Virchows Arch. A Path. Anat. and Histol. 384, 285–294 (1979)

Virchows Archiv A

Possible Evidence for Secondary Degeneration of Central Nervous System in the Pathogenesis of Anencephaly and Brain Dysraphia

A Study in Young Human Fetuses*

Donald Ganchrow** and Asher Ornoy

Department of Anatomy and Embryology, Hebrew University-Hadassah Medical School, P.O.Box 1172, Jerusalem, Israel

Summary. In an attempt to help elucidate pathogenetically those human cases exemplifying secondary degeneration of the neural tube causing brain dysraphia, macroscopic and histologic observations of two young human fetuses are described. A nine-week-old anencephalic fetus exhibited an absence of spinal cord (amyelia) with retention of neural crest derivatives (dorsal root ganglion cells and their processes, and sympathetic ganglia) implying the presence of a neural tube in early gestation. The second, ten-week-old exencephalic case exhibited restricted brain hemorrhage and necrosis of the telencephalon and brain stem amongst otherwise normal brain and spinal cord tissue. These two young fetal cases may represent examples of a previously normal neural tube which has undergone degeneration at a stage where neural crest has already undergone differentiation, and thus distinguishes them from cases of complete dysraphism which probably results from primary degeneration during neurulation.

Key words: Anencephalus – Amyelia – Secondary degeneration – Central nervous system: abnormalities.

The aetiology of central nervous system (CNS) dysraphias often is attributed to environmental (Brent, 1977; J.H. Elwood, 1976; J.M. Elwood, 1976; Naggan, 1971), and/or genetic (Hanaway and Welch, 1970; Patten, 1953; Warkany, 1971) factors. A recent approach in human studies (Carter, 1974) combines both genetic and environmental elements in a multifactorial analysis of the aetiology of neural tube malformations. In the genetic category, CNS malformations in man may result from primary defects of the developing neural tube or its derivatives (Dekaban, 1963; Warkany, 1971), or, from primary degeneration of neural elements due to anomalies induced within the neuroectodermal-mesodermal milieu (Marin-Padilla, 1970). Environmental factors also may

* Supported in part by Myra Kurland Heart Fund Heart Research

** To whom offprint requests should be sent

0340-1227/79/0384/0285/$02.00

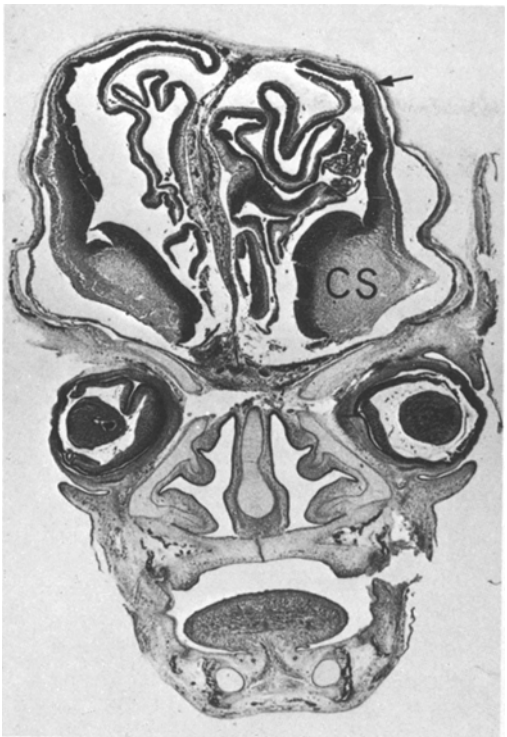


Fig. 1. Coronal section through the head of a ten-week-old control fetus showing developed cortical formation. Arrow points to cortex seen in higher magnification in Fig. 2. Note that the palatal shelves are normally fused at the midline; compare with the anencephalic case with accompanying cleft palate seen in Fig. 6. *CS*, corpus striatum. Case 588. H&E stain. × 12

