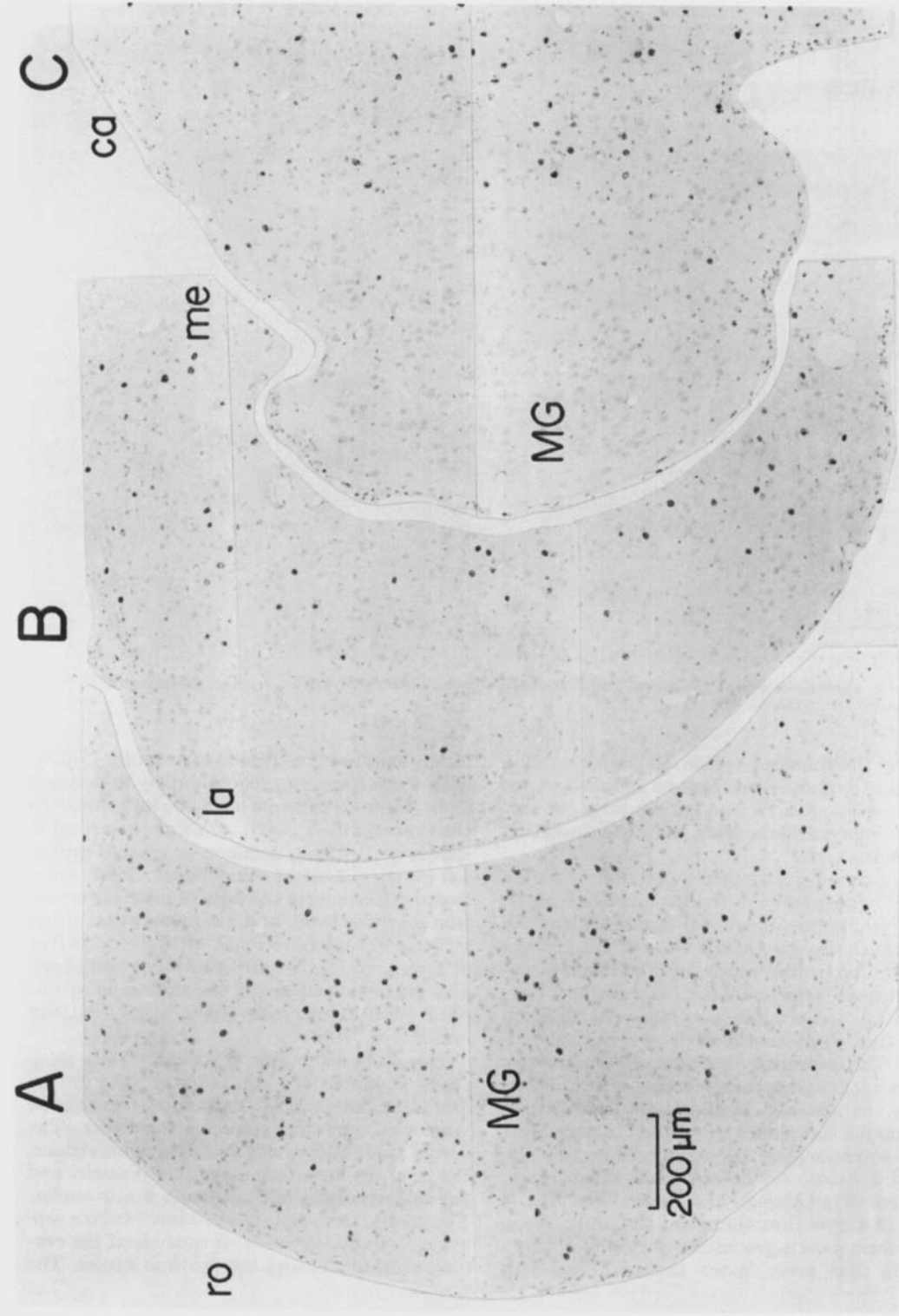


Fig. 16 Coronal sections through MG from rostral (A) to caudal (C) from a rat injected on days E15 + 16. The proportion of labelled cells rostrally was higher in this animal than in the majority injected with the same schedule (compare with fig. 2).

