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The Mechanism of Arrest of Neuronal Migration in the Zellweger Malformation: An Hypothesis Based upon Cytoarchitectonic Analysis*

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Summary. The brain from a clinically typical case of the Zellweger malformation, dying at 5 weeks of age, is studied in general histologic preparations and in Bielschowsky impregnations. Cytoarchitectonic abnormalities, typical of previously described cases and unique to the Zellweger malformation, are observed in the cerebral hemispheres, the cerebellum and the inferior olivary complex. Neocortical malformation is associated with neuronal heterotopia. The impediment to neuronal migration has affected, principally, neurons destined for the outer cortical layers. The impediment to migration appears to be only partially effective in that a portion of neurons destined for cortical layers II and III are in their normal laminar positions whereas others lie in heterotopic intra-cortical and subcortical positions. The cerebellar cortex in this malformation is distinctive for large Purkinje cell heterotopias, subjacent to intact Purkinje and granule cell cortical laminae. Bielschowsky preparations identify multiple primary dendritic processes extending from the somata of heterotopic Purkinje cells. Finally, there are laminar discontinuities, unique to this malformation, in the principal nucleus of the inferior olivary complex. By analogy with the cerebellar cortical malformation in the weaver mutant mouse, the Zellweger cortical malformation may result from incomplete disruption of neuronal migration caused by circulating toxic metabolites.

Key words: Zellweger malformations – Migration arrest – Developmental pathology.

The Zellweger syndrome in man comprises a complex array of developmental abnormalities which involve the central nervous system as well as the liver, kidneys and other viscera (Bowen et al., 1964; Smith et al., 1965; Passarge and McAdams, 1967; Optiz et al., 1969; Vuia et al., 1973; Danks et al., 1975; Liu, 1976; Agamanolis et al., 1976). It may arise consequent to an autosomal recessive mutation (Volpe and Adams, 1972). If so, these varied structural abnormalities may be the direct or indirect consequences of a single molecular abnormality. Malformation of the central nervous system is associated with gyral abnormalities and subcortical neuronal heterotopias. It may be inferred, therefore, that development of the central nervous system is disrupted at least as early as the second trimester of gestation, that is, during the migratory epoch (Volpe and Adams, 1972; Garzuly et al., 1974).

The present study is a pathological-anatomical analysis of a brain from a clinically typical case of the Zellweger malformation. Attention is focused upon neuronal pattern, particularly the relative positions of neurons of different classes and the character of the radial assembly of neurons in malformed neocortex. Certain features of cell pattern suggest that the disorder of neuronal migration in the Zellweger malformation, though unique in man, may be similar in its mechanism to the disorder of migration causing the cerebellar croitcal malformation in the weaver mutant mouse.

Materials and Methods

The brain and the spinal cord were fixed in 10% formalin and then cut into coronal slabs less than 2 cm in width. Slabs at interrupted intervals were embedded in celloidin and sectioned at 20 μ. Additional tissue blocks, embedded in paraffin, were sectioned at 8–10 μ. Celloidin and paraffin embedded tissue were stained with Nissl,