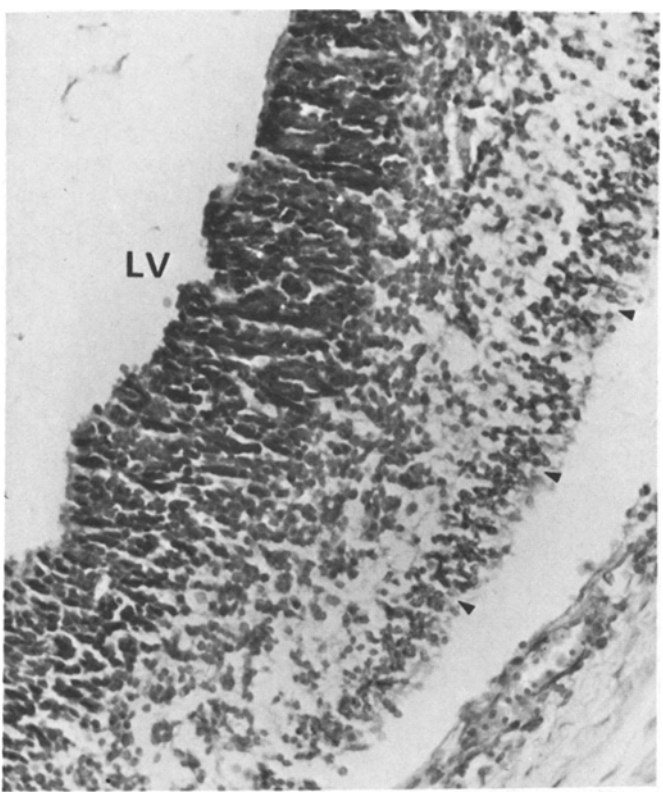


Fig. 2. Developing cortical formation of the ten-week-old control fetus seen in Fig. 1, under higher magnification. Arrowheads denote the relatively narrow neocortex; the periventricular cell layer appears as a denser, darker and wider cell band adjacent to the lateral ventricle (*LV*). Case 588. H&E stain. × 190

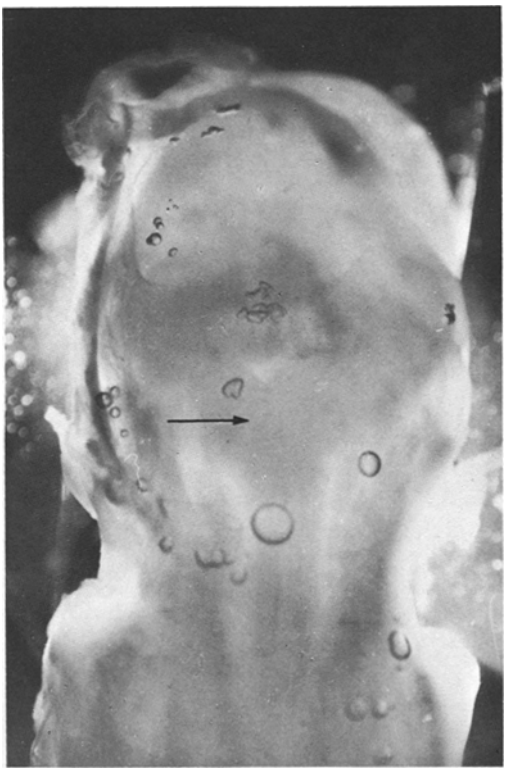


Fig. 3. Transilluminated view through the head and back of a ten-week-old control fetus to show the medullary substance, and spinal cord within the vertebral canal (*arrow*). Compare this with the anencephalic case with accompanying amyelia seen in Fig. 7. Case 588

contribute to the destruction of once normally developed neural tissue causing secondary degeneration of the latter. For example, clinical (Dekaban, 1968) and animal experimental (Hicks et al., 1959; Rugh and Grupp, 1959) data show that exposure to X-irradiation during various stages of pregnancy, even after neural tube closure, significantly affects the frequency of exencephaly, microcephaly, cortical heteropias, and abnormal neuronal architecture in the offspring.

