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Migration of Neuroblasts through Partial Necrosis of the Cerebral Cortex in Newborn Rats–Contribution to the Problems of Morphological Development and Developmental Period of Cerebral Microgyria

Histological and Autoradiographical Study

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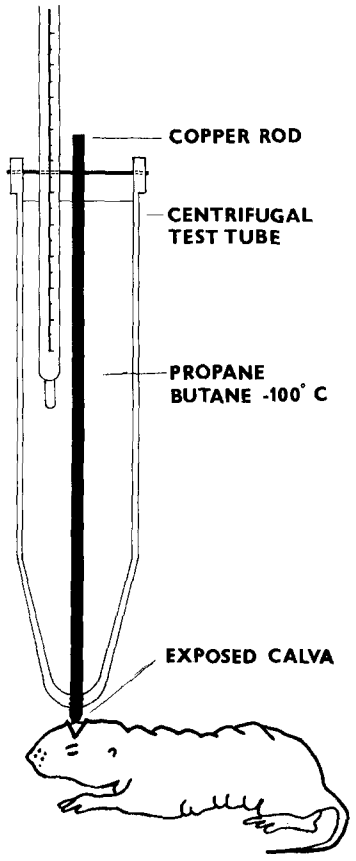
Summary. Focal aseptic necrosis of the cerebral cortex was induced in newborn rats by focal contact freezing. In the region of freezing the following changes took place: necrosis of the pia mater, total necrosis of the differentiating Ist–IVth layers of the cortex and partial necrosis of the Vth and VIth layers of the cortex. The VIth-b layer was mostly preserved. In partial necrosis the differentiating neuroblasts died. The capillaries and migrating neuroblasts destined for the Ist, IInd, and IIIrd cortex layer survived. They stopped only at the periphery of total necrosis and continued to differentiate. After healing, an atypical cortex, consisting of four layers, was formed in the necrotic region, quite similar to the microgyric cortex of four layers known in the human. After deeper necrosis a cortical microsulcus developed, also formed by a cortex of four layers. The newly formed first microgyric (molecular) layer had its histologic structure homologous to the molecular layer of the surrounding cortex. The second microgyric layer (outer, cellular one) was formed by neuroblasts assigned to the IInd and IIIrd normal layers, which migrated through partial necrosis and took up their final position at the periphery of total necrosis. The third microgyric (light) layer was formed by the original Vth layer destroyed by partial necrosis, and it contained single neurons and glial cells. The fourth microgyric layer was formed by the persistent deep part of the VIth layer. The four layered cortex was formed only during the time of neuroblastic migration. The findings are discussed in relation to the normal pathogenesis of cortical microgyria in children. The experimental findings show that the microgyric cortex is formed only during the course of neuroblastic migration.

Key words: Neuroblast migration and differentiation – Microgyria – Necrosis of the cerebral cortex – Autoradiography.

Current views on the period of formation and the mechanism of morphological development in human cerebral microgyria are based on an analysis of the stationary states found by histopathologic examination after autopsy and they are not quite uniform. Some authors (Crome, 1952; Crome and Stern, 1967; Dekaban, 1965; Ostertag, 1956) are of the opinion that microgyria develops in the course of neuroblast migration, which means by the end of the 16th week of intrauterine life (see review by Sidman and Rakic, 1973). There are not yet any reliable data to confirm these suggestions. The original explanation by Bielschowsky (1918, 1923) that the neuroblasts of the deepest layer of the microgyric cortex migrated last and the superimposed layer was homologous with the subcortical "U" fibre zone of white substance has repeatedly been found incorrect. Other authors (Nivenhuijse, 1913; Jacob, 1940; Bertrand and Gruner, 1955; de Leon, 1972; Levine et al., 1974; Richman et al., 1974), starting from a structural analysis of the microgyric cortex, suggest that microgyric development is a postmigration event, and place its formation within the 5th and 6th month of intrauterine life. In our experiments we studied the reaction of the cerebral cortex to focal necrosis in newborn rats. The cortex of newborn rats is rather immature. The neuroblasts destined for the IInd and IIIrd layers migrate in the deeper layers of the cortex as well as in the intermediate zone (Hicks and D'Amato, 1968) and for this reason the rat represents a very suitable subject for experiments aimed at a pathological study of the migration period. Our experiments show that microgyria may be formed after the cortex has been damaged during neuroblastic migration. The finding are presented in the following report.

Materials and Methods

Necrosis was induced by contact freezing, employing the method illustrated in the diagram. A copper rod (⌀ 3 mm × 100 mm, the



diameter of the point being 2 mm) was fixed, by means of a screw thread, to the bottom of a centrifugal test tube of plastic material. The test tube was filled with liquid propane-butane and was cooled by immersing the test tube in liquid N_2. After the propane-butane had reached a temperature of $-100°$ C the point was applied to the exposed calvarium in the area of the frontal or parietal lobe. The procedure took place under ether anaesthesia and the skin cut is stitched after the procedure. Microscopic changes were studied in 86 newborn rats at 1, 2, 3, 4, 6, 8, 16, 24 and 48 h and at 3, **4**, 6, 10, 16 and 21 days after freezing. Three pregnant rats were on one occasion given H^3-thymidin intraperitoneally (5 μCi/g), in order to label the migrating neuroblasts postnatally in the IInd and IIIrd layers of the cerebral cortex (Hicks and D'Amato, 1968). Focal necroses were induced 0.5–2 h after birth and the rats were decapitated after 1, 2, 3, 4, 5, 8, 10, 14 and 21 days. The brins were fixed in Bodian's solution. Paraffin sections (5 μm) were cut in the sagittal plane through the region of focal necrosis, and 5 sections were fixed to each glass slide. The slides were alternately employed for the following procedures: staining with haematoxilin-eosin, with cresylviolet; covering with Kodak autoradiographic stripping emulsion AR 10, exposure time was 6 weeks. The developed slides were stained additionally with haematoxylin-eosin. Some brains were cut in the coronal plane.