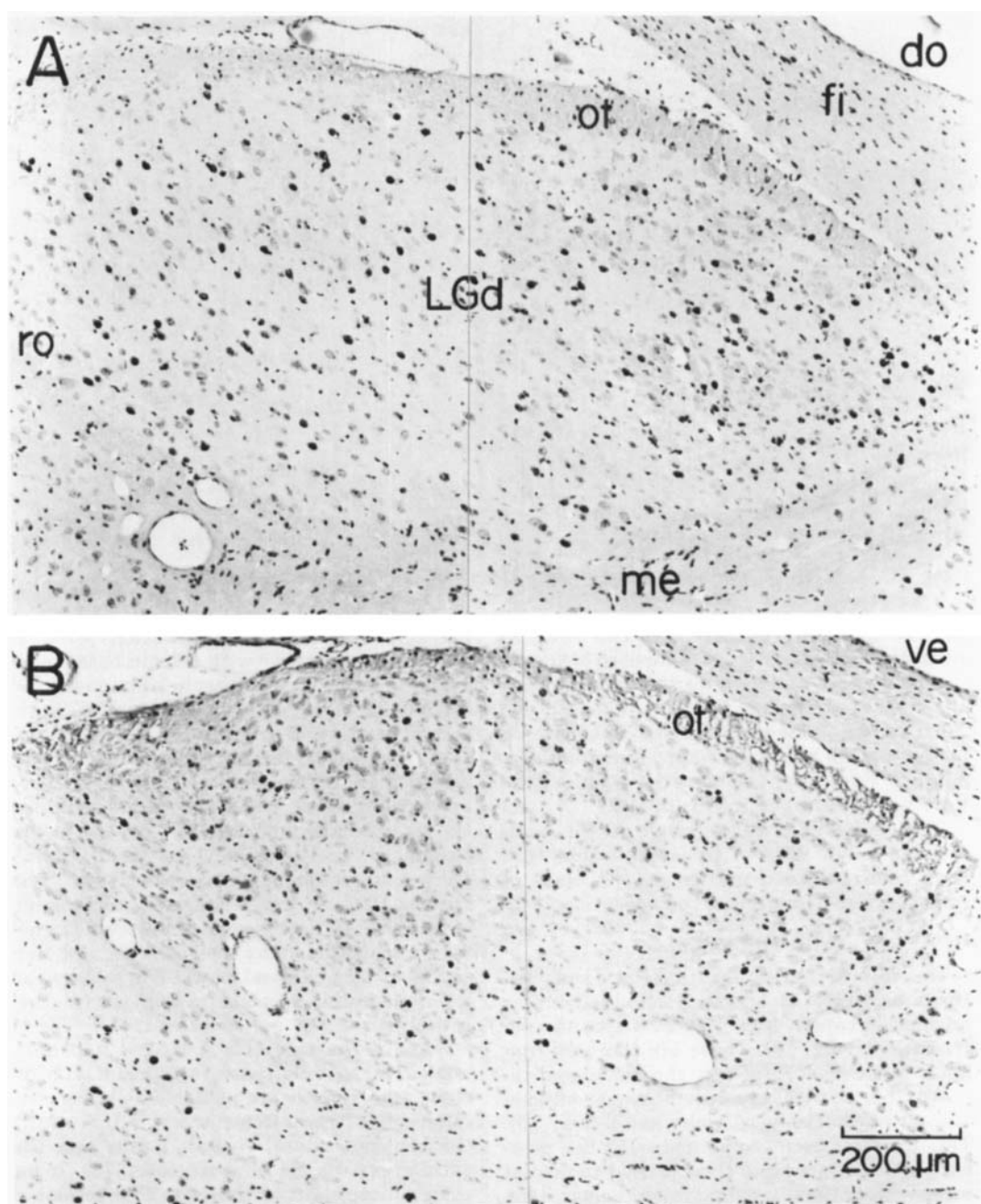


Fig. 17 Horizontal sections through LGd from dorsal (A) to ventral (B) in a rat injected on days E15+16.