Evidence in newborn infants often may support arguments favoring primary, or secondary degeneration of nervous system. On the other hand, the study of young fetuses may better clarify the aetiology and pathogenesis of brain dysraphias. We present two such young human fetuses, one anencephalic with accompanying amyelia, and the other exencephalic. Both examples raise the possibility that CNS dysraphia in humans may occur secondary to degeneration of a previously formed, normal neural tube. These cases exhibited normal neural crest derivatives either in the absence of spinal cord and brain (case I) or in parallel with local destruction of brain tissue (case II).

Case Reports

Controls

As controls we selected two spontaneously aborted fetuses without anomalies: case 616 with a crown-rump length (CRL) of 3.2 cm and case 588 with a CRL of 4.1 cm, which correspond to developmental ages of nine and ten weeks, respectively (Mall, 1910; Patten, 1968).

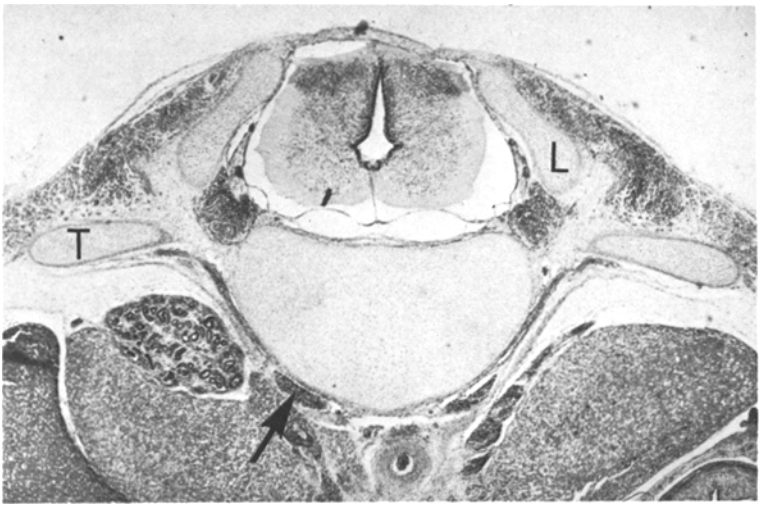


Fig. 4. Transverse section through the upper lumbar region of the vertebral column of a ten-week-old control fetus to show presence of meninges, sympathetic ganglion (arrow), dorsal root ganglia and dorsal roots, and spinal cord. Note transverse processes (*T*) and laminae (*L*) of the vertebrae fused across the midline by connective tissue. Case 588. H&E stain. ×17

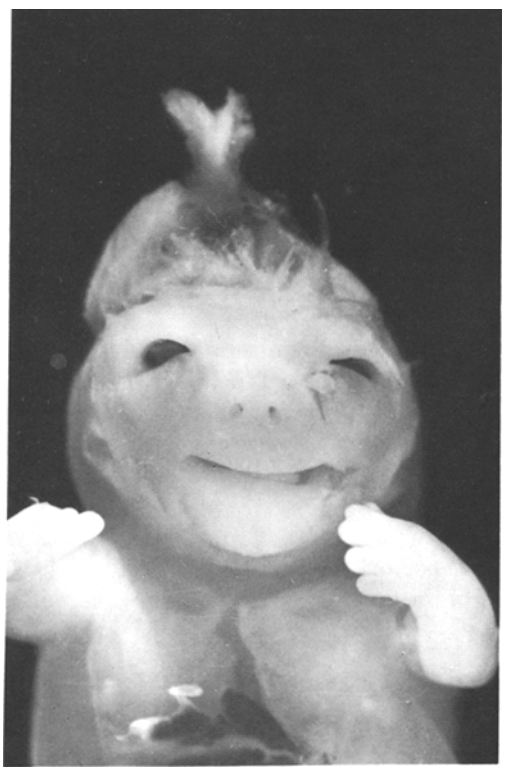


Fig. 5. Head and upper trunk of anencephalic case of ten weeks to show the commonly presented facial signs: broad face, large flattened nose, shortened forehead, a wide interocular distance, low-set ears and short neck, as well as a protruding mass in the area of the sagittal suture. Though not seen in the photograph, cleft palate was also evidenced

