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# A localised growth zone in the wall of the developing mouse telencephalon

I. H. M. SMART

*Department of Anatomy, Medical Sciences Institute, The University, Dundee DD1 4HN*

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## INTRODUCTION

In a recent study of isocortical histogenesis in the mouse (Smart, 1983) it was suggested that a zone of maximum pallial growth is located along the boundary between the lateral and medial telencephalic walls. The basis of this suggestion is that in this area few neurons are being produced yet the incidence of mitosis among the ventricular cells is high. It was inferred that cell division along this 'watershed zone' between the medial and lateral wall cortices produces additional ventricular cells rather than neurons and is thus primarily engaged in increasing the area of the ventricle.

The purpose of the present study is to describe the history of this watershed zone in more detail and to examine some of the implications of the concept in the assessment of cortical growth.

## MATERIALS AND METHODS

The study was based on an extensive library of serially sectioned embryonic mouse brains taken at daily intervals between E10 and E19. The brains were fixed in Bouin's solution, sectioned at 6 $\mu$m and stained with haematoxylin and eosin. Sets of sections were selected which were cut symmetrically in the coronal plane and which were judged to be representative of the histological status at each day of age. The same sets of sections were used in previous studies of other aspects of mouse telencephalic histogenesis (Smart, 1983, 1984). From this material atlases had been prepared consisting of photographs of every twentieth section printed at a $\times 100$ enlargement. Measurements from these atlases had been used to construct: (1) solid models of the ventricular cavity and (2) sets of orthogonal drawings of the ventricular surface seen in lateral and medial views. The method of construction of these items has been described elsewhere (Smart, 1983). The location of the areas of the ventricle which were related to sites of mitotic activity and minimal neuron release were marked on the drawings and models.

A similar series of serially sectioned embryonic ferret and rabbit brains were also available and were used to check the presence of a growth zone in these species.

## RESULTS

### *Site of minimal neuron release*

At ten days postconception (E10), the cerebral vesicle formed an approximately hemispherical dilatation of the lateral wall of the neural tube. The medial wall at this stage was minimally present as the diameter of the interventricular foramen