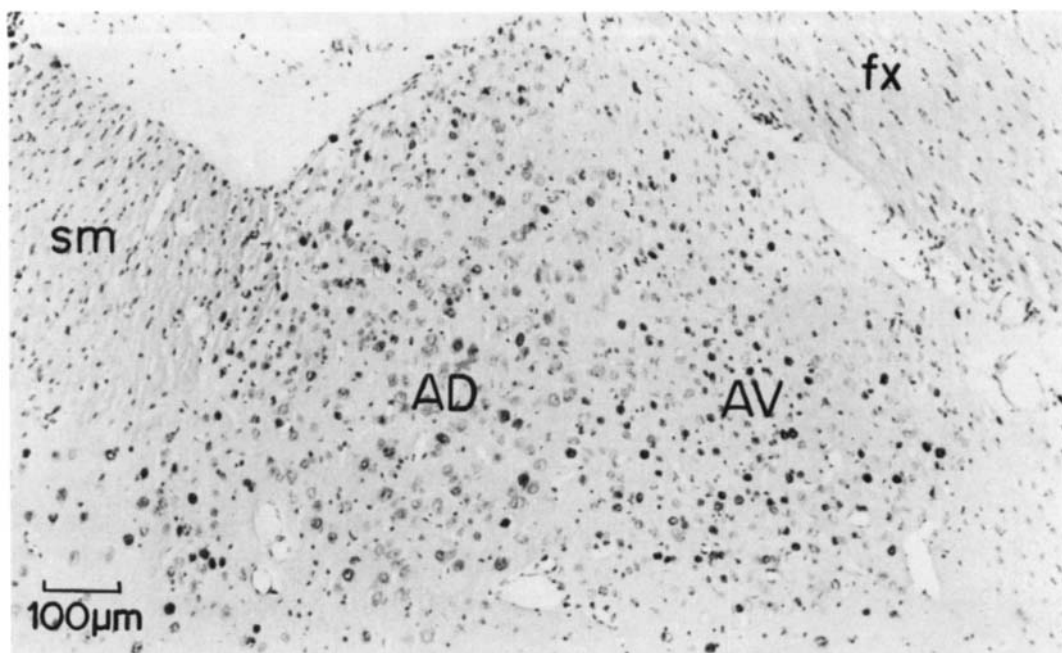


Fig. 18 Horizontal section through AD and AV in a rat injected on days E16+17.

ventral thalamus has at least two subdivisions, the *marginal nuclei*, composed of the reticular nucleus and perhaps the ventral lateral geniculate body, and the *ventral nuclei*. The subdivisions of the *posterior thalamus*, which includes some pretectal components and perhaps the nucleus of the posterior commissure, were not determined in this study.

Our cytogenetic parcellation of the thalamus parallels most of the subdivisions that have been proposed earlier on the basis of structural and functional considerations.

#### *The epithalamus*

The lateral habenular nucleus forms between days E13-16, and the medial habenular nucleus between days E15-20 (Altman and Bayer, '79a: fig. 10). These are the only thalamic nuclei that form over the protracted period of four to five days, resembling the nuclei of the hypothalamus (Altman and Bayer, '78). This characteristic, combined with the presence of an isolated and clear lateral-to-medial internuclear (figs. 1, 6) and intranuclear (figs. 7-9) gradient, qualify the epithalamus as a cytogenetic unit.