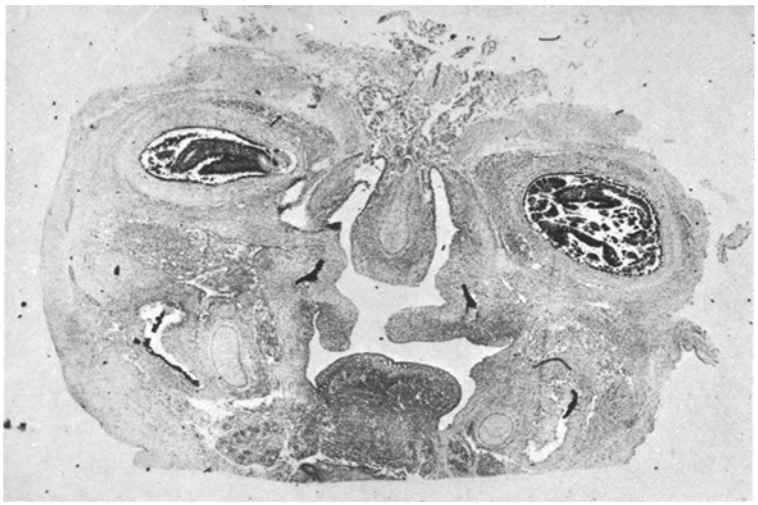


Fig. 6. Coronal section through the head of the anencephalic case, to show protruding neurovascular mass in the area where parietal bone primordia were absent. In addition, palatal shelves remain unfused presenting cleft palate; compare with control case in Fig. 1. H&E stain. ×12

Analysis of hematoxylin-and-eosin (H-and-E) stained sections of the head in the younger fetus showed that neurons had migrated peripherally from the periventricular zone to form the cortex. In the ten-week-old fetus cortex was wider and further developed (Figs. 1, 2). In addition, in both control fetuses spinal cord and meninges, and sympathetic ganglia, were seen normally positioned within, and without the spinal canal, respectively. Dorsal root ganglion cells and their distal and proximal processes also were evident, the latter entering the cord as dorsal roots. Transverse processes and laminae of the vertebrae were present but not vertebral spines (Figs. 3, 4). Finally, established primordia of different organs were identified in both control cases.