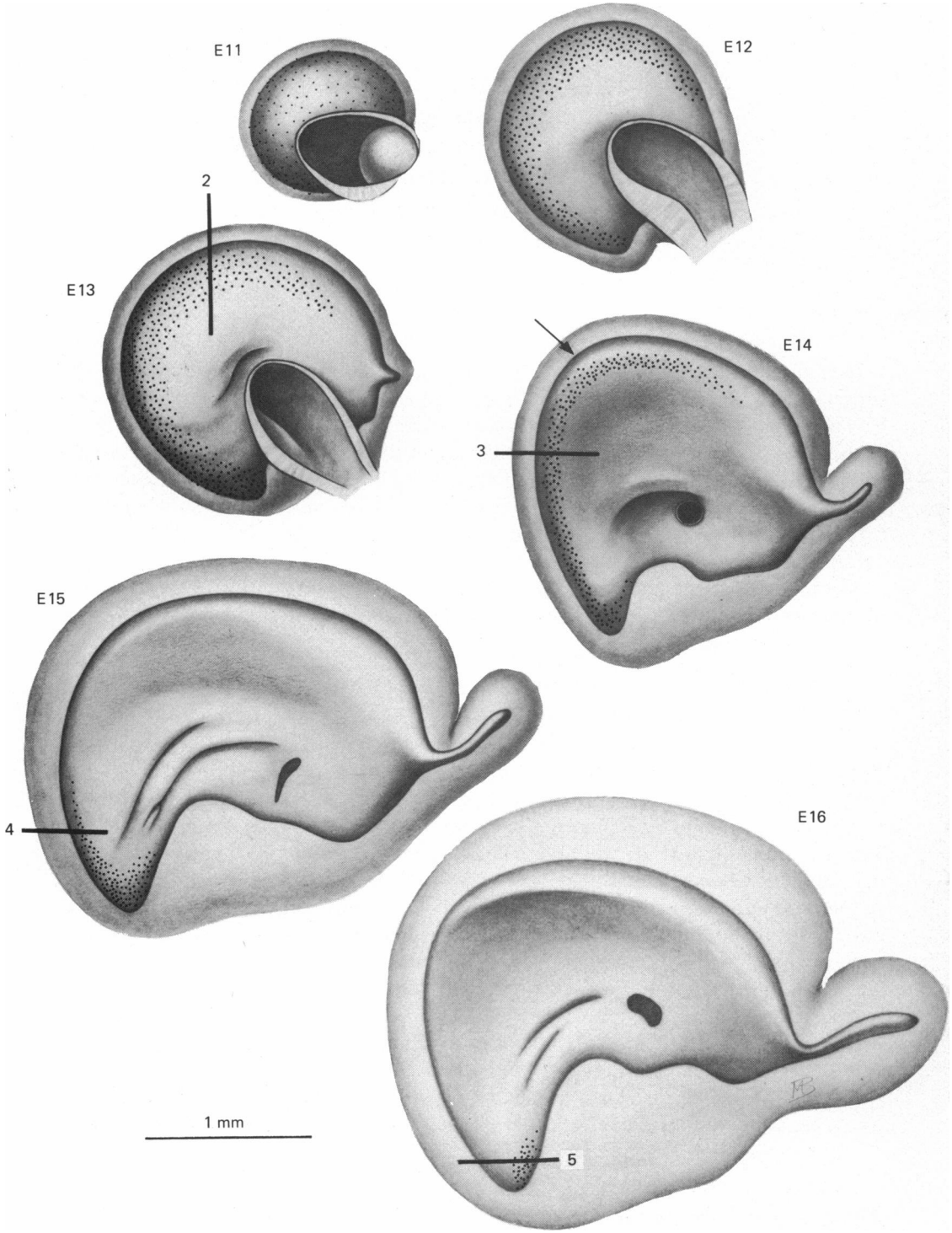
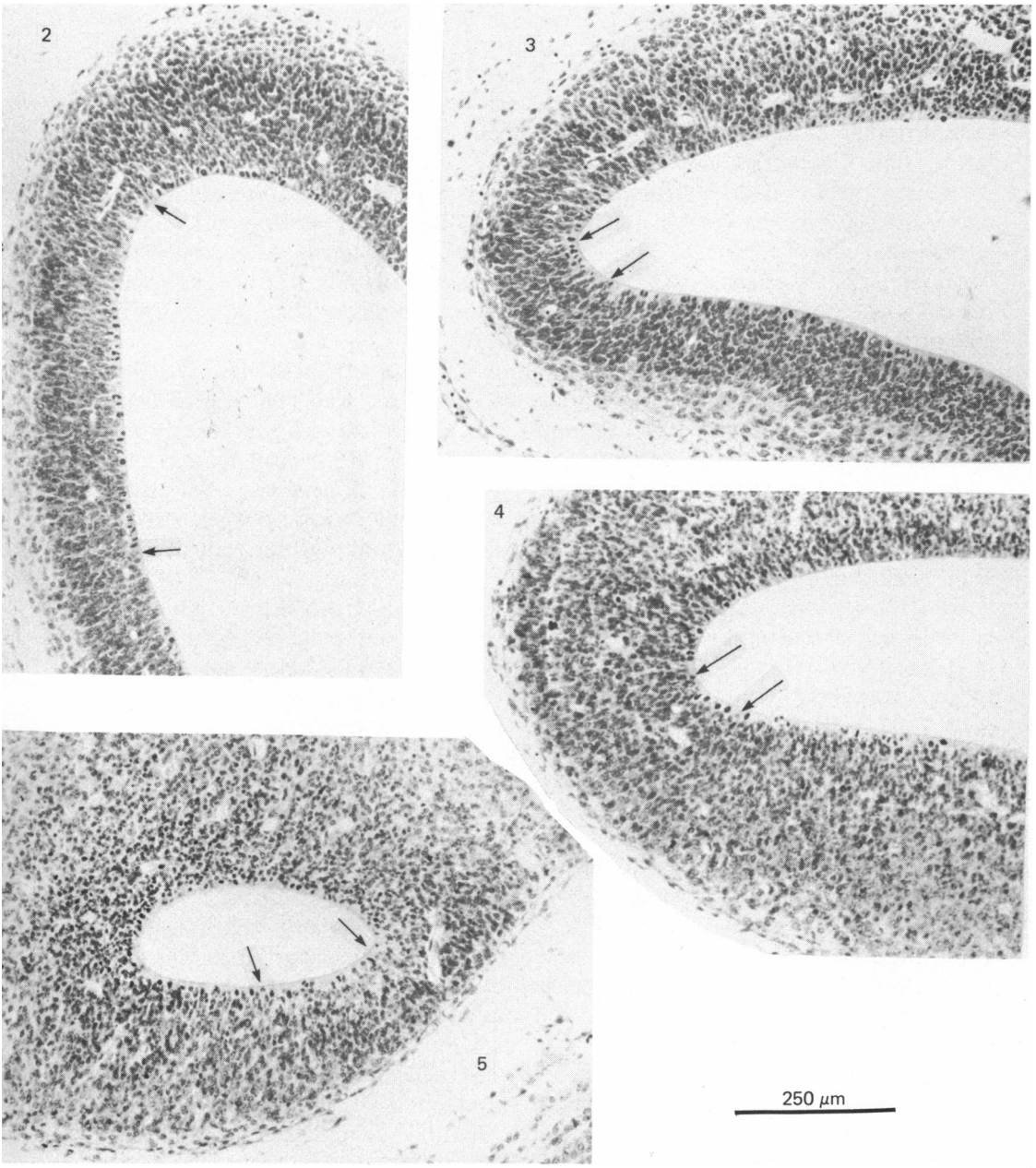