The uniqueness of the epithalamus in relation to other thalamic systems is well estab-

lished. It has no direct connections with the neocortex but rather with certain basal telencephalic structures and brain stem nuclei. According to Herkenham and Nauta ('77) the lateral portion of the lateral habenular nucleus receives its largest input from the entopeduncular nucleus and the lateral preoptic and hypothalamic areas; the medial portion of the lateral habenular nucleus and the medial habenular nucleus receive afferents mainly from the postcommissural septum. This implies that the earliest arising components of the epithalamus receive fibers from the oldest components of the telencephalon and diencephalon (Altman and Bayer, '78) whereas its later generated components from the relatively younger septal region (Bayer, '79). The efferents of the medial and lateral habenular nuclei reach caudally the interpeduncular nucleus, the tegmental nuclei of Gudden and some other brain stem nuclei and, rostrally, the septum, lateral hypothalamus and preoptic areas (Smaha and Kaelber, '73). It has been conceptualized that the connections of the epithalamus are with the nuclear components of the limbic system: the septum, the lateral hypothalamic and preoptic areas, and certain tegmental nuclei. This would now be

TABLE 2

*Cytogenetic parcellation of the thalamus*

Division	Subdivision	Specific nuclei	Birth dates	Generation speed
1. Epithalamus	Habenular nuclei	Lateral habenula Medial habenula	E13-16 E15-19	Very slow (4-5 days)
2. Ventral thalamus	<div> <div>Anterior</div> <div>Posterior</div> </div>	<div> Reticular Ventral lateral genic. Zona incerta Subthalamus </div>	E13-15	Slow (3 days)
3. Dorsal thalamus	<div> <div>Relay nuclei</div> <div>?</div> <div>Intralaminar nuclei</div> </div>	<div> Medial geniculate Dorsal lateral genic. Ventrobasal complex Ventrolateral complex Lateral, anterior Lateral, posterior Central lateral Centromedian (?) Parafascicular </div>	<div> E14-15 E14-15 E15-16 </div>	Very fast (1-2 days)
4. Medial thalamus	<div> <div>Rostromedial nuclei</div> <div>Midline nuclei</div> </div>	<div> Anterodorsal Anteroventral Anteromedial Mediodorsal Rhomboid Reuniens Paraventricular Paratenial </div>	<div> E15-16 E16-17 E16-17 </div>	Very fast (1-2 days)
5. Posterior thalamus	Not determined	Posterior nucleus Pretectal area	E13-15 14-16	Slow

valid only if the entopeduncular nucleus (a component of the basal ganglia) could be put into such a classification. The little information that is available about the functions of the epithalamus, such as involvement in ingestive (Donovick et al., '69) and sexual (Modianos et al., '74) behavior is reconcilable with such a view.

*The ventral thalamus*

The early generated nuclei (E13-15) that form over a relatively protracted period (3 days) include the zona incerta, the subthalamic nucleus, the reticular nucleus, the ventral lateral geniculate nucleus, and the posterior nucleus (Altman and Bayer, '79a: figs. 6, 10, 12). Excluding the posterior nucleus, which together with the pretectal area and other caudal structures may be part of a separate posterior system, these nuclei are considered to compose the ventral thalamus.

The only nucleus in this complex that is not always assigned to the ventral thalamus is the

reticular nucleus. Some investigators (e.g., Jasper, '49) have classified it, with the intralaminar and midline nuclei, as part of the "nonspecific thalamocortical system." But there is ample anatomical evidence that the reticular nucleus does not project to the cortex but rather to the thalamus (Scheibel and Scheibel, '66; Minderhoud, '71; Jones, '75), possibly in a precise topographic manner (Montero et al., '77). On the basis of developmental and morphological affinities, Rose ('42) included the reticular nucleus in the ventral thalamus. The reticular nucleus differs in many respects from the other components of the ventral thalamus and we shall refer to it as its pars anterior.

It is generally agreed upon that the pars ventralis of the lateral geniculate body is a component of the ventral thalamus. It shares one feature with the dorsal lateral geniculate nucleus, namely direct retinal input (Hayhow et al., '62; Swanson et al., '74; Mathers and Mascetti, '75). But it also has input from other

regions, including the superior colliculus (Altman, '62; Ribak and Peters, '75) cerebellum (Graybiel, '74) and the vestibular system (Magnin and Putkonen, '78). Unlike the dorsal lateral geniculate nucleus, it does not project to the visual cortex (Swanson et al., '74) but rather to subcortical structures, including the pretectum (Swanson et al., '74; Ribak and Peters, '75), superior colliculus (Edwards et al., '74; Graybiel, '74) and at least one component of the ventral thalamus, the zona incerta (Altman, '62; Swanson et al., '74; Ribak and Peters, '75).