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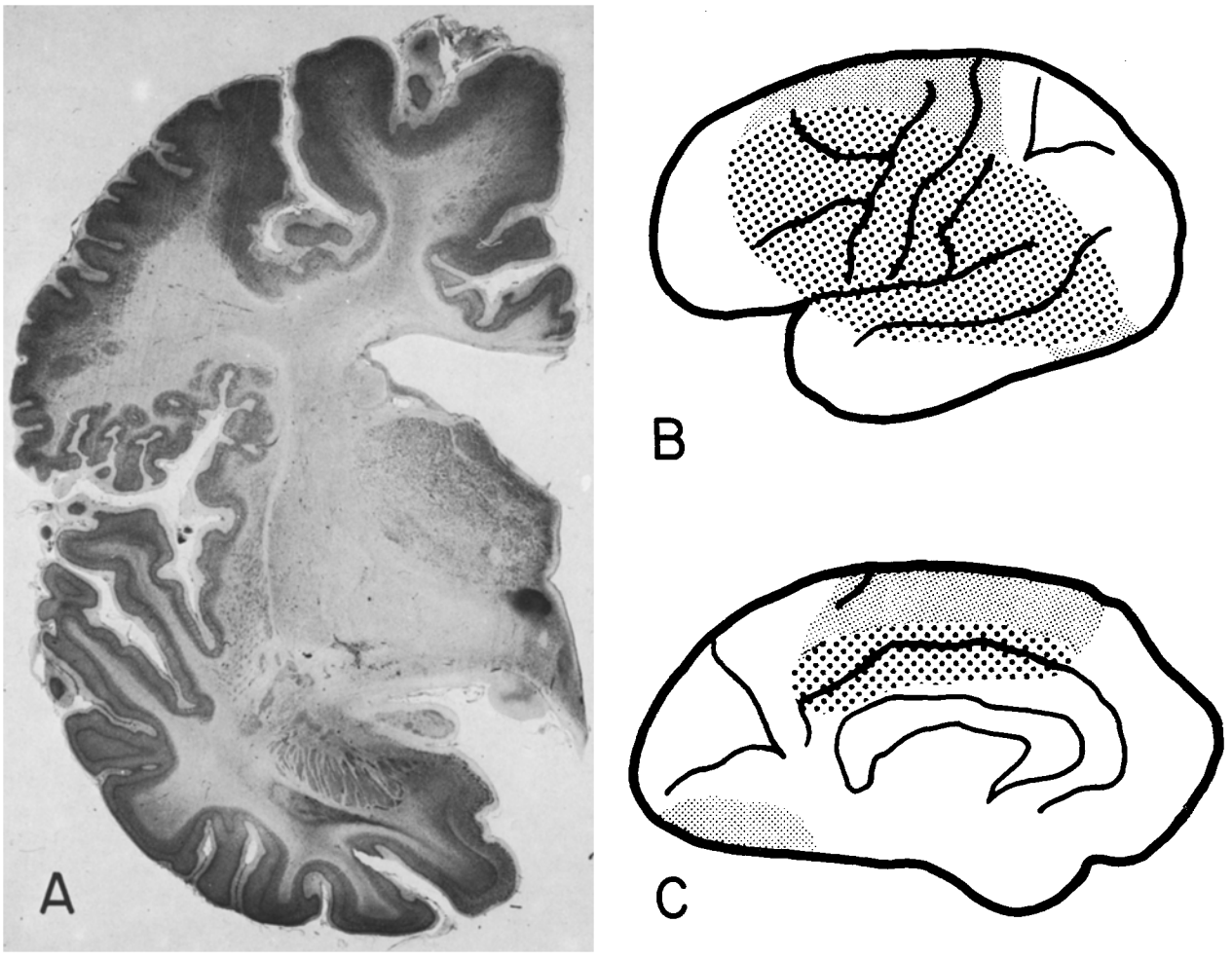

Fig. 1. A Cerebral hemisphere at mid-sylvian level. Gyral width is increased dorso-medially but decreased laterally. Heterotopic neurons lie subjacent to abnormally convoluted cortex. Coronal plane, × 2.2, cresyl violet. Schematic views of lateral (**B**) and medial (**C**) aspects of cerebral hemisphere. Fine stippling corresponds to area of increased gyral width and course stippling to areas of decreased gyral width

Heidenhain, H.-E., and PTAH methods. Finally, formalin fixed tissue, sectioned at 30 μ on a freezing microtome was subjected to the following stains and reactions: Bielschowsky, Scharlach R, oil red O, Sudan black, Nile blue sulfate and PAS.

Case History

The patient, a Caucasian male infant, was the first-born child of normal parents. He was born at full term. Pregnancy and delivery were uneventful. Weight at birth was 2890 g, length 52 cm, and head circumference 35 cm. The suck reflex was poor. There were axial hypotonia, micrognathia, equino-calcaneovarus foot deformities and the testes were undescended. Jaundice was noted at birth. A serum bilirubin level of 15.84 mg%, predominantly indirect, was recorded on the fifth day of life, but decreased towards normal values over the next 3 weeks. Additional laboratory examinations performed during the first weeks of life included a serum iron of 154 μg%, a normal chromosomal pattern and normal nerve conduction velocities. Punctate calcifications in the scalpulo-humeral and coxo-femoral joints, and in the patellae were observed in X-rays. The cinical state prior to death on the 35th postnatal day was notable for extreme hypotonia, apathy, dysphagia, and, ultimately, hepatomegaly. There was no family history of similar disease.

General Autopsy

Reviewed briefly, the general pathologic findings included intrahepatic cholestasis associated with hepatic fibrosis and hemosiderosis, dilation of intrapancreatic ductules, polycystic kidneys, lung cysts and emphysema.