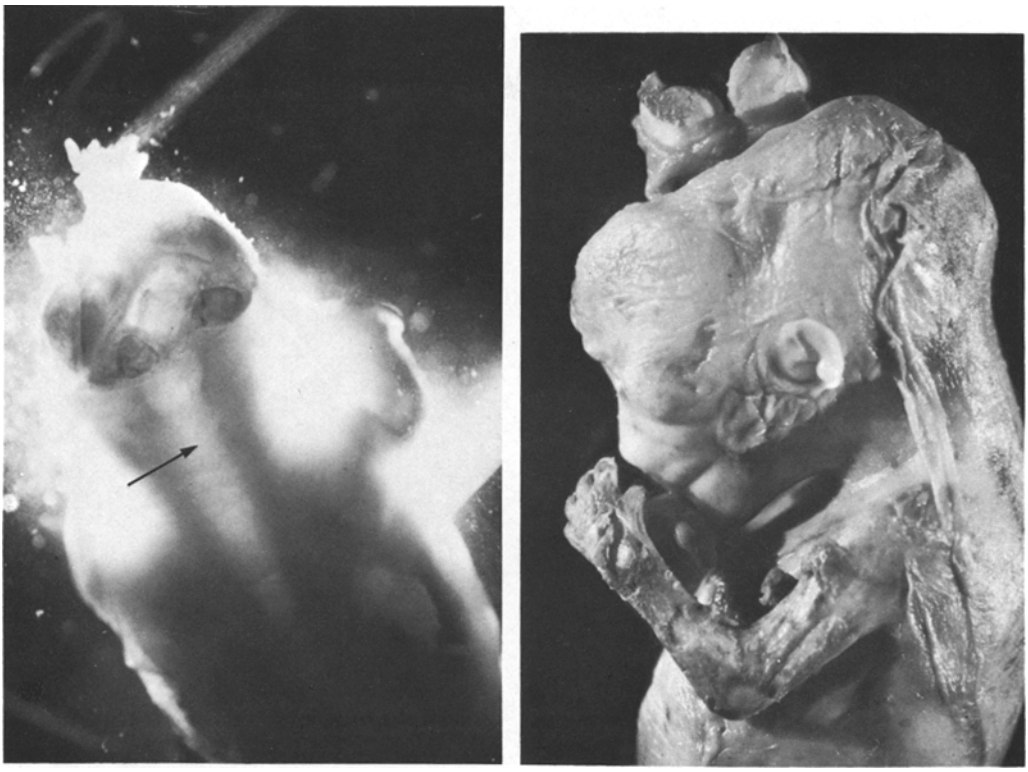
Affected Cases

Case I: Anencephaly and Amyelia

The mother was a healthy 29-year-old woman who had experienced a normal first birth six years previously, and who aborted spontaneously during the third month of her second present pregnancy. The fetus and placenta, without membranes, were submitted for examination. Microscopic examination of the placenta showed hypovascular villi, fibrosis and calcification, findings usually suggestive of missed abortion.

The fetus measured 4.0 cm CRL and weighed 2.96 g, corresponding to a developmental age of 9 weeks (Mall, 1910; Patten, 1968). In addition to a protruding mass in the area of the sagittal suture, and evidence of cleft palate, the facial signs commonly presented in anencephaly were seen: broad face, large flattened nose, shortened forehead, a wide interocular distance, low-set ears and a short neck (Fig. 5).

Microscopic examination of coronal sections through the head further emphasized the following features characteristic of anencephaly: parietal bone primordia were absent whereas those of the frontal bone were present. Most striking was a lack of recognizable brain structures and the presence of a neurovascular tissue mass caudal to frontal bone primordia, which probably represents brain remnants (Fig. 6). Standard H-and-E staining showed the presence of retinal pigmented epithelium, but neither this nor Nissl (cresylecht violet) stains decisively revealed retinal ganglion cells, absence of which may accompany anencephaly (Mann, 1957; Sabato, 1973; Warren, 1951). Trigeminal ganglia also were evident, and all other facial and visceral organs were structurally normal. The vertebrae appeared normal for their developmental age.



Fig,. 7. Transilluminated view through the head and back of the anencephalic case, to show the total absence of spinal cord within the vertebral canal (*arrow*). Compare this empty spinal canal with cord substance seen in the control case in Fig. 3

Fig. 8. Lateral view of the head and upper trunk of the exencephalic case of ten weeks to show a cerebrovascular mass protruding between frontal and occipital bone primordia

