Virchows Arch. A Path. Anat. and Histol. 384, 1–18 (1979)

Virchows Archiv A

Review

Teratogenetic Periods for the Principal Malformations of the Central Nervous System

Lucía Zamorano* and Benedicto Chuaqui** ***

Department of Pathology, Catholic University, Marcoleta 347, Santiago, Chile

Summary. The teratogenetic periods of the most important CNS malformations are defined and briefly discussed. The results are presented in a synoptic figure.

The present study is based on the analysis of normal CNS development and on morphogenetic interpretations of the pertinent anomalies. The data compiled from the literature concerning normal development are presented in an analytical table and are also summarized in a synoptic figure.

Key words: Teratogenetic periods – CNS malformations.

Zusammenfassung. Die teratogenetischen Perioden der wichtigsten Mißbildungen des ZNS werden bestimmt und kurz besprochen. Die Ergebnisse sind in einer Übersichtstabelle dargestellt.

Die vorliegende Studie beruht auf der Analyse der normalen Entwicklung des ZNS und auf der morphogenetischen Interpretation der betreffenden Anomalien. Die aus der Literatur zusammengestellten Daten über die normale Entwicklung sind tabellarisch angegeben und in einer Übersichtstabelle zusammengestellt.

Introduction

The numerous malformations of the CNS may arise during almost the whole period of intrauterine life. In the available literature, we have been unable to find comprehensive studies giving a panoramic view on the timing of the possible teratogenetic periods. This has stimulated this synthetic study, based exclusively on the abundant but dispersed data in the literature.

* 7th year medical student. Lecturer in Pathology

** Head of the Department of Pathology

*** Formerly Fellow of the Alexander von Humboldt Foundation

Send offprint requests to: Prof. Dr. B. Chuaqui

0340-1227/79/0384/0001/$03.60

Method

The method used in this study consists of a double approach:

a) the analysis of data concerning the normal development of the CNS, and

b) the morphogenetic interpretation of the pertinent malformations.

In the delineation of the teratogenetic periods, we first studied the morphogenesis of the anomalies and then, using these data and those related to the normal development of the corresponding structures, we attempted to define precisely the time period during which the malformations seem to arise. The conclusions reached on several aspects of the CNS development and the genesis of the malformations were in agreement with data found in the clinical pathological reports.

Malformations may be regarded as a peculiar response of tissue *under development* to any noxa (Chuaqui, 1976). The teratogenetic periods defined in this study are valid for harmonic malformations (Werthemann, 1955) which are explained mainly as a result of developmental inhibitions. Disharmonic malformations, where destructive and abnormal proliferative processes are important pathogenetic factors (Werthemann, 1955) – for example in Tuberous Sclerosis (cf. Brun, 1965) – are not considered in this paper.

Embryonic stages were defined according to Streeter's horizons (Streeter, 1942, 1945, 1948, 1951; Heuser and Corner, 1957).

Results

The data on normal development concerning the malformations discussed here are presented chronologically in Table 1. The different events of normal development related to anomalies are disclosed in synoptic Table 2. The teratogenetic periods are shown in Table 3.

Table 1. Development of the principal structures of the CNS

Time from conception	Morphological features	References
Horizon VIII. 15–16 days	– General area of the neural plate autoradiographically discernible	Lemire et al., 1975; O'Rahilly and Gardner, 1971
Horizon IX. 18 ± 1 day (1–3 somites. 1.5 mm)	– Neural folds appear	Langman, 1969; Lemire et al., 1975; O'Rahilly and Gardner, 1971; Smith, 1970
	– Prosencephalon, mesencephalon and rhombencephalon are distinguished	O'Rahilly and Gardner, 1971
Horizon X. 22 ± 1 day (4–12 somites. 2 mm)	– Partial fusion of the neural folds and initial development of the neural tube	Heuser and Corner, 1957; Heuyer, 1959; Lemire et al., 1975; O'Rahilly and Gardner, 1971; Smith, 1970
	– Cephalic circulation begins with the appearance of dorsal aortas and future internal carotid arteries	Heuyer, 1959; Pease, 1971
Horizon XI. 24 ± 1 day (13–20 somites. 2.5–3 mm)	– Closure of the anterior neuropore	Hamilton et al., 1960; Lemire et al., 1975; Loeser and Alvord, 1968; O'Rahilly and Gardner, 1971; Patten, 1958; Streeter, 1942)

Table 1 (continued)