The afferents of the subthalamic nucleus are mostly from the entopeduncular nucleus, or external segment of the globus pallidus (Nauta and Mehler, '66; Carpenter et al., '68; Nakamura and Sutin, '72) and its efferents go to the internal segment of the globus pallidus (Whittier and Mettler, '49; Carpenter and Strominger, '67). It thus represents a nodal point in a telencephalic loop. Interestingly, it has been argued that the subthalamic nucleus is itself of telencephalic derivation (Richter, '65). However, this is counterindicated by the laterodorsal-to-medioventral cytogenetic gradient observed in this study (figs. 10-12) which suggests a medioventral origin in the diencephalic neuroepithelium possibly as far caudally as the aqueduct. Such a laterodorsal-to-medioventral gradient is also suggested for the entire complex composed of the zona incerta, subthalamic nucleus and ventral lateral geniculate nucleus (fig. 19). This may be the only common link among the heterogeneous components of this division of the ventral thalamus, which we shall tentatively refer to as its pars posterior.

#### *The dorsal thalamus*

##### The relay nuclei

The nuclear system that is generated after the ventral thalamic nuclei is characterized by an extremely brief period (E14+15) with the majority of the neurons (60-80%) arising on a single day. Its components are the medial geniculate and the dorsal lateral geniculate nuclei, the ventrobasal and the ventrolateral nuclear complexes, and the lateral nucleus pars posterior; that is, with the exception of the latter, the sensory relay nuclei of the thalamus. A definite internuclear gradient was noted between the medial geniculate and the dorsal lateral geniculate nuclei, with the neurons of the former arising predominantly on day E14, that of the latter on day E15 (Altman

and Bayer, '79a: fig. 13). But there was no internuclear gradient among the other components of these relay nuclei.

In most of these nuclei we could not observe intranuclear gradients, possibly because of extremely brief generation times. There was a hint of a lateral-to-medial gradient in the ventrobasal complex. If the latter is correct, it would indicate that in terms of established topographic organization in the rat somesthetic thalamus (Emmers, '65; Davidson, '65; Lund and Webster, '67; Waite, '73; Donaldson et al., '75; Saporta and Kruger, '77), the neurons representing the trunk region arise before those representing the forelimbs and the head. Although representation of the body in the ventrolateral complex of the rat has not been investigated, a similarly oriented topographic organization has been described in some other species (Rispaal-Adel et al., '73; Strick, '76) in this relay station from the cerebellum (Angaut and Bowsher, '70; Rinovik and Grofova, '74) and the basal ganglia (Nauta and Mehler, '66; Severin, Young and Massopust, '76) to the motor cortex.

According to Angevine ('70) the oldest neurons of the dorsal lateral geniculate nucleus of the mouse are situated superficially, the youngest medially. Brückner et al. ('76) found in the mouse that neurons formed simultaneously in the whole nucleus, but they did not reject the possibility of a somewhat earlier generation of superficial neurons. An intranuclear gradient from the "superficial" to the "deep" parts of the nucleus in the rat was noted by Lund and Mustari ('77) whereas McAllister and Das ('77) referred to a slight caudal-to-rostral gradient. Rakic ('77) described an "outside-to-inside" gradient in the more slowly developing and highly laminated dorsal lateral geniculate nucleus of the monkey, one that becomes re-oriented ventrodorsally during development. After examination of the dorsal lateral geniculate nucleus in three planes in a large number of rats, we concluded that a simple directional gradient is not present. Although the labelled and unlabelled cells did not seem to be randomly distributed, the pattern varied from animal to animal. Several authors (Hayhow et al., '62; Cunningham and Lund, '71) described a "concealed" lamination in the rat lateral geniculate nucleus, one which may be related to a small and variable contingent of ipsilateral optic tract fibers (Creel and Giolli, '76; Hickey and Spear, '76). The lamination described bears some re-