Fig. 1. Reconstruction of the medial wall of the mouse lateral ventricle at the stated embryonic ages (E 11–16). The stippling represents the extent of the watershed zone or area where mitotic figures are numerous and neuron release minimal. The lines labelled 2, 3, 4, 5 in the E13, E14, E15 and E16 brains refer respectively to the plane of section of the photomicrographs in Figs. 2–5. The arrow in the E14 diagram indicates the site of what may possibly be a modest attempt at creating a posterior horn.




Figs. 2–5. Photomicrographs of sections through embryonic mouse brains of different ages. The arrows in each photograph lie within the ventricular cavity and indicate the boundaries of the watershed zone. Fig. 2. Section through E13 brain in the coronal plane at the level marked 2 in Fig. 1. Fig. 3. Section through E14 brain in the horizontal plane at the level marked 3 in Fig. 1. Fig. 4. Section through E15 brain at the level marked 4 in Fig. 1. Fig. 5. Section through E16 brain at the level marked 5 in Fig. 1.

virtually corresponded to that of the vesicle. Neuron release at E10 was minimal. Mitotic figures were located at the ventricular surface, were distributed fairly uniformly and were less numerous than at later stages.

By E11 (Fig. 1) the vesicle had undergone further dilatation and its diameter now exceeded that of the interventricular foramen, producing a medial as well as a lateral wall. The vesicle also became laterally compressed, particularly caudally, producing a greater degree of curvature at its sagittal perimeter. This line of increased curvature between the medial and lateral walls was a useful landmark and was termed the 'roof flexure'. At E11, neuron release had commenced rostrally in the basal region of the telencephalon and in the adjacent lateral wall. Elsewhere neuron release was minimal. Mitotic figures were now more numerous along and on each side of the roof flexure.

By E12, isocortical neuron release had spread further across the lateral wall but did not extend as far as the roof flexure. On the medial wall two sites of neuron release had appeared: one, rostroventrally, was associated with the genesis of the first septal neurons and the other, a curved site along the caudal margin of the choroid plate, marked the location of the first hippocampal neurons. Between these sites of neuron release on the medial and lateral walls, a broad watershed area remained where neuron release was minimal and mitotic figures were numerous (Fig. 1, E12).

By E13, neuron release covered the lateral wall as far as the roof flexure and rostrally had united with medial wall neuron release to obliterate the watershed area in this most rostral region (Fig. 1, E13). At E14, the watershed area had contracted to a narrow band along the medial side of the caudal perimeter of the ventricle (Fig. 1, E14). By E15 the area of minimal neuron release had retreated towards the temporal pole of the ventricle (Fig. 1, E15) and at E16 was restricted to a small patch on the medial side of the temporal pole (Fig. 1, E16).

## DISCUSSION

The regions of the ventricular wall surface where mitotic activity is high and neuron release minimal are self-evidently those in which cell multiplication is contributing mainly to an increase in the volume of the ventricular layer. Since there is a limit to the degree of pseudostratification that can be attained (Smart, 1972) this proliferative activity must be resolved into an increase in the area of the ventricular layer and hence of the ventricular surface.