Time from conception	Morphological features	References
	– Upon fusion of the neural folds the lamina terminalis forms causing the disappearance of the terminal notch	Loeser and Alvord, 1968; O'Rahilly and Gardner, 1971
	– Optic vesicle present	O'Rahilly and Gardner, 1971; Streeter, 1942
Horizon XII. 26 ± 1 day (21–29 somites. 3.5 mm)	– Closure of the posterior neuropore	Hamilton et al., 1960; Lemire et al., 1975; Streeter, 1942
Horizon XIII. 28 ± 1 day (30–38 somites. 4–5 mm)	– Primitive ependymal layer, mantle and primitive marginal layers evident in the neural tube	Streeter, 1945
	– Impending subdivision of the prosencephalon	Patten, 1958; Streeter, 1945
	– Middle cerebral, posterior communicating and ophtalmic arteries present	Heuyer, 1959; Patten, 1958
Horizon XIV. 29 ± 1 day (6–7 mm)	– Cerebellar plate visible	O'Rahilly and Gardner, 1971; Streeter, 1945; Tridon, 1959
	– Thickening of the lamina terminalis and optic chiasm primordium appear	Friede, 1975; Sharp, 1959
	– Basilar artery present	Heuyer, 1959
Horizon XV. 31 ± 1 day (7–8 mm)	– Cerebral vesicles with pallium and floor. The pallium made of a germinal layer and a periependymal zone	Streeter, 1948; Tridon, 1959; Tuchmann-Duplessis, 1970
	– Beginning subdivision of the rhombencephalon	Tuchmann-Duplessis, 1970
	– Primitive meninges and first traces of spinal piamater appear	O'Rahilly and Gardner, 1971
Horizon XVI. 33 ± 1 day (9–10 mm)	– Thalamus and striate bodies well delineated	Hewitt, 1961; Lemire et al., 1975; Tridon, 1959; Yokoh, 1968
	– Lamina terminalis broadens to form the commisural plate	O'Rahilly and Gardner, 1971; Tridon, 1959
	– Appearance of the posterior commisure	Hogg, 1945; Streeter, 1948
Horizon XVII. 35 ± 1 day (11–14 mm)	– Beginning reduction of the ependymal channel	Heuyer, 1959
Horizon XVIII. 37 ± 1 day (14–16 mm)	– Choroid plexus of the lateral ventricles start to develop	Heuyer, 1959; O'Rahilly and Gardner, 1971; Yokoh, 1968
Horizon XIX. 39 ± 1 day (17–20 mm)	– Commisural plate differentiates into pars tenuis and pars crassa	Loeser and Alvord, 1968
Horizon XXII. 45 ± 1 day (25–27 mm)	– Union of the striatum and thalamus forms the opto-striate system	Tridon, 1959

Table 1 (continued)

Time from conception	Morphological features	References
Horizon XXIII. 47 ± 1 day (28–30 mm)	– The pallium has differentiated into archipallium and neopallium, and the floor into lateral and medial striate bodies	Tuchmann-Duplessis, 1970
End of the second month (25–50 mm)	– Cerebellar plates fuse and traces of cerebellar bodies appear	Tridon, 1959
	– Anterior and hippocampal commisures appear	Loeser and Alvord, 1968; Tridon, 1959; Walker, 1944
	– Appearance of the mantle layer in the cerebral hemispheres, which are composed of: germinal layer, mantle layer and marginal velum	Hamilton et al., 1960; Ostertag, 1956; Tuchmann-Duplessis, 1970
	– Beginning of the first migration wave which will form the cortical plate	Sidman and Rakic, 1973
	– Cystic necrosis within the commisural plate (initial cavum septi)	Loeser and Alvord, 1968
Third month. (70–80 mm)		
A) At the beginning of the third month	– Initial formation of the cortical plate (cerebral primordial layer according to Tridon 1959 and Tuchmann-Duplessis 1970)	Sidman and Rakic, 1973
	– Fusion of the cerebellar bodies, with vermis and cerebellar hemispheres recognizable. Vermis completely developed.	Patten, 1958; Tridon, 1959
	– Trigone formed	Heuyer, 1959; Ostertag, 1956; Tridon, 1959
	– Anlage of corpus callosum	Abbie, 1939; Heuyer, 1959; Loeser and Alvord, 1968; Magee and Olson, 1961; Ostertag, 1956; Patter, 1958; Tridon, 1959
	– Spinal cord displays its typical cytoarchitecture (including the formation of the median raphe)	Pease, 1971; Tridon, 1959
B) From the beginning of the third month on	– Differentiation of archipallio- and neocortex begins	Tridon, 1959
	– Appearance of the cerebellar superficial cortical layer	Jacob, 1928; Kuhlenbeck, 1950
	– Appearance of the subpial granular layer in the cerebral allocortex	Brun, 1965
	– End of the first migration wave (11th week) and commencement of the second migration wave	Sidman and Rakic, 1973
	– Splenium corporis callosi recognizable (end of 3rd month)	Loeser and Alvord, 1968

Table 1 (continued)

Time from conception	Morphological features	References
	– Thalamus and IIIrd ventricle in their definitive aspect	Patten, 1958; Tridon, 1959
	– Choroid plexus of the IVth ventricle formed	Tridon, 1959
	– Circle of Willis formed	Heuyer, 1959
	– Interhemispheric fissure appears	Chi et al., 1977
Fourth month (120–130 mm)	– End of the second migration wave (16th week)	Sidman and Rakic, 1973
	– The cerebral primordial cortical layer appears subdivided into external layer (corresponding to cells of the second migration wave) and internal layer (corresponding to cells of the first migration wave), separated by the zone of the future granular layer	Streeter, 1932
	– End of the differentiation of the archi- and palleocortex	Filiminov, 1947; Tuchmann-Duplessis, 1970
	– Appearance of the subpial granular layer in the isocortex	Brun, 1965
	– Adult morphology of the corpus callosum is achieved	Loeser and Alvord, 1968
	– Migration of cells that will form the cerebellar granule cells, Golgi cells and Purkinje cells.	Tuchmann-Duplessis, 1970
	– Appearance of the laminar structure of the cerebellar surface. Cerebellar lobules and fissures recognizable.	Hamilton et al., 1960; Streeter, 1948
	– Formation of foramina Luschka and Magendie	Harvey and Burr, 1926; Tuchmann-Duplessis, 1970
	– Sylvian, parieto-occipital and calcarine fissures appear. Callosal and olfactory sulci formed. Gyrus rectus present.	Chi et al., 1977
Fifth month (167–185 mm)	– Complete differentiation of the cerebellum achieved	Patten, 1958
	– Foramen of Magendie patent	Heuyer, 1959; Tridon, 1959
	– Septum pellucidum present	Heuyer, 1959; Tridon, 1959
	– End of cell migration from the germinal cortical layer	Brun, 1965; Ostertag, 1956; Poliakov, 1961
	– Rolandic and cingulate sulci appear. Insula present	Chi et al., 1977
Sixth month (215 mm)	– Lamination of the cerebral cortex: the internal layer appears subdivided into layers V and VI	Patten, 1958; Tridon, 1959; Tuchmann-Duplessis, 1970
	– Subpial granular layer reaches its maximum development. It involutionates afterwards.	Brun, 1965