Gross Examination of the Brain

The fresh brain weighed 460 g. The size and general shape of the cerebral hemispheres were normal. There were abnormalities in the cerebral convolutional pattern (Fig. 1) which were bilateral, and approximately symmetrical. Convolutions in opercular regions of the frontal, parietal and temporal lobes, as well as within the insular regions, were increased in number and of decreased amplitude (Fig. 1 A). The degree was less than that of "classic four-layered" microgyria, however. Superiorly over the fronto-parietal convexities, the microgyric cortex merged with a more "pachygyric" cortex, that is, cortex where convolutions were abnormally broad and reduced in number. Otherwise the gyral patterns of the cerebral hemispheres were normal. The corona radiata, subjacent to microgyric and pachygyric cortex, was reduced in volume. The lateral ventricles were mildly enlarged. There were no grossly evident ab-

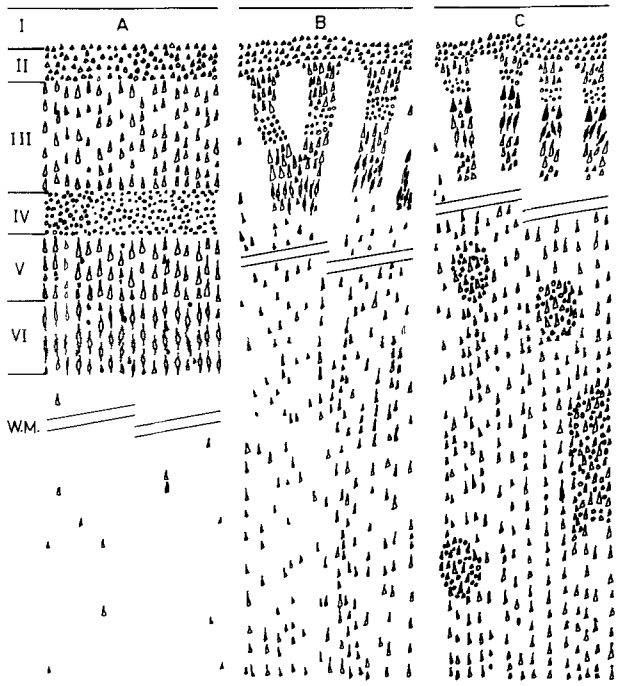

Fig. 2. Schematic representation of cell pattern in normal (**A**), microgyric (**B**), and pachygyric (**C**), neocortical regions. Roman numerals to left correspond to normal cortical layers. W.M. and horizontal slashes mark junction of cortex and central white matter (**A**) or heterotopic subcortical neuronal fields (**B** + **C**). See text for details

normalities of the brainstem, cerebellum, leptomeninges or major cerebral vessels.

Cytoarchitectonic Patterns

Cerebral Cortex

Normally convoluted cerebral cortex has a normal cytoarchitectonic pattern (Fig. 2 and 3A). Cortical neurons are entrained in radials with polymorphic, large pyramidal, granular, medium to large-sized and small pyramidal neurons, corresponding to cortical layers VI-II, repectively, stacked in ascending succession. Adjacent radial groupings of neurons are equally spaced, as in the normal infant brain. Homologous cell classes on adjacent radials are in tangential register, imparting the normal pattern of cellular lamination. In normal fashion, at the level of cortical layers VI, V and III, large cells entrained along a single radial overlap each other by no more than half the length of the cell body. The overlap is greater among the smaller neuron classes, ranging from 2--4 cells for the granule cells and small pyramids of layers IV and II, respectively.

The cytoarchitecture of microgyric and pachygyric cortex is abnormal, and subcortical heterotopias underlie the region of cortical abnormality. The abnormalities may be characterized in terms of the relative positions of neuronal classes as well as the patterns of arrangement of neurons into radial groups. In general, it appears that many cells found normally in the outer cortical layers are distributed, instead, in heterotopic position within the deep cortical layers, and in the corona radiata below the cortex. The anomaly is milder in microgyric cortex (Figs. 2B and 3B) where the complement of small and medium-sized pyramidal cells in normal positions in layers II and III, respectively, is only mildly reduced. In pachygyric cortex (Figs. 2C and 3C), by contrast, layers II–IV, are defined with difficulty and a stratum of large pyramidal cells typical of those found normally in layer V lies superficially in the cortex just below the molecular layer. To a greater extent in pachygyric than in microgyric cortex layers V and VI are more than normally cellular, because of an increased complement of small and medium-sized pyramids such as are normally found in layers II and III. Especially in pachygyric cortex such cells, as well as larger neurons, are distributed throughout an uninterrupted subcortical heterotopic field which extends through the corona radiata (Figs. 2B, C and 3D). Particularly in the pachygyric region, cells similar in size, shape and staining character to the granule cells which normally form layer IV, are aggregated into spherical to cylindrical masses which continue through layers V and VI and into the subcortical heterotopic field.