Results

After freezing for 1–2.5 s the changes were confined to the cortex. Focal damage to the cortex was evident at 4 h after freezing (Fig. 1). Forty-eighth hours after freezing the development of changes was rather advanced and it was possible to distinguish totally and partially necrotic regions.

Total necrosis was sharply defined (Fig. 2–7), being of conical and hemispherical shape and affecting the pia mater as well as the cortex below the pia mater. The cell contours were indistinct or shadowy, the nuclei of all cells were pyknotic or fragmented. On the periphery there were macrophages with phagocytized erythrocytes and single scavenger cells.

Partial necrosis surrounded the total necrosis (Fig. 2). After freezing for 1–2 s it involved the upper part of the VIth-a layer (layer denomination by Sugita, 1917). The differentiating neurons only were necrotic, their processes disintegrated, and their nuclei pyknotic. The capillaries were preserved and proliferated; outside the capillaries there were clusters of erythrocytes. In the forefront of the microscopic findings was the presence of migrating elements which did not show any regressive changes and had spindle- and drop-like nuclei with a few minute nucleoli as well as slightly basophilic long processes directed to the surface and short "basal" processes (Fig. 14). The migrating elements were regularly orientated in lines along their long axes (Figs. 7, 8, 10) and were reminiscent of beads on a taut string. In some lines the terminal parts of the cell processes made contact (Figs. 8, 10). At the interface of total and partial necrosis the migrating elements accumulated and formed clusters (Figs. 11–13). The majority of migrating cells were strongly labelled

Fig. 1. Cortex of the newborn rat 4 h after freezing. Area of total necrosis (*tn*), area of partial necrosis (*pn*). H.-E. ×46

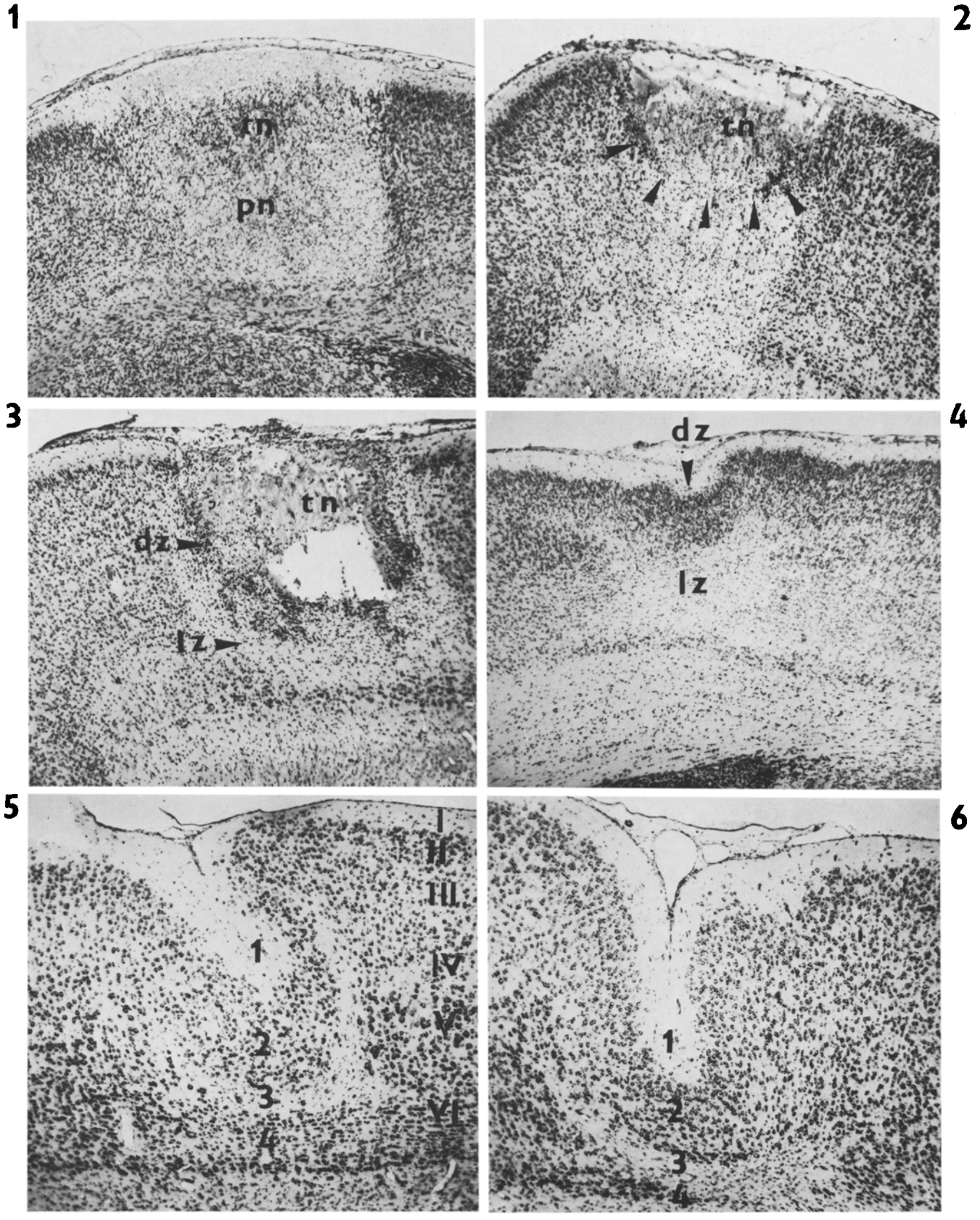
Fig. 2. Cerebral cortex 48 h after freezing. The boundary between the total and partial necrosis is indicated by the arrow-heads. H.-E. ×46