Table 1 (continued)

Time from conception	Morphological features	References
	– Corpus callosum completely developed	Loeser and Alvord, 1968; Magee and Olson, 1961; Patten, 1958; Rakic and Yakovlev, 1968; Tridon, 1959
	– Foramina of Luschka patent	Heuyer, 1959
	– Superior temporal and prerolandic sulci appear. Parahippocampal gyrus develops.	Chi et al., 1977
Seventh month (210–230 mm)	– Subdivision of the external cortical layer into layers II and III	Tridon, 1959; Tuchmann-Duplessis, 1970
	– End of differentiation of the neocortex	Filinimov, 1947; Tuchmann-Duplessis, 1970
	– Establishment of the different architectonic patterns of the cerebral cortex	Heuyer, 1959; Patten, 1958; Tridon, 1959
	– Most of the cerebral gyri and sulci present	Chi et al., 1977
Eighth month (285–310 mm)	– Disappearance of the germinal zone of the hemispheres	Heuyer, 1959; Poliakov, 1961; Robinowicz, 1964
	– Inferior temporal sulcus appears. Angular, supramarginal, and inferior temporal gyri develop	Chi et al., 1977
Ninth month (320–350 mm)	– Involution of the embryonic granular layer of the cerebellum	Jacob, 1928; Langman, 1969
	– The Sylvian fossa becomes the Sylvian fissure	Patten, 1958
	– Anterior and posterior orbital, and paracentral gyri appear	Chi et al., 1977
After birth	– Involution of the subpial granular layer of the cerebral cortex	Brun, 1965

Discussion

Amyelia, Arhaphia. Persistence of the spinal neural plate or sulcus (Minkowsky, 1954; Tridon, 1944, 1959) in turn determines a failure of closure of the posterior vertebral arches and lack of development of the spinal meninges (Friede, 1975; Langman, 1969; Patten, 1958; Peters, 1974; Smith, 1970; Tridon, 1944; 1959). The teratogenetic period is very early in development (horizon IX) and is a very restricted one (Minkowsky, 1954) (for the different theories concerning neural tube anomalies see Lemire et al., 1975, 1978).

Anencephaly, Acrania. This anomaly occurs at the neural plate or neural sulcus stage (Lemire et al., 1978; Minkowsky, 1954; Tridon, 1944, 1959) and is manifest as a lack of closure of the encephalic cavity. This in turn determines a defect

Table 2. Chronological development of the principal structures of the CNS

Age	Days															Months							
	18	22	24	26	28	29	31	33	35	37	39	41	43	45	47	end 2th	3rd	4th	5th	6th	7th	8th	9th
Length (C-R, mm)	1.5	2	2.5	3.5 3	4 5	6 7	7 8	9 10	11 14	14 16	17 20	21 23	22 24	25 27	28 30	25 50	70 80	120 130	167 185	215	243 285	285 310	320 350
Horizon	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23								
Somites	1–3	4 12	13 20	21 29	30 38																		
Structure																							
Neural plate	—																						
Neural tube		—	—	—																			
Closure of the ant. neuropore			—																				
Closure of the post. neuropore				—																			
Prosencephalon	—	—	—	—	—																		
Rhombencephalon	—	—	—	—	—	—	—																
Spinal cord	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—					
Narrowing of ependymal duct								—	—	—	—	—	—	—	—	—	—	—					
Dorsal medial raphe												—	—	—	—	—	—	—					
Cerebellum					—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—			
Vermis															—	—	—	—					
Cerebellar hemispheres																	—	—					
Commissures			—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—		
Lamina terminalis, commissural plate			—	—	—	—	—	—	—	—	—	—	—	—	—	—							

Table 2 (continued)

Age	Days															Months								
	18	22	24	26	28	29	31	33	35	37	39	41	43	45	47	33	2th	3rd	4th	5th	6th	7th	8th	9th
White anterior commissure																—	—	—						
Hippocampal commissure																—	—	—						
Corpus callosum																			—	—	—			
Septum pellucidum																				—				
Closure of the cava																						—	—	—
Foramina of the 4th ventricle																			—					
Permeabilization of Magendie's foramen																				—				
Permeabilization of Luschka's foramina																					—			
Optostriate bodies								—	—	—	—	—	—	—	—									
1st migration wave (cerebral cortex)													—	—	—	—	—	—						
2nd migration wave (cerebral cortex)																			—					
Archeocortex and paleocortex																		—	—					
Neocortex																		—	—	—	—	—		
Subpial granular layer																		—	—	—	—	—	—	—
Encephalic vascularization	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—						

Table 3. Teratogenic periods for the principal malformations of the CNS

Age	Days															Months							
	18	22	24	26	28	29	31	33	35	37	39	41	43	45	47	end 2nd	3rd	4th	5th	6th	7th	8th	9th
Length (C-R, mm)	1.5	2	2.5 3	3.5	4 5	6 7	7 8	9 10	11 14	14 16	17 20	21 23	22 24	25 27	28 30	25 50	70 80	120 130	167 185	215	243 285	285 310	320 350
Horizon	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23								
Somites	1–3	4 12	13 20	21 29	30 38																		
Malformation																							
Amyelia and arhaphia	——																						
Anencephalia, acrania		——																					
Rachischisis spina bifida		——	——	——																			
Diplomyelia		——	——	——																			
Cyclopia and arrhinencephalia				——	——	——	——																
Encephalocele and craneoschisis				——	——	——	——																
Cerebellar agenesis						——	——	——	——	——	——	——	——	——	——	——	——						
Cerebellar hypoplasia																	——	——					
Vermis agenesis															——	——	——						
Agenesis of all commissures						——	——	——	——	——	——	——	——	——	——	——	——						
C. callosum agenesis and hypoplasia																——	——	——	——	——	——		