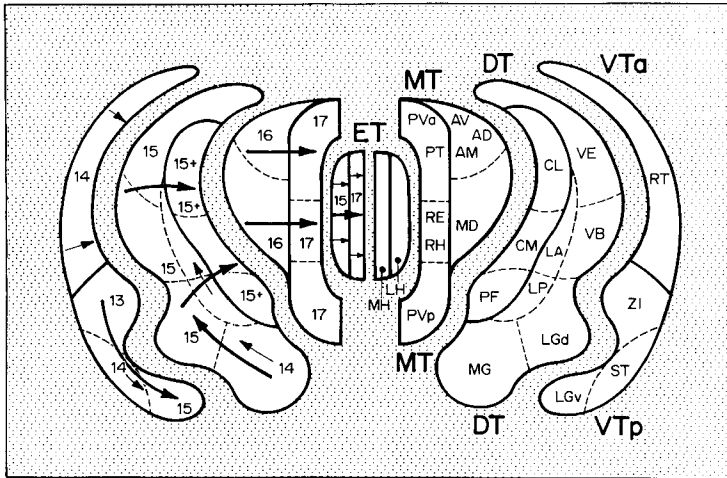


Fig. 19 Schematic illustration of the major cytogetic divisions of the thalamus (posterior thalamus not shown). Structures situated in different rostrocaudal planes shown in a single plane, and the four major divisions are shown as separate bodies. The right panel illustrates the subdivisions of the epithalamus, medial thalamus, dorsal thalamus and ventral thalamus (thick lines) and their nuclear components (broken lines). The left panel indicates regional dates of cytogenesis (embryonic days in terms of peak time of cell production); and the directions of internuclear gradients (thick arrows) and intranuclear gradients (thin arrows).

semblance to the cytogetic pattern seen in some of our animals (fig. 17), but the resemblance may be fortuitous. Different cell types have been distinguished in the lateral geniculate nucleus that differ in perikaryal size (Grossman et al., '73; Kriebel, '75), but we did not observe a systematic difference in the time of origin of large versus small cells here.

Of all the sensory relay nuclei the strongest cytogetic gradient was noted in the medial geniculate body. Apparently the lateral portion, described as the small-celled or principal nucleus (Rioch, '29), forms before the medially situated magnocellular portion. These two regions may represent two separate structures, the principal nucleus being mostly involved in auditory functions (Rose and Woolsey, '49; Aitkin and Webster, '71; Gross et al., '74), the magnocellular nucleus in vestibular functions (Wepsic, '66; Roucoux-Hanus and Boisacq-Schepens, '77). The cytogetic gradient observed could not be related to the finer subdivision of the principal nucleus into a dorsal and ventral component that was made by Morest ('64) on the basis of cytological differences.

The structure that is not a component of the thalamic sensory relay system but has a comparable generation time and generation span is the nucleus lateralis, pars posterior (E14-15; Altman and Bayer, '79a: fig. 12). It is a

structure that has been homologized with the pulvinar of primates; it has no direct optic projection in the rat (Hayhow et al., '62). In the cat its cortical projections have been described to a "rim-area" alongside the major sensory areas (Graybiel, '73). Either this nucleus is part of a separate posterior system that receives a rich corticofugal projection (Jones and Powell, '71) or else it constitutes an auxiliary system of the relay nuclei, together with the lateral nucleus, pars anterior. As we noted (Altman and Bayer, '79a: fig. 10), the neurons of the pars anterior arise significantly later than those of the pars posterior, paralleling the caudal-to-rostral gradient that is present between the adjacent (and possibly related) medial geniculate and dorsal lateral geniculate nuclei, respectively.

In summary, the evidence obtained indicates that the sensory relay nuclei of the thalamus differ from all the others in terms of several cytogetic criteria and qualify as a separate cytogetic system. Unlike in so many other thalamic nuclei, a definite intranuclear gradient may not exist in the individual nuclei of this system.