Fig. 3. Cerebral cortex 3 days after freezing. The area of partial necrosis consists of the dark zone (*dz*) and the light zone (*lz*). Dark zone is formed by the neuroblasts which stopped their migration in front of the total necrosis (*tn*). H.-E. ×46

Fig. 4. Cerebral cortex 10 days after freezing for 2 s. Atypical four-layered cortex. Dark zone (*dz*) forms the 2nd layer and the light zone (*lz*) forms the 3rd layer of the atypical cortex. The second layer of the atypical cortex is broader than would correspond to the IInd and IIIrd layers of the normal cortex. H.-E. ×32

Fig. 5. Cerebral cortex 14 days after freezing for 3 s. In the area of the formed total necrosis is situated the newly formed microsulcus, with the atypical, four-layered cortex. The 4th layer is identical with sublayer VIb of the normal cortex. Cresyl, violet. ×46

Fig. 6. Cerebral cortex 21 days after freezing for 3 s. Microsulcus with the atypical four-layered cortex. Cresyl, violet. ×46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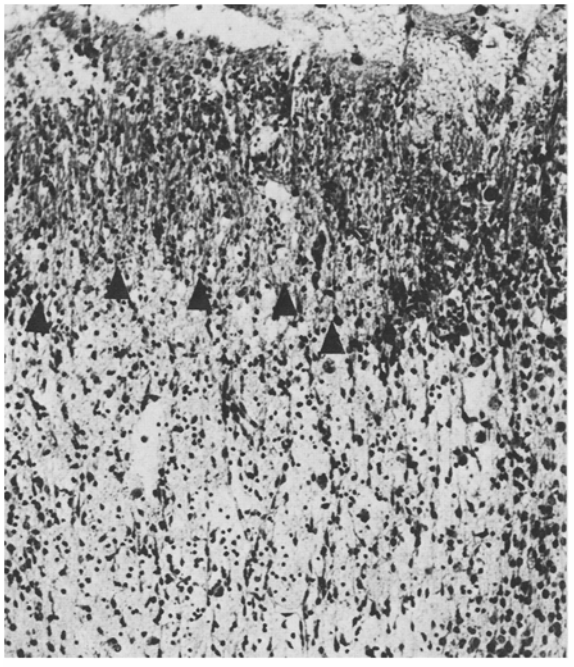

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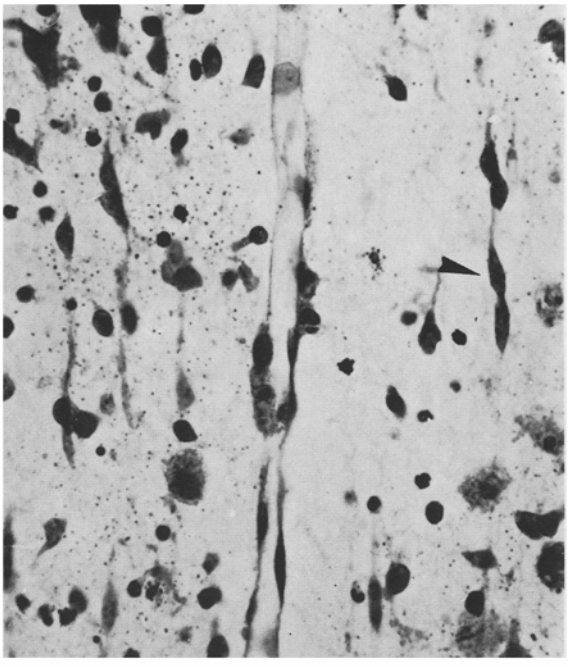