Table 3 (continued)

Age	Days														Months								
	18	22	24	26	28	29	31	33	35	37	39	41	43	45	47	end	2nd	3rd	4th	5th	6th	7th	8th	9th
Microcephalia																								
Hydromyelia																								
Agenesis of optostriate bodies																								
Syringomyelia																								
Heterotopies																								
Agyria																								
Pachygyria																								
Micropolygyria																								
Dandy-Walker syndrome																								
Cavum septi pelluc. (5th ventricle)																								
Cavum Vergae (6th ventricle)																								
Marginal heterotopies																								

in the development of the cranial vault (Friede, 1975). The teratogenetic period is an early one (horizons X and XI) (Heuyer, 1959; Langman, 1969; Lemire et al., 1975; Patten, 1958; Smith, 1970). For some cases of anencephaly Ostertag (1956) suggests a reabsorptive process affecting the initially well differentiated, already closed brain anlage. (For discussion of this hypothesis see Lemire et al., 1978.) Anyway, the teratogenetic period will be set before the second month (Lemire et al., 1978).

Neuro-Spinal Dysrhaphism (rachisquisis, spina bifida). This is a localized dysrhaphic defect, usually affecting the more caudal vertebrae (Ingraham, 1944; Tridon, 1944, 1959). It is due to a defect in the induction of closure of the corresponding vertebral arches, which is produced by a lack of closure of the underlying neural sulcus (Heuyer, 1959). Due to the fact that the closure of the caudal part of the neural sulcus occurs between the horizons X and XII (O'Rahilly and Gardner, 1971; Tridon, 1959), the teratogenetic period lasts until the latter horizon (Heuyer, 1959; Ingraham, 1944; Lemire et al., 1975; Tridon, 1944).

Diplomyelia. This anomaly corresponds to the formation of a medial, dorsovertebral fissure in the spinal neural plate. The malformation may occur as long as the neural plate stage exists (horizons X, XI and XII) (Benstead, 1953; Herren and Edwards, 1940; Netzky, 1953). It may be attributed to a disturbance in the induction of either the paracordal mesoblast or the precordal plate on the neural plate (Peters, 1974; Tridon, 1959).

Agenesis of Commisures. Under this heading four groups of malformations may be distinguished representing different degrees of severity of dorsal dysgenesis (Loeser and Alvord, 1968):

1) Agenesis of all commisures;

2) Total agenesis of corpus callosum (with normally developed anterior commisure and trigone);

3) Partial agenesis of corpus callosum, and

4) Hypoplasia of corpus callosum.

These anomalies occur as a continuous spectrum of malformations; their teratogenetic periods, especially those of the last three, cannot be sharply defined from each other.

A) Agenesis of all commisures. The teratogenetic period of this group extends from the time when the lamina terminalis thickens (horizon XIV) to the end of the second month when the first commisure (anterior commisure) should appear. This concurs with data in the literature based on the interpretation of isolated cases (Heuyer, 1959; Lehmann, 1955; Magee and Olson, 1961; Morsier, 1934; Tridon, 1944, 1959). The anomaly may be attributed to a defective development of the whole pars crassa (Loeser and Alvord, 1968).

B) Agenesis and hypoplasia of corpus callosum. The period of normal development of the corpus callosum extends from the third to the sixth month (see Tables 1 and 2). A disturbance occuring at the beginning of the third month will produce a total agenesis of corpus callosum (Loeser and Alvord, 1968). If the disturbance occurs later, at the middle of the third month, a partial

agenesis will result affecting only the posterior portion of the corpus callosum (Baker and Graves, 1933; Heuyer, 1959; Josephi, 1944; Lehmann, 1955; Loeser and Alvord, 1969; Tridon, 1959), since the splenium forms later than the rostral portion (cf. Lemire et al., 1975 and Loeser and Alvord, 1968). Between the fourth and sixth month hypoplasia of the corpus callosum may occur, with associated anomalies of the fornix and psalterium (Josephi, 1944; Marburg, 1949; Tridon, 1959).

Cyclopia, Arhinencephaly. These malformations are characterized by incomplete or failure of division of the cerebral hemispheres and fusion of the double angle of the eyeballs (due to the destruction of the germinal tissue between them – Torus opticus – (Starck, 1965). There is an absent corpus callosum and defective fornix; in addition, an absent olfactory bulb and optic nerve, and defects in the development of the nasal primordium. If fusion of the hemispheres involves only the anterior portion, a rudimentary splenium may be present (Friede, 1975). Experimentally, the anomaly can be produced by altering the archencephalic inductor (Heuyer, 1959; Lehmann, 1955). The teratogenetic period has been considered by different authors to be set between the stages of 3 and 5 encephalic vesicles (2 and 4 according to Starck's concept (1965)). It has been fixed particularly during the period of division of the prosencephalon (horizons XII to XV) (Ebaugh and Hoft, 1963; Friede, 1975; Heuyer, 1959; Marburg, 1948; Mosberg and Voris, 1954).

Encephalocele, Cranioschisis. This anomaly corresponds to a defective closure of the cranial bones, more commonly the occipital one, thus causing an exencephaly (Heuyer, 1959; Tridon, 1944, 1955). The teratogenetic period extends from the time when differentiation of the cranial base scleroblastema begins (horizon XII, Lemire et al., 1975; O'Rahilly, 1952; this process beginning in the occipital segments) to the time when the occipital base becomes cartilaginous (horizon XV, O'Rahilly, 1952).