In both microgyric and pachygyric cortex neurons in normal relative intracortical positions, as well as those in heterotopic intracortical and subcortical positions, are entrained into radials like their homologs in normal cortex. The patterns of radial assembly are anomalous, however (Figs. 2B, C and 3B, C). Particularly at deeper cortical levels, as many as 2–3 pyramidal cells may be abreast of each other within a single radial group. Further, as many as 3–8 adjacent radial groups may be clustered together. The intervals separating adjacent clusters are equivalent to the width of 4–6 radial groups. This pattern of "fasciculation" of radial groups confers a radially striated appearance to the anomalous cortex. Particularly in the microgyric region where the degree of heterotopia is less, it is evident that cells of the same class are in register within a group of radials but those of adjacent groups are out of register. As a consequence. the boundaries between cell layers follow an irregular, step-like course from one fascicle of radial groups to another. In favorable sections, it may be recognized that the cells of granular appearance in subcortical aggregates are also radially entrained and intermixed with pyramidal cells along the same radial formation.

Allocortical formations, and subcortical nuclear structures of the forebrain, with the exception of the claustrum, appear normal. The claustrum, though lying in normal position deep to the insular and piriform cortex, is abnormally cluttered with heterotopic neurons (Fig. 1A).

Cerebellum, Brainstem and Spinal Cord

In the cerebellum, heterotopic neuronal aggregates are scattered in a wide arc peripheral to the fundus of the dentate gyrus. Most are small spherical or disc-shaped collections of Purkinje cells embedded in dense plexiform neuropil (Fig. 4A). The heterotopias are, in general, completely surrounded by the fibers of the subcortical central white matter. However, a few large staghorn-shaped aggregates lie close to and parallel the cortex of the lateral ansiform, paramedian and biventer lobules. Favorable Bielschowsky impregnations reveal that heterotopic Purkinje cells have multiple large primary dendritic processes (Fig. 4C). Purkinje cells, though the predominant, are not the exclusive neuronal element in these larger heterotopias. Particularly near the base of folia, the heterotopias may become continuous with the internal granular layer of the cortex. Where this occurs, the subcortical heterotopic mass may contain many granule cells clustered among the Purkinje cells (Fig. 4B). In such instances aggregates of Purkinje cell somata and granule cells are interspersed with areas of cell-sparse plexiform neuropil. The structure of the cerebellum, including cortex and central nuclear masses, is otherwise unremarkable. It is of note that where the cortex overlies heterotopias there are no discontinuities in either the Purkinje cell or the granule cell layers.

With the exception of the inferior olivary complex the brainstem is normal. All nuclear subdivisions of the inferior olivary complex are in normal position relative to each other. However, there are remarkable complete discontinuities in the cellular lamella of the principal olivary nucleus (Fig. 5A, B). These discontinuities are in