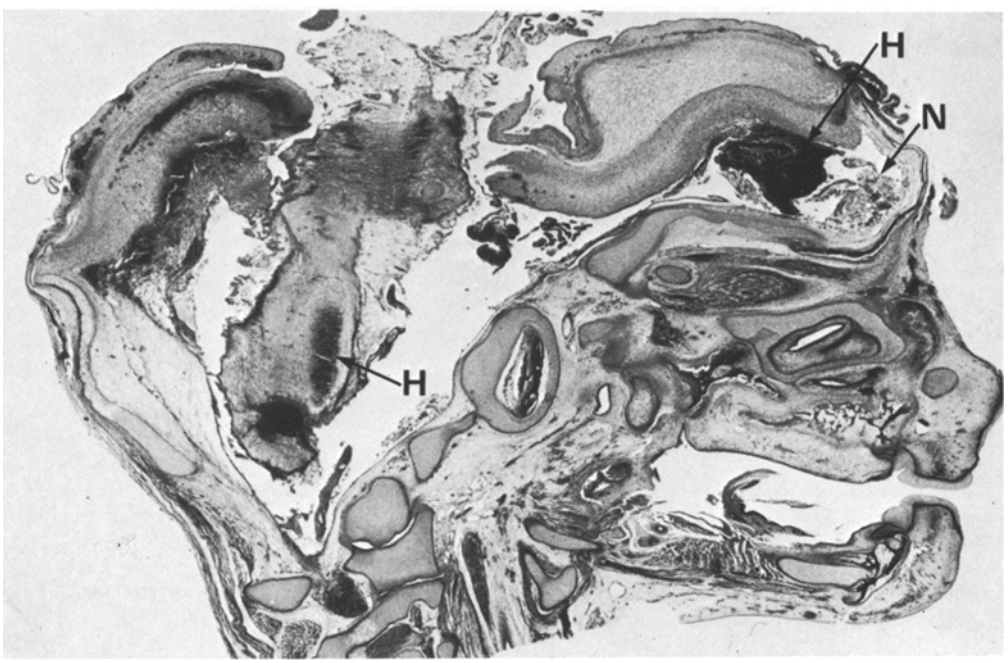


Fig. 9. Parasagittal section through the head of the exencephalic case. Note absence of calvarium in parietal region. Arrows denote areas of hemorrhage (*H*) in the telencephalon and brain stem, and necrosis (*N*) below the frontal bone primordia. H&E stain. ×9

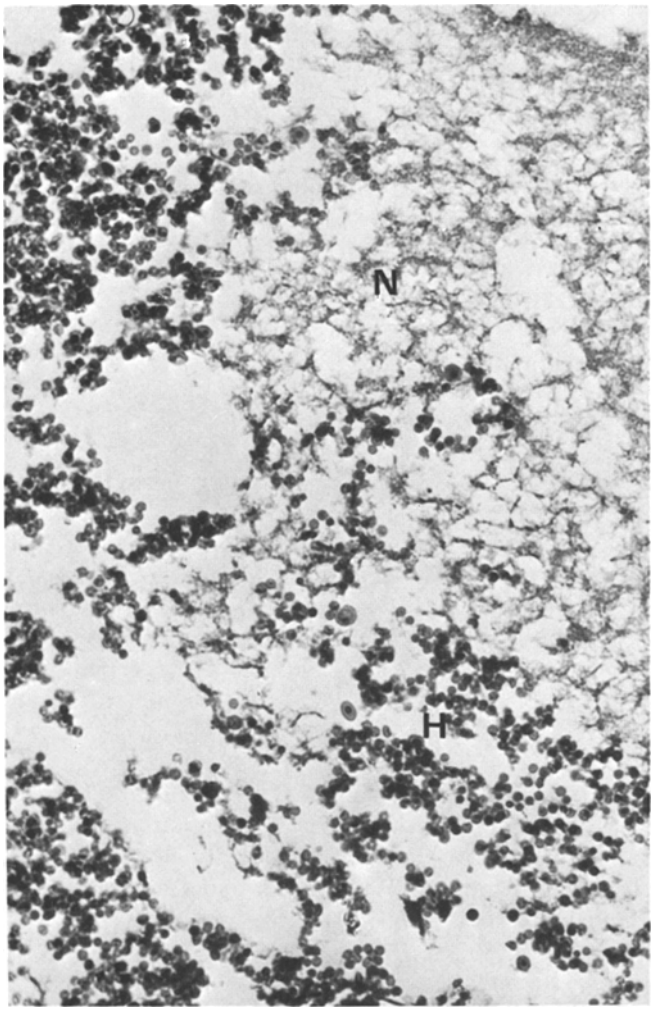


Fig. 10. Higher magnification of necrosis (*N*) and hemorrhage (*H*) in the telencephalon of the exencephalic case. H&E stain. ×252

Further macroscopic study, and histologic examination of serial sections revealed that the vertebral canal contained meninges but lacked spinal cord substance (Fig. 7). However, H-and-E staining showed that neural crest derivatives were evident, that is, dorsal roots and their ganglia as well as sympathetic ganglia. Unfortunately, Nissl staining was not definitive for identifying dorsal root ganglion and satellite cells, possibly due to the limited amount of extranuclear cytoplasm amongst the intraganglionic cell population. Many vessels within the vertebral canal contained small darkly-stained mononuclear, lymphocyte-like cells, and a lesser number of nucleated red blood cells.