Cerebellar Agenesis and Hypoplasia. Agenesis may occur as a consequence of an incomplete development of the cerebellar plate (horizon XIV; Baker and Graves, 1931; Morsier, 1955a, b; Rubinstein and Freeman, 1940; Sahs, 1941). However, if the plates are already developed, isolated agenesis of the vermis may result (Morsier, 1955a, b); the teratogenetic period of this malformation has been set during the fusion phase of the cerebellar plates (end of 2nd month) (Heuyer, 1959; Sahs, 1941). Cerebellar hypoplasia usually affects the hemispheres, and is due to a delay in cellular multiplication or to an arrest of cell migration (Heuyer, 1959). Its teratogenetic period corresponds to the stages of development of the cerebellar hemispheres (3rd month until the beginning of the 4th month).

The estimated teratogenetic periods for cerebellar agenesis and hypoplasia (horizon XIV until the beginning of the 4th month) do not differ substantially from those in the literature (Baker and Graves, 1931; Heuyer, 1959; Morsier, 1955a, b; Rubin, 1969; Rubinstein and Freeman, 1940; Sahs, 1941; Tridon, 1959).

Microcephaly. The principal underlying morphogenetic mechanism is a delay in cell multiplication or an arrest of cell migration (cell death – as for example after irradiation – seems to play an important pathogenetic role). Therefore, brains with a low cellular density and brains with a reduced number of cortical layers are included in this category (Friede, 1975). The teratogenetic period may be set between the time of development of the cerebral vesicles (horizon XIV) and the 3rd month, when the macroscopic aspect of the cerebral hemispheres is already defined (except for sulci and gyri) and the first migration wave which will form the primordial cortical layer is finished (Greenfield and Wolfsohn, 1933; Heuyer, 1959; Peters, 1974; Sidman and Rakic, 1973; Wilson, 1940).

Hydromyelia. This malformation corresponds basically to an incomplete involution of the central canal, which is manifested by an anomalous juxtaposition of the lateral walls of the spinal canal (Andre, 1951; Heuyer, 1959). It is due to a relative lack of ventral migration of the posterior ependyma (which in turn determines absence of the dorsal raphe) (Heuyer, 1959; Tridon, 1944). These abnormalities do not affect the secretory functions of the structures involved (Heuyer, 1959). The teratogenetic period corresponds to the stages of reduction of the ependymal canal; this process includes the initial apposition of the lateral walls (5th to 6th week) and the later formation of the dorsal raphe (7th to 10th week) (Herren and Edwards, 1940; Peters, 1974; Tridon, 1944, 1959).

Agenesis of the Optostriate Body. This abnormality is caused by a lack of fusion of the primordium of the striate body with that of the thalamus. The disturbance may be due to an incomplete development of either primordium (Tridon, 1944, 1959). The estimated teratogenetic period thus extends from horizon XVI to horizon XXII.

Syringomyelia. A disturbance in the formation of the posterior raphe of the spinal cord is generally thought to be the cause of this malformation (Andre, 1951; Heuyer, 1959). The same basic disturbance would be a condition for the later dissolution of spinal cord parenchyma (Gardner and Angel, 1959; Netzky, 1953). The teratogenetic period of this malformation corresponds to the development of the posterior raphe (horizon XX until the 3rd month) (Peters, 1974; Tauber, 1935; Tridon, 1959).

Heterotopic Nests (of Gray Matter) in Hemispheric White Matter. An arrest of neuroblast migration causes this abnormality, thus causing the presence of subcortical masses of gray substance (Friede, 1975; Heuyer, 1959). Although the heterotopic cells are derived from the same cells which form the cerebral cortex, the anomaly is not strictly a cortical dysplasia: the gyri and, particularly, the cortical laminar architecture are normal (Popoff and Feign, 1964; Tridon, 1944). The teratogenetic period thus corresponds to the period of migration of neuroblasts, which occurs from the 7th to the 16th week (Sidman and Ra-

kic, 1973) (from the second to the fourth month according to Feld et al., 1955; Heuyer, 1959; Peters, 1974; Popoff and Feign, 1964; Tridon, 1944, 1959).

Agyria, Pachigyria. Agyria and pachigyria are different degrees of the same basic disturbance. In agyria (lissenencephaly) there is an absence of gyri; in pachigyria there is a reduced number, those present being broader and less convoluted than normal (Brun,1965). In both anomalies the neocortex is affected, with sparing of hippocampus and limbic cortex (Friede, 1975; Heuyer, 1959; Josephi, 1944). The cortex is broader than normal, although made up of only 4 layers, and the amount of white matter is reduced. When there is normal cortex in adjacent areas, the deepest layer of the abnormal cortex is subcortically placed in relation to the normal cortex. The superficial cell layer is continuous with the normal cortex (Brun, 1965; Miller, 1963; Rubin, 1969). It is believed that the abnormality is due to an arrest of neuroblast migration from the periventricular matrix towards the superficial cortex (Friede, 1975; Heuyer, 1959; Tridon, 1959). This interpretation is supported by the close similarity of the abnormal cyto-architecture with certain fetal stages of normal development showing a subpial granular layer (Brun, 1965). It has been postulated that the neuroblasts in the second phase of migration (which normally forms the superficial layer), are incapable of moving beyond the location of the neuroblasts which have already migrated in the first phase. As a consequence, the larger cortical neurons, normally located in the deepest cortical layers, would be found in the superficial layers (Brun, 1965; Heuyer, 1959). Thus, the teratogenetic period of both anomalies would correspond to the second migration phase (11th to 16th week, Sidman and Rakic; end of the 2nd to beginning of 4th month according to Brun, 1965; Heuyer, 1959; Josephi, 1944; Miller, 1942; Peters, 1974; Rubin, 1969; Tridon, 1959; Walker, 1942).