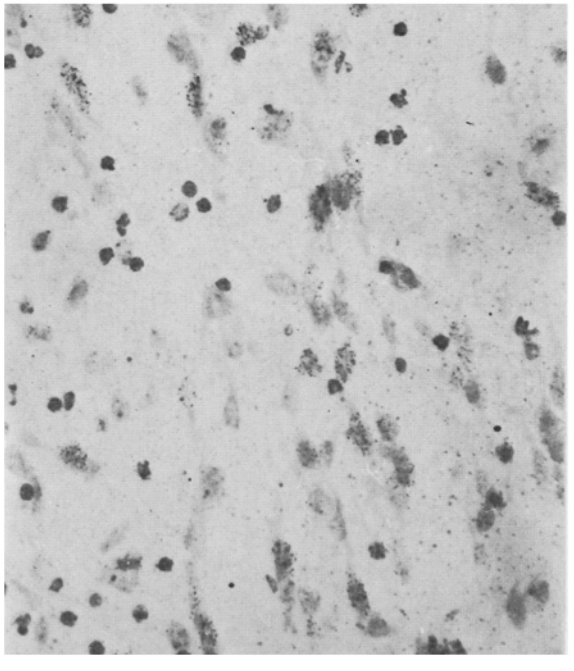

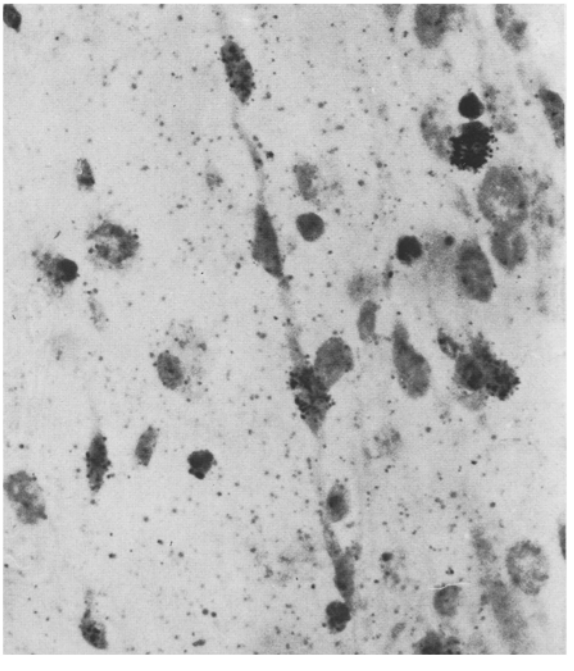

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Fig. 7. Cerebral cortex 2 days after freezing for 2 s. The boundary between total and partial necrosis is indicated by arrow-heads. The migrating neuroblasts form regular lines along their long axes. The differentiating neurons are necrotic, the whole area of partial necrosis appears to be light. H.-E. ×60

Fig. 8. Cerebral cortex 24 h after freezing. A detail of the light zone. Migrating neuroblasts do not show any regressive changes and are arranged regularly in lines. H.-E. ×460

Fig. 9. Cerebral cortex 24 h after freezing for 2 s. A detail of the partial necrosis (light zone). The majority of the migrating neuroblasts are strongly labelled with H^3-thymidine applied on the 20th day of intrauterine life. H.-E. ×460

Fig. 10. Cerebral cortex 24 h after freezing; the area of partial necrosis. The line of labelled neuroblasts is reminiscent of "beads put on taut string". Autoradiograph. H.-E. ×700