#### The intralaminar nuclei

The nuclei that arise following the lateral system, on days E15-16 but predominantly on day E15, are the nucleus lateralis, pars ante-

rior (previously considered) and the parafascicular nucleus (Altman and Bayer, '79a: fig. 10). Although we did not gather quantitative data, a similar time of origin was indicated for a group of nuclei that are not clearly demarcated or well developed in the rat. This we designated as the nucleus centralis lateralis (Altman and Bayer, '79a: figs. 6, 10, 13); it may include the centromedian nucleus.

This is a system that is well developed in carnivores and primates. In the cat it has been subdivided into the central medial, paracentral, central lateral, and parafascicular nuclei (Murray, '66; Kennedy and Baleyrier, '77) and is considered a single system because of presumed "nonspecific" activating effects exerted from here on the cortex (Dempsey and Morison, '42; Jasper, '49). The major input to this region is thought to be from the basal ganglia and motor cortex (Mehler, '66) and the outflow is to the basal ganglia (Walker, '38; Jones and Leavitt, '74; Simke and Saelens, '77) and to widespread areas of the cortex (Rose and Woolsey, '49; Powell and Cowan, '54; Murray, '66; Jones and Leavitt, '74); but not to layer IV and III but, rather, as a "nonspecific projection" (Lorente de Nó, '49) to layers I and VI (Killackey and Ebner, '73). Recent physiological studies have implicated components of this system in oculomotor and related "attentional" functions (Schlag and Schlag-Ray, '71; Orem et al., '73; Hunsperger and Roman, '76).

#### *The medial thalamus*

##### *The rostromedial nuclei*

The nuclei that arise following the intralaminar system, on days E15-16 but predominantly on day E16, are the anterodorsal, anteroventral and anteromedial nuclei, the mediodorsal nucleus, and the paraventricular nucleus, pars posterior. The anterior nuclei and the mediodorsal nucleus may be viewed as relay nuclei of the limbic system. The afferents of the anterior nuclei are from the medial (cingulate) cortex (Domesick, '69), mammillary body (Powell and Cowan, '54; Guillery, '57; Cruce, '75) and the hippocampus (Dekker and Kuypers, '76); its efferents reach the medial cortex and the subiculum (Domesick, '72). The connections of the mediodorsal nucleus are also with limbic structures. Afferents have been traced to its medial portion from the amygdaloid region (Nauta, '61; Krettek and Price, '74) and the olfactory cortex (Powell et al., '65; Heimer, '72; Leonard, '72),

and to its lateral part from the amygdala (Nauta, '61) and prefrontal cortex (Leonard, '69, '72; Siegel et al., '77). Mediodorsal nucleus efferents, according to classical studies (Walker, '40; Rose and Woolsey, '48), reach the prefrontal neocortex but in the rat the target structure appears to be allocortical rather than neocortical (Leonard, '72).

On the basis of similarities in connections and time of origin, the anterior nuclei and the mediodorsal nucleus are considered a single thalamic subdivision. The paraventricular nucleus, pars posterior, which we found to be isochronic with these structures, may be part of a second subdivision of the medial thalamus.

##### *The midline nuclei*

The latest forming nuclei of the thalamus (excluding the medial habenular nucleus previously considered) are the rhomboid and reuniens nuclei (E16-17; peak on day E16), and the paraventricular (anterior) and paratenial nuclei (E16-17; peak on day E17; Altman and Bayer, '79a: figs. 6, 10). Relatively little is known about the afferent and efferent connections of these midline nuclei; those that have been described suggest limbic affiliations (Domesick, '72; Herkenham, '78). It is conceivable that these midline structures are somehow related to the neighboring third ventricle. We shall tentatively assume that the midline nuclei are part of the medial thalamus. If so, there is an evident internuclear gradient from lateral to medial: the medial portion of the medial thalamus forming ahead of its midline portion.