Micropolygyria. The micropolygyric neocortex is characterized by an excessive folding and an abnormal cyto-architectonic pattern which most typically displays a four-layered cortex: molecular layer, upper dense cell layer, intermediate cell-sparse layer, and deep cell layer. This pattern is similar to that of the archicortex (Brun, 1965; Crome, 1952; Friede, 1975; Heuyer, 1959). According to most authors, the total thickness of the micropolygyric cortex is less than that of the normal adjacent cortex; the upper layer continues with layers II and III, and the deep layer continues with layer V of the adjacent cortex (Brun, 1965; Friede, 1975). Somewhat different topological relationships are described by other authors (see below).

Three morphogenetic principles have been postulated to explain micropolygyria: an arrest of neuroblast migration, an imbalance of intracortical cell multiplication, and a post-migratory laminar destruction. According to Brun (1965), an arrest of the first cell migration wave, which forms the deep cortical layers (Sidman and Rakic, 1973) takes place, thus accounting for the frequent presence of subcortical heterotopic cell nests (Brun, 1965). However, the disturbance is thought to affect the intracortical migration more than the migration towards the cortex (Friede, 1975); since the second migration wave occurs normally (11th to 16th week, Sidman and Rakic, 1973) a relatively dense upper layer

forms and the excessive superficial folding is explained by differences in growth velocity of the supragranular and infragranular layers (Crome, 1952; Friede, 1975; Greenfield and Wolfsohn, 1933; Heuyer, 1959). Thus the teratogenetic period extends from the time when formation of the cell cortical plate begins (8th week, according to Sidman and Rakic, 1973) throughout the whole period during which the six-layered neocortex is constituted (7th month). This estimated period is in agreement with data obtained in cases of micropolygyria due to carbon monoxide poisoning, the latter occured in none of the reported cases before the 20th or after the 28th week of gestation (Richman et al., 1974). The hypothesis of a post-migratory laminar destruction is based upon a few reported cases where the deep and the cell-sparse layers appeared continuous with layers VI and V, respectively, whereas the upper layer displayed three sublayers blended with layers II, III and IV (Richman et al., 1974). It is assumed that in upper and deep cell layers located in this way both early and late migration waves are normally represented; the cell-sparse layer is regarded as the result of a post-migratory encephaloclastic event affecting mainly the layer V of the neocortex (Richman et al., 1974). The first determination point of the teratogenetic period would thus coincide with the end of cell migration (5th month). If no further morphogenetic event is postulated, the second determination point cannot be defined, that is to say, micropolygyria could also occur after the 7th month, which does not seem to be the case.

Dandy-Walker Malformation. This anomaly has been regarded as a form of hydrocephalus resulting from the obstruction of the foramina of Luschka and Magendie (Benda, 1954; Fowler and Alexander, 1956; Heuyer, 1959). On this assumption, it can reasonably be expected that the teratogenetic period will be located during the period of opening of the foramina (5th and 6th month) (Benda, 1954; Heuyer, 1959; Tridon, 1944, 1959). However, the following triad is also designated as the Dandy-Walker anomaly and has patent foramina: malformation of the vermis, a cystic roof of the IVth ventricle, and an elevated tentorium (Lemire et al., 1975; Peters, 1974). This triad could be explained by an arrest in the development of the hind-brain, with persistence of the anterior membranous area (which normally disappears before the foramina become patent). Such an arrest would include an absence of the cerebellar foramina. The teratogenetic period for this triad would be located in an earlier stage, namely the 3rd month (Benda, 1954; Fowler and Alexander, 1956; Friede, 1975; Tridon, 1944, 1959).

Fifth and Sixth Ventricle. Cavum septi pellucidi and cavum Vergae are normal structures which disappear in the last three months of development (Basu, 1935; Hughes et al., 1955; Taggort and Walker, 1942; Tridon, 1959). If they persist as large midline cysts, they are considered to be abnormalities in the development of the septum pellucidum (Basu, 1935; Hughes et al., 1955; Mosberg and Voris, 1954; Peters, 1974; Schwidde, 1952; Taggort and Walker, 1942; Tridon, 1959; Wolf and Bamford, 1935).

Marginal Heterotopies ("brain warts", Jacob, 1940). This refers to the marginal glio-neuronal heterotopies, particularly to the hyperplastic and polypoid forms

(Brun, 1965). They are continuous with the molecular layer, and it is believed that they represent a persistence of the subpial granular layer (Bertrand and Gruner, 1955; Brun, 1965). The teratogenetic period will be found in the stages of regression of this layer. This involution begins after the 24th week, although there are certain differences in the different cortical areas (Bertrand and Gruner, 1955; Brun, 1965; Grcevic and Robert, 1961).

References

Abbie, A.: The origin of the corpus callosum and the fate of the structure related to it. J. Comp. Neurol. **70**, 9–15 (1939)

Andre, M.: Essai nosologique sur la syringomyélie et l'hydromyélie. Acta Neurol. Psychiat. Belg. **51**, 669–672 (1951)

Baker, R., Graves, G.: Cerebellar agenesis. Arch. Neurol. Psychiat. **25**, 547–570 (1931)

Baker, R., Graves, G.: Partial agenesis of the corpus callosum. Arch. Neurol. Psychiat. **29**, 1054–1061 (1933)

Basu, B.: Complete absence of septum pellucidum. J. Anat. **69**, 121–128 (1935)

Benda, C.: The Dandy-Walker syndrome. J. Neuropath. Exp. Neurol. **13**, 14–18 (1954)

Benstead, J.: Diastematomyelia. J. Path. Bacteriol. **66**, 553–558 (1953)

Bertrand, F., Gruner, J.: The status verrucosus of the cerebral cortex. J. Neuropath. **14**, 331–338 (1955)

Brun, A.: The subpial granular layer of the foetal cerebral cortex in man. Acta Pathol. Microbiol. Scand. Suppl. **179**, 7–98 (1965)