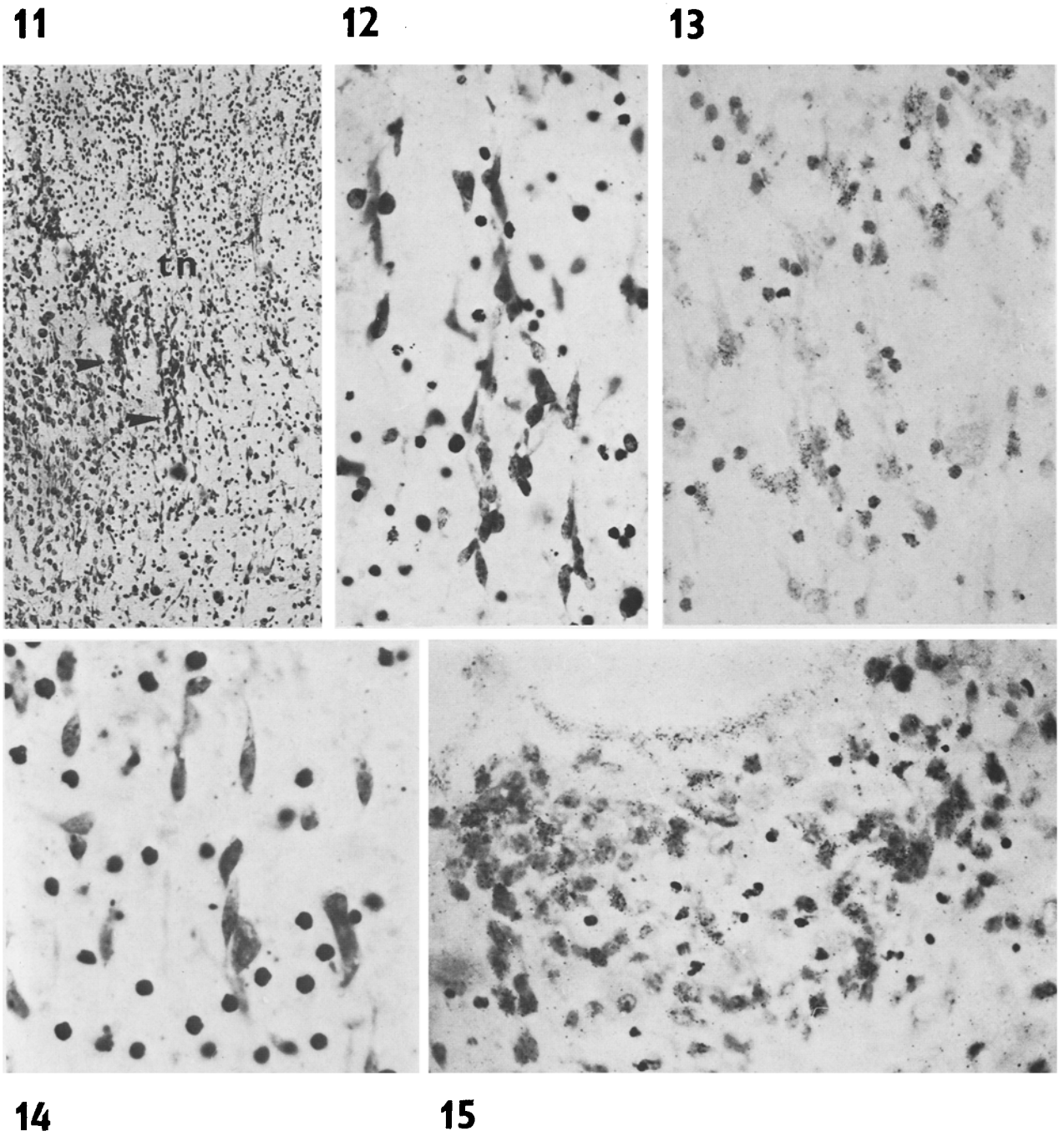

Fig. 11. Cerebral cortex 48 h after freezing for 2 s. The migrating neuroblasts accumulate and form clusters at the interface of the total and partial necrosis. H.-E. ×60

Fig. 12. A detail from a similar situation as in the Figure 11. Clusters of the migrating neuroblasts at the interface of total and partial necrosis. Cresyl, violet. ×460

Fig. 13. Clusters of neuroblasts are labelled with H^3-thymidine applied on the 20th day of intrauterine life. Autoradiograph. A similar situation as in Figures 11 and 12. H.-E. ×460

Fig. 14. The partial necrosis 24 h after freezing. The differentiating neuroblasts are pyknotic, the migrating neuroblasts continue to migrate. H.-E. ×460

Fig. 15. Cerebral cortex 3 days after freezing for 3 s. Immature neuroblasts, labelled with H^3-thymidine applied on the 20th day of intrauterine life, accumulate in the dark zone. An analogous situation to Figure 3. Autoradiograph. H.-E. ×460

with H^3-thymidine applied on the 20th day of intrauterine life (Figs. 9, 10, 13). Labelling the shape of the cells and the trend of differentiation unambiguously showed that these were migrating neuroblasts destined for the IInd and IIIrd cortical layers. In the deep part of partial necrosis there were sporadically distributed astrocytes with moderately labelled nuclei. In the intact cortex close to partial necrosis there were dilated capillaries with swollen endothelium and single macrophages which were also sporadically distributed over the whole partial necrosis. There were focal groups of erythrocytophages.

On the 3rd day after freezing the capillaries invaded the region of total necrosis and numerous phagocytic cells were present. The migrating neuroblasts stopped at the margin of the region of total necrosis and at the end of the 3rd day dark and light zones could be distinguished in the partial necrosis (Fig. 3).

A dark zone was formed by densely packed immature neuroblasts which were labelled with H^3-thymidine (Fig. 15) in the same way as the immature neuroblasts in the IInd and IIIrd layer of the intact surrounding cortex were labelled. The neuroblasts of the dark zone were evidently assigned to the IInd and IIIrd layer of the cortex which was destroyed by focal necrosis. They had taken up a dystopic position and continued in their differentiation.

A light zone contained sporadically distributed astrocytes, isolated neurons and a small number of migrating neuroblasts. This zone continued without a break into the Vth and VIth-a layers (Figs. 3, 5, 6). Below the light layer was the persisting part of the VIth cortical layer. By this development the basis of an atypical cortical arrangement was laid, consisting definitely of 4 layers (Figs. 4–6). In the figures we have indicated the layers of the atypical cortex with Arabic numerals as opposed to the normal cortex of six layers, which we have indicated with Roman numerals according to convention. In the dark and the light zones there were numerous proliferating capillaries and macrophages. The phagocytic cells and the cellular elements of the capillaries were not labelled with H^3-thymidine. The pia mater was slightly thickened and penetrated by newly formed capillaries, macrophages and fibroblasts. On the 4th day after freezing numerous capillaries and fibroblasts grew into the total necrosis from the pia mater and the partial necrosis. Numerous macrophages were present in the total necrosis but mostly in its peripheral part. Between the total necrosis and the dark zone was a thin layer, mostly consisting of the peripheral parts of apical processes of pyramidal cells. This thin layer later developed into a newly formed molecular layer (the first layer of the atypical cortex – Figs. 16, 17, arrow head). The dark cellular layer with partial necrosis (the 2nd layer of the atypical cortex) merged with the IInd and IIIrd layers of the intact cortex. The neuroblasts deposited there were equally differentiated cytologically and labelled with H^3-thymidine applied on the 20th intrauterine day (Fig. 17) like the neuroblasts of the IInd and IIIrd layer. They had the shape of bipolar, immature neuroblasts; their apical processes grew and mostly pointed towards the cortical surface; the cytoplasm was basophile (Fig. 16). In the 2nd and 3rd layers of the atypical cortex there were sporadically distributed macrophages. In the surrounding cortex there were dilated capillaries and there were numerous perivascular mitoses. The pia mater was thickened, vascularized, with numerous proliferating elements of fibroblast type.