From E10 to E11 few neurons are released anywhere across the pallial vault. Consequently, this is a period when cell production is contributing entirely to ballooning of the ventricle. By E11, neuron birth has commenced ventrally in the lateral wall and, by E12, in the medial wall. The intervening area straddling the roof flexure continues to produce ventricular cells and the major increase in ventricular area therefore occurs at this site. As the area of ventricular wall producing cortical neurons is observed to increase while the growth zone is present, it follows that at the margin of the zone ventricular cells are turning over to neuron production. The medial and lateral wall cortices are thus increasing in area by increments received at their periphery. By E13, the front of isocortical neuron release advancing across the lateral wall reaches the horizon of the ventricle, so that the growth zone is displaced from the roof flexure on to the less curved medial surface (Fig. 1). An adventitious effect of this shift may be to mitigate the effect of ventricular 'choke' (Smart, 1972),

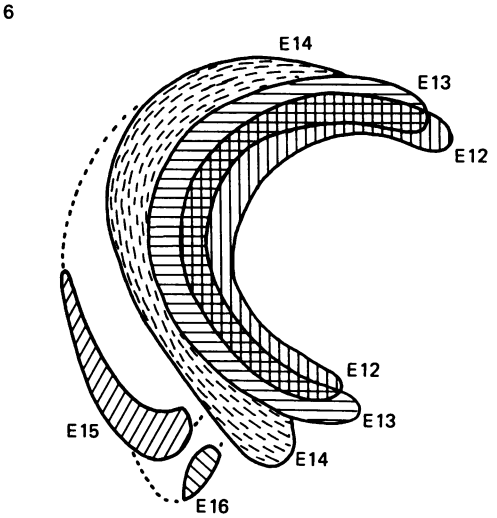



Fig. 6. Outlines of the watershed zone at stated embryonic ages (E12–16). These have been superimposed with the dorsal aspect of the interventricular foramen in register in each case. The outlines have been filled with differently orientated bars. Extensive overlap only occurs between the E12 outline (vertical bars) and the E13 outline (horizontal bars).

as any tendency for the ventricular surface to become fully occupied by interkinetically migrating mitotic figures is enhanced at sites where cell apices converge on a concave surface with a small radius of curvature, as obtains at the roof flexure.

From E13 onwards, the growth zone is progressively eliminated in a rostrocaudal direction as mesocortical neuron release commencing rostrally spreads caudally across the medial wall of the hemisphere to cover the territory between the roof flexure and the septohippocampal line (Smart, 1984). This sequence of elimination of the growth zone correlates well with the changing shape of the ventricular profile as depicted in Figure 6. In this Figure the boundaries of the watershed zone at successive ages are superimposed, indicating that growth of the ventricle ceases first rostrally and lastly at the temporal pole. Differential growth at the watershed zone may therefore make an important contribution to sculpting the general form of the lateral ventricle. For example, the noticeable angle to the ventricular profile occurring transiently at E14 as the dorsal border turns ventrally to form the caudal boundary (Fig. 1) seems to correspond to the position of the future adult occipital cortex as depicted in Caviness' (1975) map; the angle may represent a modest attempt at creating a posterior horn. Similarly, if growth continued at the residuum of the growth zone remaining at E16 (Fig. 1), an inferior horn could be produced. The inherently spiral course of the watershed zone may thus set the gross pattern of cerebral morphogenesis which results in a common tendency in mammals to produce a recurved temporal lobe when brain growth is scaled up.

Inspection of the rabbit and ferret series of embryonic brains indicates that in both species a growth zone of the type found in the mouse is present in early development. The degree of initial ballooning of the ventricle in the rabbit and ferret is greater, however, and after neuron release has commenced a broader growth zone persists for longer than in the mouse. This is consistent with the establishment of a greater area of ventricular layer available for generation of a greater area of cortex. In the rabbit and ferret, as in the mouse, there appears to be little increase in ventri-

cular area once the growth zone disappears, which suggests that in these three species cortical growth occurs mainly by increments received at the perimeter of the cortex.

SUMMARY

In sections of the prenatal mouse brain, sites of maximum area increase of the lateral ventricle were mapped onto reconstructions of the ventricular surface. This was done by identifying areas of ventricular layer where mitotic density was high and the adjacent intermediate layer either absent or thinly populated with neurons. It was assumed that in these areas, cell division was producing ventricular cells rather than neurons and that they were therefore gaining in area, whereas sites against which neurons were accumulating were either ceasing to increase in area or at least were increasing more slowly. Such an area occupied a zone at the junction between the medial and lateral telencephalic walls. The zone was eliminated during development in a rostrocaudal direction. It is suggested that modulation of growth along this zone may be an important factor in fashioning the form of the ventricular cavity.

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