Chi, J.G., Dooling, E.C., Gilles, F.: Gyral development of the human brain. Ann. Neurol. **1**, 86–93 (1977)

Chuaqui, B.: Algunas nociones de patomorfología general de las malformaciones. Cuadernos Chilenos de Cirugía (Santiago) **20**, 275–279 (1976)

Crome, J.: Microgyrie. J. Path. Bacteriol. **64**, 479–482 (1952)

Ebaugh, S.: Congenital malformations of the nervous system. Am. J. Med. Sci. **246**, 104–112 (1963)

Feld, M., Gruner, J., Heuyer, G.: Hétérotopies volumineuses et malformations de l'hémisphère droit. Rev. Neurol (Paris) **92**, 297–305 (1955)

Filiminov, I.: A rational subdivision of the cerebral cortex. Arch. Neurol. Psychiat. **58**, 296–299 (1947)

Fowler, F., Alexander, E.: Atrésie des trous de Luschka et de Magendie. Am. J. Dis. Child. **92**, 131–134 (1956)

Friede, R.L.: Developmental neuropathology. New York-Wien: Springer 1975

Gardner, W., Angel, J.: The mechanism of syringomyelia and its surgical correction. Clin. Neurosurg. **6**, 131–140 (1959)

Grcevic, N., Robert, E.: Verrucose dysplasia of the cerebral cortex. J. Neuropath. Exp. Neurol. **20**, 399–403 (1961)

Greenfield, J., Wolfsohn, J.: Microcephalia vera. A study of two brains illustrating the agyric form and the complex microgyric brain. Arch. Neurol. Psychiat. **33**, 1296–1301 (1933)

Hamilton, W., Boyd, J., Mossman, N.: Human embryology. Baltimore: William and Wilkins 1960

Harvey, S., Burr, H.: The development of meninges. Arch. Neurol. Psychiat. **15**, 545–550 (1926)

Herren, R., Edwards, J.: Diplomyelia. Arch. Path. **30**, 202–212 (1940)

Heuser, C., Corner, G.: Developmental horizons in human embryos. Description of age group X, 4 to 12 somites. Contr. Embryol. **36**, 29–39 (1957)

Heuyer, G.: Malformations congénitales du cerveau. Paris: Masson 1959

Hewitt, W.: The development of the human internal capsule and lentiform nucleus. J. Anat. **95**, 191–198 (1961)

Hogg, I.: The embryological development of the commisura posterior in the human brain. J. Comp. Neurol. **82**, 255–260 (1945)

Hughes, R., Kernohan, J., Craig, W.: Caves and cysts of the septum pellucidum. Arch. Neurol. Psychiat. **74**, 259–266 (1955)
Ingraham, F.: Spina bifida and cranium bifidum. Boston: Harvard University Press 1944
Jacob, A.: Das Kleinhirn. In: Handbuch der mikroskopischen Anatomie des Menschen. M. v. Möllendorff (Hrsg.), Bd. IV/1 Nervensystem I, S. 674. Berlin: Springer 1928
Jacob, H.: Die feinere Oberflächengestaltung der Hirnwindung: die Hirnwarzenbildung und die Mikropolygyrie. Z. ges. Neurol. Psychiat. **170**, 64–84 (1940)
Josephi, H.: Congenital agyria and defect of corpus callosum. J. Neuropath. **3**, 63–72 (1944)
Kuhlenbeck, H.: The transitory superficial granular layer of the cerebellar cortex. J. Am. Med. Women's Ass. **5**, 347–353 (1950)
Langman, J.: Embriología médica. 2a. ed. esp. México: Nueva Ed. Interamericana 1969
Lehmann, F.E.: Die embryonale Entwicklung. In: Handbuch der allgemeinen Pathologie, F. Büchner, E. Letterer u. F. Roulet (Hrsg.), Bd. VI/1, S. 1. Berlin-Göttingen-Heidelberg: Springer 1955
Lemire, R.J., Beckwith, J.B., Warkany, J.: Anencephaly. New York: Raven Press 1978
Lemire, R.J., Loeser, J.D., Leech, R.W., Alvord, E.C., Jr.: Normal and abnormal development of the human nervous system. New York-Evanston-San Francisco-London: Harper & Row, Publ. 1975
Loeser, J.D., Alvord, E.C., Jr.: Agenesis of corpus callosum. Brain **91**, 553–562 (1968)
Magee, K.R., Olson, R.N.: The effect of absence of the corpus callosum on the position of the hippocampus and on the formation of Probst's bundle. J. Comp. Neurol. **117**, 371–379 (1961)
Marburg, O.: Cyclopia, arhinencephalia and callosal defect. J. New Born Dis. **107**, 430–441 (1948)
Marburg, O.: So-called agenesia of the corpus callosum (callosal defect). Arch. Neurol. Psychiat. **61**, 132–139 (1949)
Miller, J.: Lissencephalia in two siblings. Neurology **13**, 841–849 (1963)
Minkowsky, M.: Sur quelques éléments généraux de morphologie et de pathogénie des malformations du système nerveux central, surtout de l'anencéphalie et l'amyélie. Paris: Masson 1954
Morsier, G.: Nouveau cas d'agénésie totale de la commisure calleuse. Essai sur la pathogénie de cette malformation. Arch. Neurol. Psychiat. **34**, 401–413 (1934)
Morsier, G.: Agénésie de vermis cérébelleux. Monatsschr. Psychiat. Neurol. **129**, 321–332 (1955a)
Morsier, G.: Etude sur les dysraphies cranio-encéphaliques. Schweiz. Arch. Neurol. Neurochir. Psychiat. **74**, 309–315 (1955b)
Mosberg, W., Voris, H.: Unusual congenital anomaly of agenesis of corpus callosum, absence of septum pellucidum and fusion of cerebral hemispheres. J. Neuropathol. **13**, 369–376 (1954)
Netzky, M.: Syringomyelia: clinico-pathologic study. Arch. Neurol. Psychiat. **70**, 741–756 (1953)
O'Rahilly, R.: Anomalous occipital apertures. Arch. Path. **53**, 509–517 (1952)
O'Rahilly, R., Gardner, E.: The timing and sequence of events in the development of the human nervous system during the embryonic period proper. Z. Anat. Entwicklungsgesch. **134**, 1–12 (1971)
Ostertag, B.: Mißbildungen. In: Handbuch der speziellen pathologischen Anatomie. F. Henke, O. Lubarsch u. R. Rössle (Hrsg.), Bd. X/4, S. 283. Berlin-Göttingen-Heidelberg: Springer 1956
Patten, B.: Embriología humana. 2a. Ed. esp. Buenos Aires: El Ateneo 1958
Pease, D.: Cellular aspects of neural growth and differentiation. Baltimore: Williams and Wilkins Co. 1971
Peters, G.: Neuropathología clínica. Barcelona: Toray, S.A. 1974
Poliakov, G.: Some results of research into the development of the neuronal structure of the cortical ends of the analyzers in man. J. Comp. Neurol. **117**, 197–212 (1961)
Popoff, N., Feigin, I.: Heterotopic central nervous tissue pervading subarachnoid space. J. Neuropath. Exp. Neurol. **23**, 177–178 (1964)
Rakic, P., Yakovlev, P.: Development of the corpus callosum and cavum septi in man. J. Comp. Neurol. **132**, 45–72 (1968)
Richman, D.P., Stewart, R.M., Caviness, V.S.: Cerebral microgyria in a 27-week fetus: an architectonic and topographic analysis. J. Neuropath. Exp. Neurol. **33**, 374–383 (1974)
Robinowicz, Th.: The cerebral cortex of the premature infant of the 8th month. Progr. Brain Res. **4**, 34–37 (1964)
Rubin, A.: Handbook of congenital malformations. Baltimore: Williams and Wilkins Co. 1969