Case II: Exencephaly

This spontaneous abortion, in the third month, consisted of a fetus, placenta and membranes; unfortunately, the mother's history file could not be located in hospital records.

Microscopic examination of the placenta showed an increased number of Hofbauer cells and edema in the villi. The decidua and membranes did not show evidence of inflammatory processes.

The fetus measured 4.6 cm CRL and weighed 3.5 g, corresponding to a developmental age of ten weeks (Mall, 1910; Patten, 1968). Macroscopic examination showed a mass protruding through an opening located between occipital and frontal bone primordia (Fig. 8). Histologic examination of the head revealed absence of the parietal bone precursor. Occipital and frontal bone primordia were intact, but most of the telencephalon was absent, and in the underlying remnants of cerebral tissue multiple foci of hemorrhage and necrosis were evident (Figs. 9, 10). Most regions of caudal brain stem, and choroid plexus, appeared normal microscopically though hemorrhagic foci were evident in the fourth ventricle and underlying brain stem. Spinal cord and dorsal root ganglion cells also were present and appeared normal.

All other fetal organs appeared normal by macroscopic and microscopic examination, and were developed to the age of ten-to-eleven weeks.

Discussion

Both young cases are presented here as possible examples of secondary degeneration of the neural tube causing brain dysraphia. The nine-week-old anencephalic fetus combined an absence of spinal cord with presence of neural crest derivatives. In cases of severe primary neural tube defects, as for example complete myeloschisis (rachischisis), the common accompanying manifestations are anomalies both of the vertebral body and of neural crest derivatives (Willis, 1962). Further, it is reasonable to assume that complete failure of the neural tube to develop would inhibit the embryo from developing beyond the trilaminar stage, probably resulting in abortion of an amorphous or nodular embryo. The fact that in this case of amyelia and anencephaly there were apparently normal neural crest derivatives and vertebral column implies that the neural tube was present during early phases of development. Differentiation of neural tube and neural crest occurs during stages X–XI of Streeter which corresponds to 22–24 days of gestation (Lemire et al., 1975; O'Rahilly and Gardner, 1971). Therefore, we believe that the degeneration of neural structures probably occurred after 24 days of gestation.

De Vries described (1927) the fascinating case of an eight-week-old (developmental age) anencephalic and amyelic embryo which most closely parallels those characteristics of the case reported here. He found an absence of all brain stem structures and cervicothoracic spinal cord while at lumbosacral levels the meningeal sac contained remnants of neural tissue. In addition, dorsal root ganglia and their communicating nerve branches with sympathetic ganglia, developing vertebral column, meninges, and cranial sensory ganglia were present and appeared normal. Limb and facial muscles and their peripheral innervation also appeared normal, whereas the proximal portions of the nerves were never found to enter the CNS and often ended within mesenchymatous tissue. Motor nerve roots were absent along the entire length of the spinal axis. From these intriguing findings De Vries reasoned that the effect of the etiologic agent was manifested after motor root outgrowth of the cranial nerves from the CNS, that is, certainly not earlier than the 10 somite stage (approximately 19–21 days of gestation). He suggested that there was late destruction of the spinal cord, and concluded:

> "... I am inclined to think that in the lumbrosacral part a spinal cord must have been present, which has degenerated afterward from some unknown cause." (p. 316).

Finally, the alternative possibility may be raised that somehow neural crest tissue differentiated despite failure of neural fold closure during neurulation.