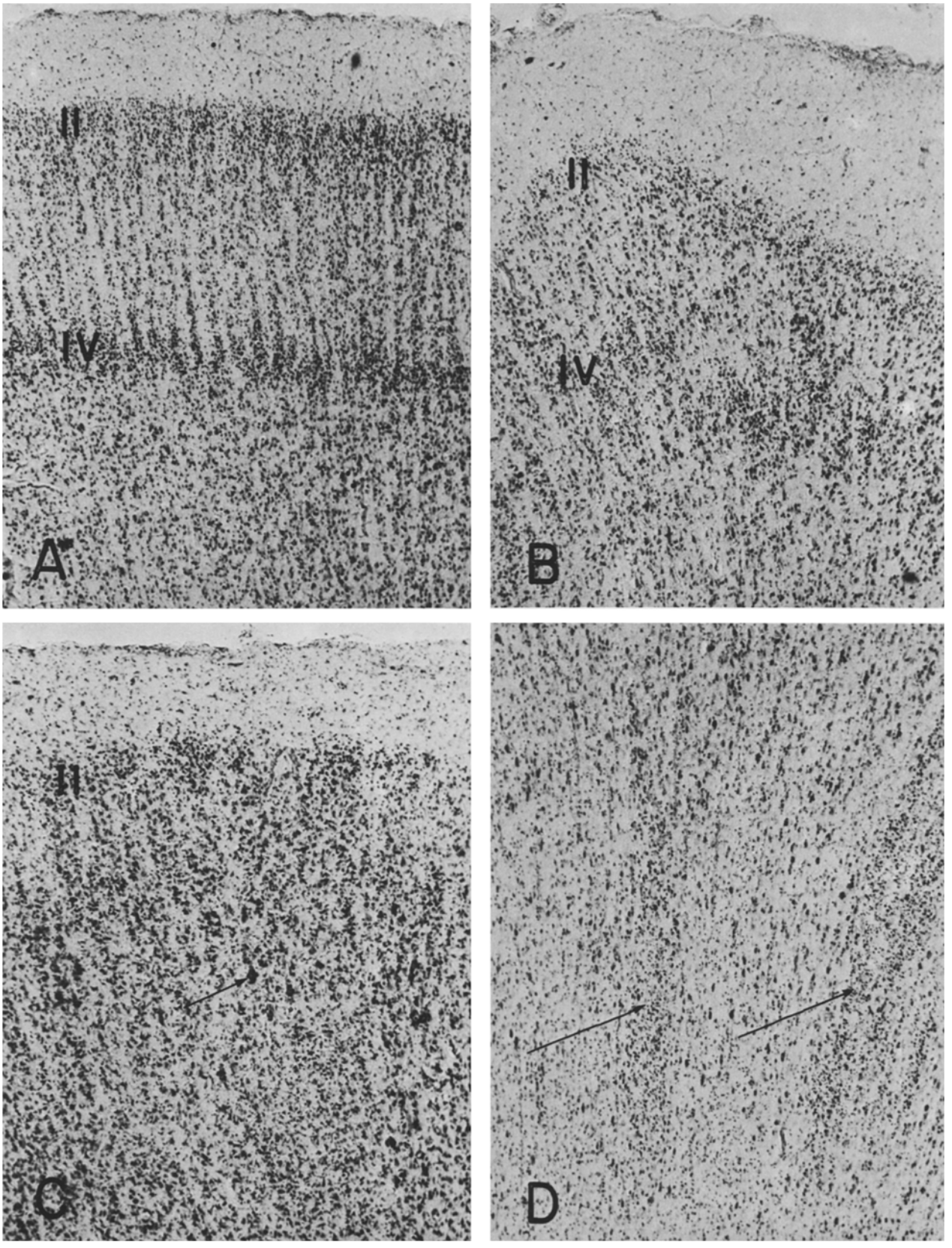

Fig. 3. Neocortex in normal (**A**), microgyric (**B**), and pachygyric (**C**), regions. Roman numerals II and IV are at levels of corresponding cortical layers. Arrow in C indicates a layer V, possibly Betz, pyramidal neuron. **D** Heterotopic neurons subjacent to pachygyric cortex. Columns of "granular" cells (see text) are marked by arrows. A–D cresyl-violet, ×68