Rubinstein, H., Freeman, W.: Cerebellar agenesis. J. Nerv. Ment. Dis. **92**, 134–145 (1940)
Sahs, A.: Congenital anomaly of vermis. Arch. Path. **32**, 52–59 (1941)
Sharp, J.: The junctional region of the cerebral hemispheres and the third ventricle in mamalian embryos. J. Anat. **93**, 159–171 (1959)
Shwidde, J.: Incidence of cavum septi pellucidi and cavum Vergae in 1032 human brains. Arch. Neurol. Psychiat. **67**, 625–632 (1952)
Sidman, R.L., Rakic, P.: Neuronal migration with special reference to developing human brain: a review. Brain Res. **62**, 1–35 (1973)
Smith, D.: Recognizable patterns of human malformation. In: Major problems in clinical pediatrics, Vol. VII. Philadelphia: W.B. Saunders Co. 1970
Starck, D.: Embryologie. 2. Auflage. Stuttgart: Thieme 1965
Streeter, G.: The peripheral nervous system in the human embryos at the end of the first month. Am. J. Anat. **8**, 285–316 (1932)
Streeter, G.: Developmental horizons in human embryos. Description of age group XI, 13–20 somites, and age group XII, 21–29 somites. Contrib. Embryol. **30**, 21–245 (1942)
Streeter, G.: Developmental horizons in human embryos. Description of age group XIII, embryos about 4 or 5 mm long, and age group XIV, period of indentation of the lens vesicle. Contrib. Embryol. **31**, 27–63 (1945)
Streeter, G.: Developmental horizons in human embryos. Description of age groups XV, XVI, XVII and XVIII. Contrib. Embryol. **32**, 113–203 (1948)
Streeter, G.: Developmental horizons in human embryos. Description of age groups XIX, XX, XXI, XXII and XXIII, being the fifth issue of the Carnegie Collection. Contrib. Embryol. **34**, 165–199 (1951)
Taggort, J., Walker, A.: Congenital atresia of foramen of Luschka and Magendie. Arch. Neurol. Psychiat. **48**, 583–592 (1942)
Tauber, E.: Study of syringomyelia and formation of cavities in spinal cord. J. Nerv. Ment. Dis. **81**, 245–285 (1935)
Tridon, P.: Les dysraphies de l'axe nerveux. Paris: A. Michel 1944
Tridon, P.: Les dysraphies de l'axe nerveux et de ses enveloppes cranio-raquidiennes. Thèse de Médicine (Nancy 1958). Paris: G. Doin 1959
Tuchmann-Duplessis, H.: Embriología. 1a ed. esp. Barcelona: Toray-Masson 1970
Walker, A.: Lissencephaly. Arch. Neurol. Psychiat. **48**, 13–31 (1942)
Walker, A.: Dilatation of the vertebral canal associated with congenital anomalies of the spinal cord. Am. J. Roentgenol. **52**, 65–72 (1944)
Werthemann, A.: Allgemeine Teratologie mit besonderer Berücksichtigung der Verhältnisse beim Menschen. In: Handbuch der allgemeinen Pathologie, F. Büchner, E. Letterer und F. Roulet (Hrsg.), Bd. VI/1, S. 58. Berlin-Göttingen-Heidelberg: Springer 1955
Wilson, S.: Microcephalie. Neurology **2**, 1423–1461 (1940)
Wolf, A., Bamford, T.: Cavum septi pellucidi and cavum Vergae. Bull. Neurol. Inst. New York **4**, 294–317 (1935)
Yokoh, Y.: The early development of the nervous system in man. Acta Anat. **71**, 492–518 (1969)

Received May 9, 1979