The Development of an Atypical Cortex from 15th to the 14th Day. The total necrosis was absorbed and gradually replaced by connective tissue. Between the 8th and 12th days the tissue diminished and on the 14th day there remained after shallow necrosis (freezing for 2 s) the thickened pia mater; after deeper necrosis (freezing for 3 s) the tissue formed a strip of varying width projecting from the pia mater into the newly formed microsulcus (Figs. 5, 6). The differentiation of the newly formed first (molecular) layer went on; on the 10th day its structure was identical with the molecular layer of the surrounding cortex. From the 5th–8th day the immature neuroblasts gradually changed to late and mature neuroblasts (terminology Peters and Feldman, 1973). From the 8th day, basal dendrites gradually grew out, the volume of the neuropil of the second layer in the atypical cortex was less voluminous than the volume of the neuropil of the IInd and IIIrd layer in the normal cortex. From the 10th postnatal day these differences disappeared. The differentiation of the second layer of the atypical cortex into sublayers, which might correspond to the IInd and IIIrd layer of the normal cortex, took place. For the most part the second layer of the atypical cortex was broader than would correspond to the IInd and IIIrd layers of the normal cortex together, and the number of neurons seemed to be greater (Fig. 4). If the findings were unambiguous. the necrosis should have stimulated the germinative layer to increased production of neuroblasts. However, we did not apply quantitative evaluation or any other such procedure in the experiment, and the above findings may be only the subject of discussion. The light third layer of the atypical cortex mostly replaced the Vth normal layer and in some cases also layers V and VI a (Fig. 4). Layer V, and sometimes layers IV and VI a, were not continuous after the focal necrosis had healed (Figs. 4–6). The third layer

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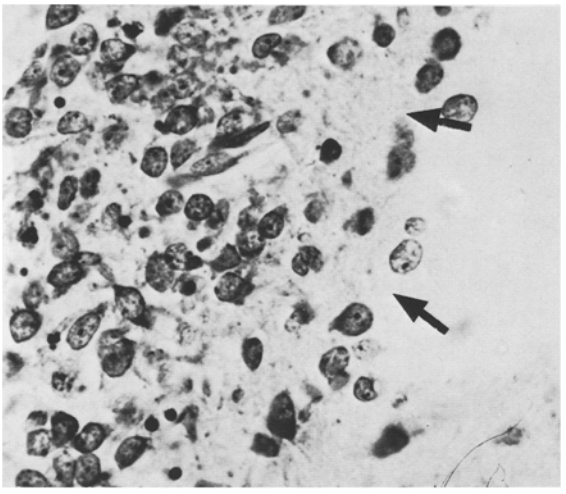

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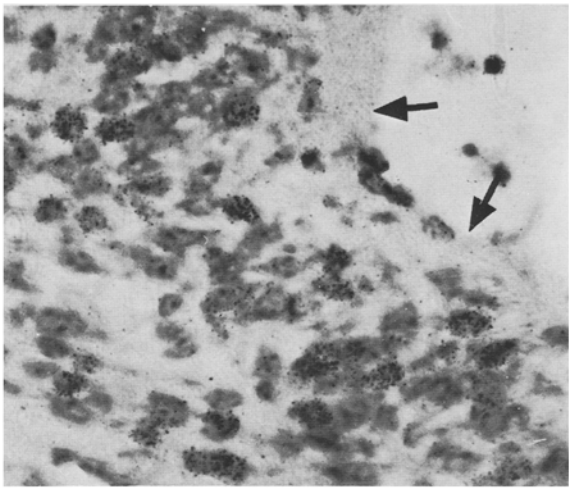

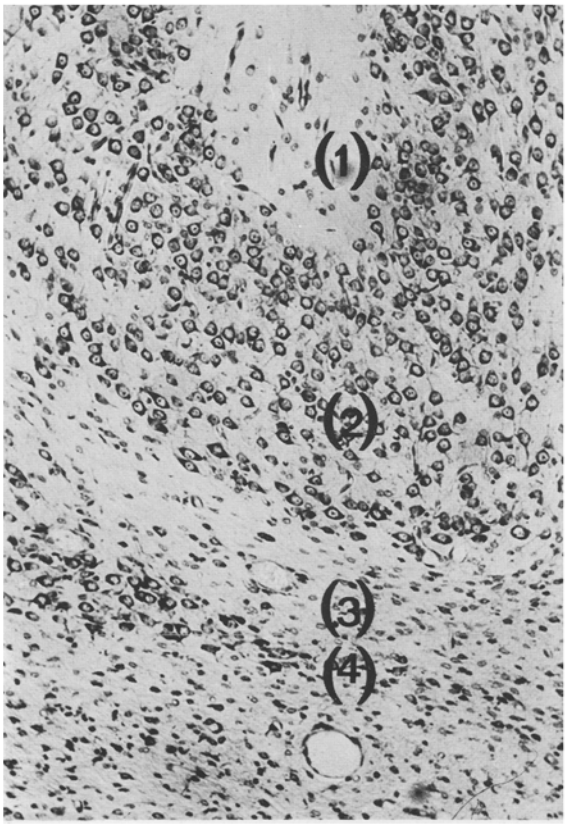

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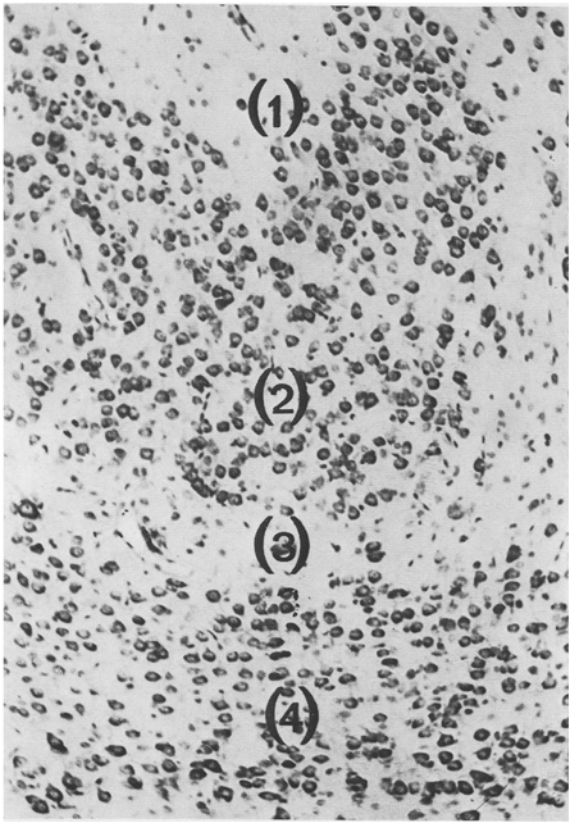