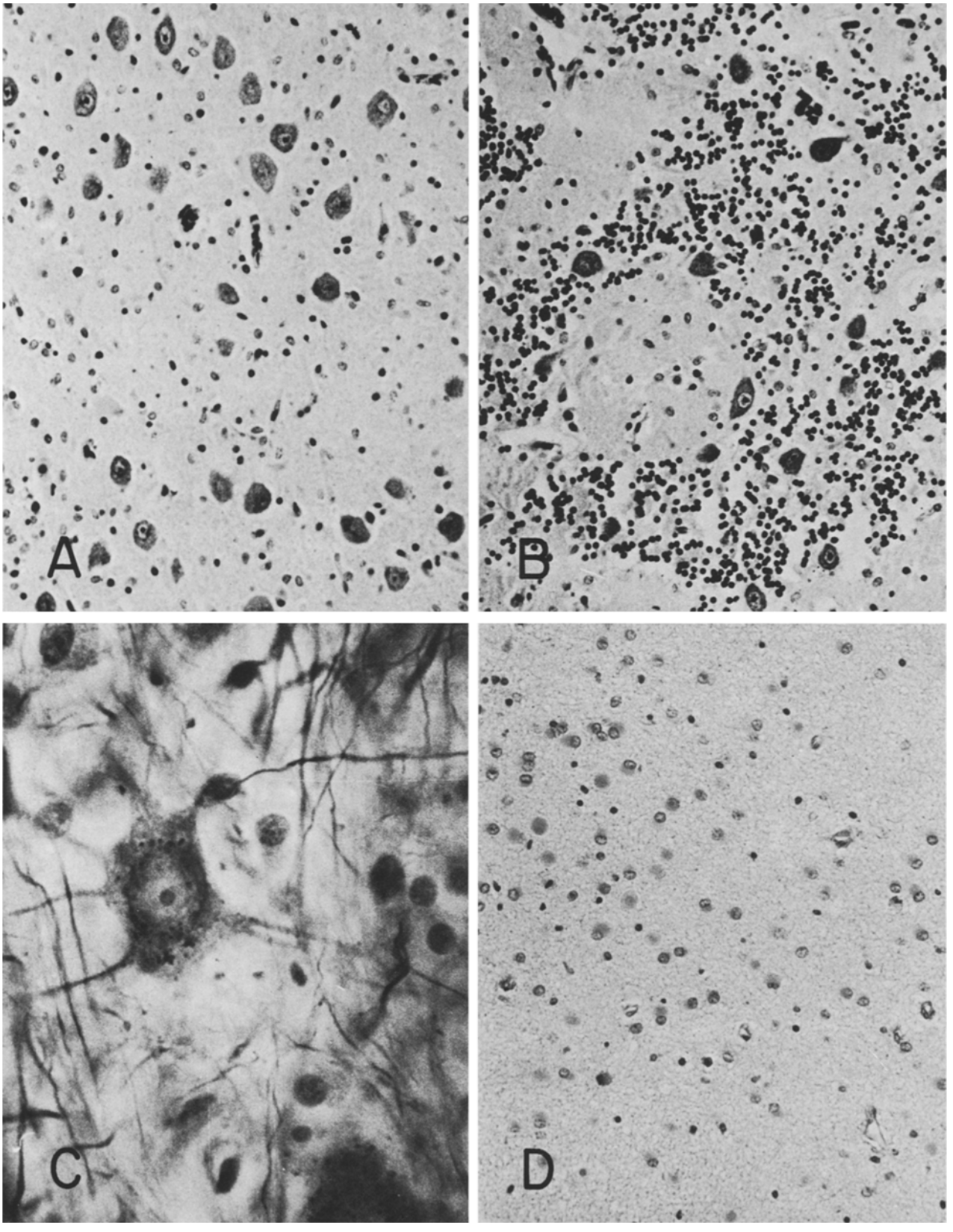

Fig. 4. Heterotopic Purkinje cells in cerebellar cortex: **A** isolated from the cortex, **B** in continuity with cortical granule cell zone. Cresyl violet, ×266. **C** Heterotopic Purkinje cell with multiple primary dendritic processes. Bielschowsky impregnation, ×765. **D** Astrocytes in central white matter of cerebral hemisphere. H.-E. ×138

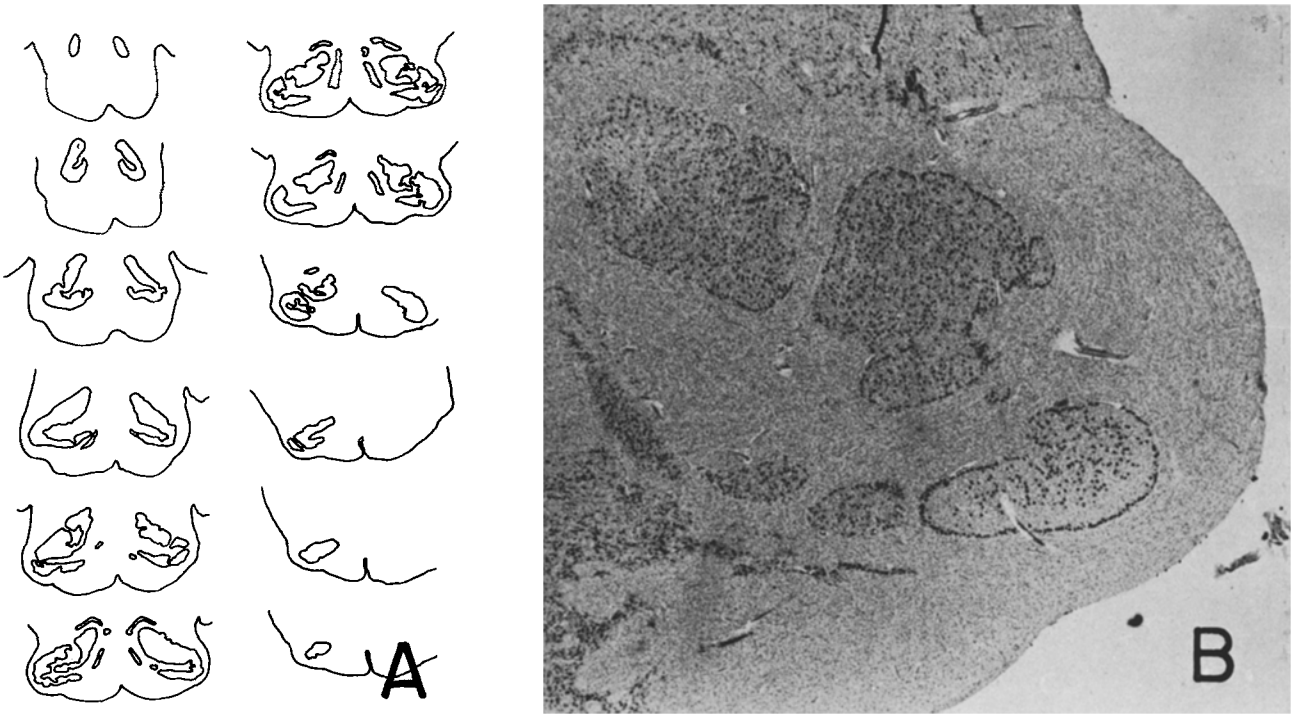

Fig. 5. **A** Drawings to scale of inferior olivary nuclear complex in sequential rostral to caudal (upper left to lower right) sections. ×2.2 **B** Micrograph of olivary complex at an intermediate, rostral to caudal level. Cresyl violet, ×19

the fundus of the nucleus and are increasingly prominent caudally. The degree of convolutional folding of the lamella is reduced. In addition, there is a tendency for the neurons at the periphery of the lamella of the principal nucleus to be aligned in a row, one cell in width. The spinal cord is normal.