#### *Concluding remarks*

The division of the thalamus into five major components was based on thymidine-radio-graphic evidence of similarities in the time of origin and duration of neuron production in the various thalamic nuclei coupled, at least in some instances, with shared cytogenetic gradients. The attempt was guided throughout by a consideration of the specific connections of the different components of the thalamus and, to a lesser extent, by functional considerations. Figure 20 summarizes graphically the afferent and efferent connections of the four cytogenetic divisions of the thalamus and some of their known or imputed functions. The dorsal thalamus can be designated with some assurance as the sensory thalamus, and the medial thalamus as the limbic thalamus. The fact that the neurons of the sensory thal-

## MAJOR CONNECTIONS OF THALAMIC SUBDIVISIONS

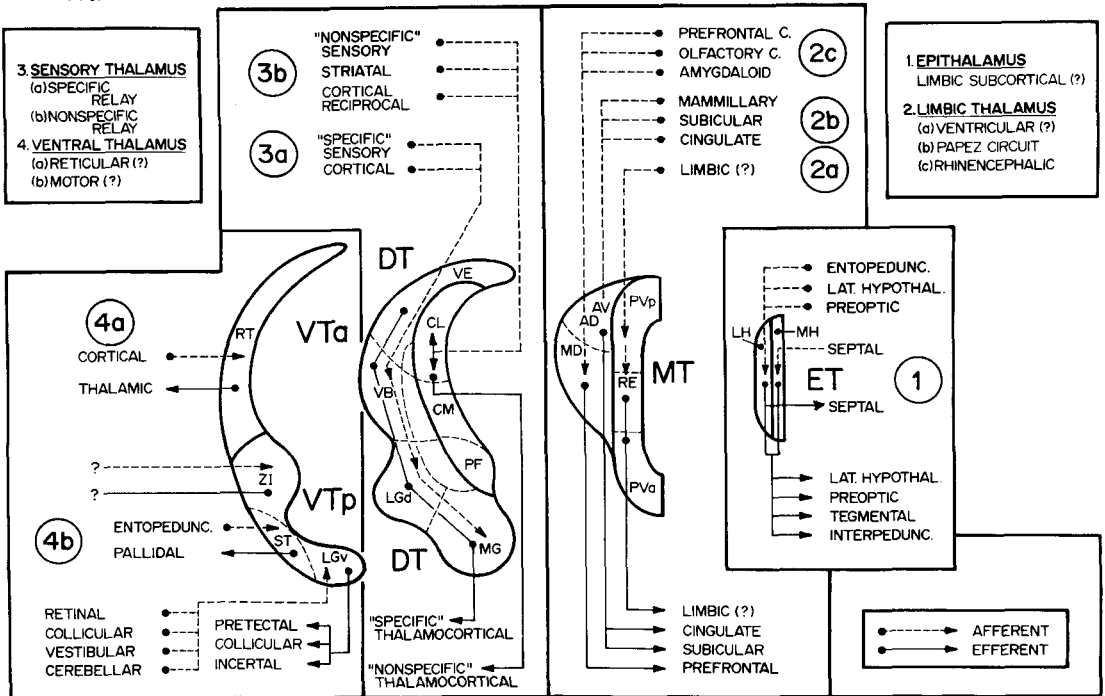


Fig. 20 The large central panels summarize the structural affiliations (arrows) of the components of the thalamus. The two upper side panels summarize some known and imputed functional involvements of the same subdivisions.

amus are generated before those of the limbic thalamus may imply that the maturation of structures mediating cognitive functions are produced at the thalamic level ahead of those mediating conative or emotional functions. Much less is known about the functions of the ventral thalamus, which is the earliest component of this system; at least some of its nuclei may have motor functions. Finally, the cytogenetic evidence suggests that the epithalamus resembles more the hypothalamus than the thalamus itself; indeed, its involvement in endocrine functions has been postulated.

The specific neuroepithelial sources of the principal divisions of the thalamus will be described in the succeeding paper (Altman and Bayer, '79b) dealing with the embryonic development of the thalamus.

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