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Fig. 16. Cerebral cortex 4 days after freezing for 3 s. Differentiating neuroblasts of the dark zone. Between the total necrosis and the dark zone the newly formed molecular layer is differentiating (arrow-heads). H.-E. ×460

Fig. 17. Cerebral cortex 4 days after freezing for 3 s. The differentiating neuroblasts are labelled with H^3-thymidine applied on the 20th day intrauterine life. Autoradiograph. H.-E. ×460

Fig. 18, 19. The atypical cortex of the microsulcus. Details of the situation in Figures 5 and 6. See text. Cresyl, violet. ×120

consisted of glial cells and in some cases it contained single persisting neurons (Fig. 5). The fourth layer of the atypical cortex was formed by neurons of sublayer VI b, sometimes by the deep parts of layer VI a which had not been damaged and destroyed by partial necrosis (Figs. 3–6, 18, 19). Between the 10th and 14th days after freezing the remnants of the exudative reaction disappeared. In the region where focal necrosis was induced we found only a slightly deepened four layer cortex and thickened pia mater (Fig. 4) or a microsulcus (Figs. 5, 6). The microsulcus was formed after deeper necrosis by the borders of the defect closing up. The connective tissue which filled the defect after partial necrosis was reduced to a narrow strip placed along the axis of the newly formed microsulcus. The cortex of the microsulcus also showed an atypical four layer structure.

Discussion

Our present knowledge of the embryonal development of the laminar arrangement of the cerebral cortex in mammals is based on the autoradiographic pursuit of the distribution of neurons labelled with H^3-thymidine. It has been found that the cerebral cortex develops according to the rule "inside-out" (Angevine and Sidman, 1961), which has been repeatedly confirmed in mice (Langman and Welch, 1967), in rats (Berry and Rogers, 1967; Hicks and D'Amato, 1968; Haas et al., 1970) and in golden hamsters (Shirama and Langman, 1973). Quite an analogous development is suggested for the embryonal development of the human brain (Sidman and Rakic, 1973). The cerebral cortex of the newborn rat is rather immature and is therefore suitable for the experimental solution of some problems arising from human neuropathology of the intrauterine and perinatal periods. Using autoradiography, it has been found that most neuroblasts assigned to the IInd and IIIrd layer are formed by mitotic activity in the subventricular zone on the 20th intrauterine day. They occupy their definite position during the first 5 postnatal days (Hicks and D'Amato, 1968). However, in newborn rats the majority of neuroblasts migrate into even deeper layers of the cortex and into the intermediate zone. In our experiment we destroyed, over a defined area of the cortex, the region to which neuroblasts were migrating. The migrating cells were thus not able to occupy their physiological position and were forced to finish their migration in an atypical topographical position and to react to abnormal conditions. In our experiment we labelled the neuroblasts with H^3-thymidine on the 20th intrauterine day and followed their migration using autoradiography. In this way we were able to follow the progress of migration in order to find the final position of the cells and to differentiate the migrating neuroblasts and glial cells. The results unambiguously showed that focal, aseptic necrosis does not stop neuroblasts migrate even through partial necrosis as far as the neighbourhood of focal necrosis and in the dystopic region they continue to differentiate, which results in the same cell type as if the neuroblasts were differentiated in the position of their original destination.

Attention should be paid to the behaviour of migrating neuroblasts in the region of partial necrosis. This region is characterized by the destruction of most neurons, the persistence and proliferation of capillaries, and by macrophage reaction. We considere the formation of partial necrosis, respecting the anatomical findings of Bär and Wolff (1973a, b), to be the consequence of hypoxia. Necrosis completely destroyed the pia mater and the superficial part of the cortex. The layers situated beneath such a pia mater were totally dependent on the blood supply from the surrounding intact cortex and from the subcortical vascular network. Such a blood supply was insufficient. Layer VI b, which was left intact in most animals, does not depend on a blood supply from the pial vessels. The hypoxia affects, most of all, the energetically more demanding late neuroblasts and maturing neurons, but it does not damage the migrating neuroblasts. Our findings show that the migrating neuroblast is not a very demanding cell regarding the supply of nutrition and oxygen. The narrowness of the cytoplasm of the cells and the few organelles support this (Peters and Feldman, 1973; Calley, 1968; Rakic, 1972).