Glial and Other Non-Neuronal Elements

Large gemistocytic astrocytes are disseminated throughout the nervous system but are most abundant in the subcortical white matter of the cerebral hemispheres (Fig. 4D). Macrophages and microglial cells are mildly increased in numbers. Both gemistocytic astrocytes and the macrophages contain Sudanophilic, Scharlach positive, non-metachromatic material that does not stain with PAS. There are no perivascular collections of inflammatory cells. The ventricular system, its ependymal lining, the meninges and the vascular structures are unremarkable throughout.

Discussion

Abnormal cortical convolutions and abnormal cortical cytoarchitecture are co-existent through the peri-Sylvian and medially adjacent fronto-parietal convexity of the cerebral hemisphere in the Zellweger malformation. Throughout the microgyric cortex of the peri-Sylvian region, a portion of the medium-sized and small pyramids are in normal relative intra-cortical positions, forming clearly defined layers III and II, respectively. However, many cells of these 2 classes are in abnormal positions, distributed through a continuous heterotopic field which extends through the corona-radiata and into the lower cortical layers. Cell pattern is even more severely abnormal in the pachygyric, parasagittal fronto-parietal convexity where the majority of neurons normally destined for layers II–IV are distributed heterotopically through layers V and VI and the vorona radiata.

These observations suggest that the mechanisms which interfere with migration in the Zellweger malformation do so to a partial degree only. Only a portion of the neurons of a given class fail to complete their migrations, and the length of migratory excursion of heterotopic neurons of a given class is variable, ranging from intra-cortical to deeply subcortical. In the primate, all neurons destined for a given cortical layer undergo their final divisions within a continuous period of a few days (Rakic, 1974). Neurons destined for the deepest cortical layer are formed first. Neurons destined for successively more superficial layers are formed in succession at progressively later embryonic periods. The fact that many of the neurons destined for layers II–III in microgyric cortex and of layers II–IV, perhaps even V, of pachygyric cortex, are affected, implies that the mechanism of migration is disturbed continuously from a relatively early stage of cortical histogenesis in the Zellweger malformation. By extrapolation from experimental observations in the macaque (Sidman and Rakic, 1973; Rakic, 1975),

neuronal migration may be disordered as early as the third month of gestation.

The present specimen has been compared with and found to be identical in its cytoarchitectonic features to the specimens described by Volpe and Adams (1972) and to a second in the archives of Professor Jean Lapresle. These cytoarchitectonic features, characteristic of other examples of the Zellweger malformation, may be unique to this specific malformation. To our knowledge the cell pattern of no other human developmental malformation is consistent with a partial disturbance of migration of multiple neuronal classes, acting throughout the greater duration of the migratory epoch. In the more common lissencephaly-pachygyria cerebral malformation, for example, intracortical heterotopic neurons are not identified within the limits of resolution of general cell stains (Stewart et al., 1975; Williams et al., 1975). This and other features of cell pattern in lissencephaly and related malformations suggest that neuron migration proceeds normally until interrupted abruptly and completely in the fourth month of gestation (Stewart et al., 1975).

Although there are major differences in the Zellweger malforation and that due to the weaver mutation in mice, the abnormality of neuronal migration in these two genetically transmitted developmental disorders may be due to a related mechanism. The weaver mutation gives rise to a malformation restricted to the cerebellum. The malformation is due at least in part to disruption of migration of granule cells from the granular layer (Rezai and Yoon, 1972; Rakic and Sidman, 1973a, b; Sotelo and Changeux, 1974), an event occurring in the postnatal period in the normal mouse (Miale and Sidman, 1961). In the homozygous state of the weaver mutation, disruption of migration of granule cells is virtually complete. In the heterozygote, on the other hand, the disruption of granule cell migration, like that of neurons destined for the neocortex of the Zellweger malformation in man, is only partial and is continuous throughout the extended postnatal migratory epoch of these cells. The granule cells migrate more slowly in the heterozygote and many cease their migrations in heterotopic positions within the molecular layer (Rezai and Yoon, 1972).

Recent in vitro experiments suggest that the physiology of granule cells in the homozygous weaver is disturbed by circulating toxic lipid metabolites (Hatten et al., 1976; Trenkner et al., 1976; Caviness and Rakic, 1978). If so, the disorder of migration in the heterozygous condition of the mutation may be the minimal expression of cellular intoxication. The selective vulnerability of granule cells in weaver is unexplained. Possibly it relates both to the fact that these cells undergo their divisions and migrations in the postnatal period when toxic metabolites can no longer be cleared from the fetus by the placental circulation and to the fact that these cells must execute relatively long migrations from their place of origin to their final destinations. The granule cells of the olfactory bulb (Hinds, 1968a, b) and the granular pyramids of the dentate fascia of the hippocampal formation (Angevine, 1965), cells which also undergo their divisions postnatally and coevally with the granule cells of the cerebellum in the mouse but which migrate short distances are unaffected in weaver.

In the Zellweger malformation, in contrast to the weaver malformation, the migrations of multiple cell classes of the forebrain and of only the Purkinje cells of the cerebellum are affected. These migrations occur during intra-uterine development. It is of interest that high concentrations of pipecolic acid are present in the serum of infants with the Zellweger malformation (Danks et al., 1975). Possibly this and other as yet unidentified cytotoxic substances capable of impairing neuron migrations are not adequately cleared by the placenta from the circulation of fetuses with the Zellweger malformation. The cerebral cortical abnormality lies superjacent to the basal ganglia and would have been superjacent to the ganglionic eminence during the migratory epoch. Cortical neuron migration in this region of the forebrain is especially extended, and neurons destined for the cortex migrate in association with neurons destined for subcortical structures. Purkinje cell heterotopias are largest and most numerous at the base of the ansiform lobule. As in the region of heterotopia in the forebrain, the migratory trajectories of cells in this region is longer and the cortical neurons must migrate in association with large numbers of neurons destined for the dentate nucleus. It is, of course, uncertain whether these factors account for the differential vulnerability of migrating neuronal populations in the Zellweger malformation.

The qualitative differences in the convolutional patterns of the malformed cortex, ranging from pachygyric to microgyric, are associated with differences in the intra-cortical cell patterns. The outer cortical layers are relatively more cellular in microgyric than in pachygyric cortex, whereas the reverse is true with regard to the deeper cortical layers. These differences might have been predicted from a mechanical model of cerebral convolutional formation (Richman et al., 1975) which proposes that the buckling of cortex to form gyri occurs only when stresses generated by cell differentiation in the outer half of the cortex becomes critically greater than those in the inner half of the cortex. Where differential stresses are sufficient to induce buckling, the intergyral distance will be an inverse function of cortical width. Abnormal cortex of the Zellweger malformation, either microgyric or pachygyric, is everywhere less than normal width. In

the peri-Sylvian region, where buckling does occur, it is to be predicted that the intergyral interval would be less than normal, that is, microgyric.

Purkinje cell heterotopias in the cerebellum, though large in some instances, are unassociated with defects in the continuity of the overlying Purkinje cell lamina of the cortex. The events which produce these heterotopias appear, therefore, not to interfere with the events through which the multicellular layer of early post-migratory Purkinje cells is redistributed into the characteristic monolayer of the mature cerebellar cortex (Rakic and Sidman, 1970; Zecevic and Rakic, 1976). Purkinje cells lying in heterotopic position below the granule cell layer are demonstrated in Bielschowsky impregnations to have multiple primary dendritic branches. In mutant mice, heterotopic Purkinje cells characteristically develop a multipolar form under 2 conditions: when they are fully submerged in the granule cell zone without entry of dendrites into the parallel fiber bed of the molecular layer and when the soma lies in isolation in a fully subcortical position without extension of dendrites among the overlying granule cells (Mariani et al., 1977; Caviness and Rakic, 1978). Under these conditions, evidently, extrinsic stimulus to dendritic growth converges in a symmetric fashion upon the Purkinje cell (Caviness and Rakic, 1978).

The laminar discontinuity in the principal olivary nucleus is evidently a constant and, in our experience, a unique feature of the Zellweger malformation, observed neither in other examples of human developmental malformations nor in experimental animals. It is of note that the fundus region of the principal nucleus, where the discontinuities occur, is topologically equivalent through connections, with the lateral ansiform lobules of the cerebellum (Evrard and Caviness, 1974). It is in this region of the cerebellum that Purkinje cell heterotopias are largest amd most abundant in the Zellweger malformation, The form of the principal olivary nucleus, specifically the quality and degree of its convolutional folding and indeed the differentiation and survival of its component neurons, are known to be critically dependent upon the integrity of its efferent climbing fiber connections with the Purkinje cells of the corresponding region of the cerebellar cortex (Harkmark, 1954; Evrard and Caviness, 1974). Although, the mechanism is unknown, the discontinuity in the olivary lamella may be consequent to the discontinuity in the laminar organization of the target Purkinje cells.

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