Using the Golgi method, the existence of radial fibres passing across the whole wall of the developing hemispheres (Cajal, 1911) has been proved. Rakic (1971, 1972) showed, by electron microscopy, the contact of migrating neuroblasts with radial fibres which he considered as a leading line. The radial fibres start from the cellular soma of the leading spongioblasts deposited in the subventricular zone. Hattori and Fujita (1974), using scanning electron microscopy, found radial fibres in the brains of chickens and human foetuses to be part of the original neuroepithelial cells, which they call matrix cells and they describe the radial processes as "radial processes of matrix cells". These authors suggest that 5–6 radial processes group into bundles. They attribute to these bundles the position of leading sructures in neuroblastic migration and a leading role in the column arrangement of the cerebral cortex. In our experiment the migrating neuroblasts in the region of partial necrosis were regularly arranged in lines one above another, quite in agreement with the findings of the above authors. The disappearance of differentiating neurons in partial necrosis within 24–48 h is an experimental situation very well suited to the study of the migration process. The neuroblastic migration in partial necrosis is very distinct (Figs. 7–14); one line of the cells corresponds without any doubt to migration along one leading radial fibre or a bundle of fibres (Figs. 7, 8, 10). The formation of clusters (Figs. 11–13) at the periphery of total necrosis is probably homologous with single column formations of neurons or with a vertical dendrite bundle of the mature cortex. The existence of vertical bundles of apical den-

drites of pyramidal cells has been shown by von Bonin and Mehler (1971). We can deduce from our findings that the leading fibres fulfil their function even in partial necrosis. The radial fibres, like migrating neuroblasts, are rather resistent to an insufficient supply of oxygen and other metabolites. The destruction of a defined section of radial fibres does not affect the functional properties of the remaining section of fibre and cellular soma belonging to it.

The findings of neuroblastic migration in the region of partial necrosis may be used to explain the morphological development in some cases of human cortical microgyria. In the neuropathological findings of the intrauterine period partial necrosis is often to be seen; it mostly takes place as a consequence of local or total circulatory defects.

As has already been mentioned, the developmental mechanism of microgyria is not yet known, nor is the precise time of the intrauterine month at which microgyria develops clear. The arguments by which some authors (de Leon, 1972; Levine et al., 1976; Richman et al., 1974) prove the postmigrational development of microgyria rely on the following findings: 1. Microgyria is not usually connected with subcortical dystopia, which may be expected in migration defects. Subcortical dystopia as a rule takes place with lissencephaly and pachygyria, which are based on an abnormal migration process (Stewart et al., 1975) and were experimentally induced by irradiating the developing brains of rats with developed neuroblastic migration (Rigs et al., 1956). 2. Lamination of the microgyric cortex has some features in common with the normal cortex. The most superficial (molecular) and the most deeply situated layers, of a four layer microgyric cortex have an structure identical with the most superficial (layer I) and the most deeply situated layers (layer VI) of the normal cortex. 3. The third microgyric (light) layer corresponds in topography and cytology of persistent neurons to the normal Vth layer. It is predominantly formed of glia and is a region where the maximum destruction should be assumed to have taken place. The authors suggest that the layer thus damaged may hinder migration to superficially situated layers because of the "inside-out" development of the cortex. 4. In the second microgyric layer individual cases of sublamination and structure analysis show types of neurons homologous to the IInd, IIIrd and IVth layer of the normal cortex.

Our experimental findings do not agree with these arguments. 1. In the region of partial necrosis the differentiating neuroblasts and neurons can be completely destroyed without any quantitative or morphological change in neuroblastic migration. 2. The neuroblasts migrating through partial necrosis align in an atypical layer (Figs. 4–6) and are connected at the periphery with the corresponding layer of the intact cortex, and they continue in their morphological differentiation. 3. Even after complete destruction the molecular layer can be completely restored in the period of neuroblastic migration. 4. The deepest cortical layer (the VIb layer in the rat) is not totally dependent on a blood supply from the pia mater; it is formed first in the "inside-out" development of the cortex; it can persist and form the IVth layer of the microgyric cortex even in the presence of pathological changes in the blood supply from pial vessels. Our experimental finding show that the microgyric cortex of four layers may develop after heavy damage to the immature cortex at the time of neuroblastic migration.

Figures 5 and 6 illustrate a microsulcus formed under such conditions. After focally freezing the cortex in the newborn rat (layers II and III have not been formed yet) the molecular layer (I) and the IVth layer were destroyed by total necrosis. Partial necrosis destroyed differentiating neuroblasts and neurons (layers V and VIa). In the newly formed microsulcus (Figs. 18, 19) the cortex consisted of four layers (Figs. 5, 6). The first (molecular) layer was histologically homologous to the intact Ist layer of the surrounding cortex, but it was formed in the period 5–10 days after freezing. The second layer consisted of neurons homologous in shape to the neurons of the IInd and IIIrd layer of the normal cortex. These neurons in the stage of neuroblastic migration migrated through partial necrosis, the position of which was defined by the third (light) layer consisting of glia and possibly of isolated persistent neurons from the Vth layer. Deepest was situated the fourth layer, homologous with the deepest layer VI of the intact cortex. The histological structure of the microsulcus was evidently very similar to the four-layer cortex of microgyria in the human. It is probable that the development of the microgyric cortex in children takes a course similar to that which we described in our experiment. The interruption or decrease of the blood supply through the vascular network of the pia mater may for a short time induce a partial necrosis of the superficial layers of the immature cortex, in a way quite analogous to our experiments, as well as the subsequent development of microgyria. All authors who have studied microgyria in children suggest a defect in blood circulation as the primary aetiological factor.

If we accept this explanation, microgyria in children takes place before the IInd and IIIrd layer of the cortex have been formed, namely in the 4th month of intrauterine life. The development of microgyria after the completion of migration is not probable, even after considering the findings of Cowen et al. (1970), who induced focal cortical necrosis using an electric current in 5 day old rats, i.e. after the end of neuroblastic migration. Various reparative reactions took place, but the development of atypical stratification was not found. In our laboratory we produced the some changes as did Cowen et al. (Dvořák, 1976).

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