In the ten-week-old exencephalic case, hemorrhage and necrosis of cerebral tissue was found parallel with normally appearing caudal brain stem, spinal cord and choroid plexus, suggesting local destruction of neural tissue in a primarily normal brain. If a primary telencephalic defect had occurred during stage XI, when normally the anterior neuropore is undergoing closure, probably most of the forebrain would have degenerated (Lemire et al., 1975) in contrast to the restricted destruction reported here. Such localized cortical degeneration within the brain case may have been the consequence of brain overgrowth, or vascular accident. It has been proposed that overgrowth may result from neural tissue protruding through the rupture of a previously closed neural tube as caused by hydrocephalomyelia (Gardner, 1961, 1973). Chaurasia (1977) has shown that in many cases of anencephaly in fetuses, some rudimentary forebrain may remain, rostral to a median dorsal opening in cranium located in the region of the posterior diencephalic roof, suggesting that the cephalic portion of the neural tube is normally closed and that degeneration of forebrain may occur thereafter.

Mononuclear, lymphocyte-like cells were present in the circulation of the anencephalic fetus, which possibly may be interpreted as a sign of infection. The placental findings in this case suggested missed abortion. Possibly, fibrosis and calcification of the villi may have masked definite morphologic signs of inflammatory lesions; unfortunately, the membranes were not presented for examination. Therefore, on may speculate that infectious agents may have been causative factors for our case of anencephaly, as similarly, have congenital rubella and cytomegalovirus been shown to produce different CNS anomalies in humans (Harris, 1974; Ornoy et al., 1973). Moreover, the neurovascular mass reported in the anencephalic may be analogous to the appearance of granulation tissue (fibroblasts and blood vessels) which forms during stages of inflammation and repair (Washburn, 1960).

In summary, we suggest that the two cases of brain and spinal cord dysraphia presented here resulted from secondary degeneration of nervous system tissue, other examples of which have been reported previously (Chaurasia, 1977; Gardner, 1973; Menashi et al., 1977; Patten, 1953). This may serve as an alternative explanation to the commonly accepted mechanism underlying neural tube defects, that is, dysraphia which results from primary defects occurring during neurulation (Dekaban, 1963; Langman and Welch, 1966).

Acknowledgements. We gratefully acknowledge the skilled histologic preparations of Mrs. Sylvia Meier and Mrs. Louise Peretz, and the photographic assistance of Mrs. Fanny Reichert.

References

Brent, R.L.: Radiations and other physical agents. In: Handbook of teratology (J.G. Wilson and F.C. Fraser, eds.), vol. 1, pp. 153–223. New York: Plenum Press 1977

Carter, C.O.: Clues to the aetiology of neural tube malformations. Dev. Med. Child Neurol. **16** (6 Suppl. 32), 3–15 (1974)
Chaurasia, B.D.: Forebrain in human anencephaly. Anat. Anz. **142**, 471–478 (1977)
Dekaban, A.S.: Anencephaly in early human embryos. J. Neuropath. Exp. Neurol. **22**, 533–548 (1963)
Dekaban, A.S.: Abnormalities in children exposed to X-irradiation during various stages of gestation: tentative timetable of radiation injury to the human fetus, Part 1. J. Nucl. Med. **9**, 471–477 (1968)
Elwood, J.H.: Anencephaly and spina bifida in the British Isles. In: Birth defects. Risks and consequences (S. Kelly, E.B. Hook, D.T. Janerich and I.H. Porter, eds.), pp. 21–39. New York: Academic Press 1976
Elwood, J.M.: Anencephalus and spina bifida in North America. In: Birth defects. Risks and consequences (S. Kelly, E.B. Hook, D.T. Janerich and I.H. Porter, eds.), pp. 3–19. New York: Academic Press 1976
Gardner, W.J.: Rupture of the neural tube. Arch. Neurol. **4**, 1–7 (1961)
Gardner, W.J.: The dysraphic states: from syringomyelia to anencephaly. Amsterdam: Excerpta Medica 1973
Hanaway, J., Welch, G.: Anencephaly: a review and interpretation in terms of modern experimental embryology. Dis. Nerv. Syst. **31**, 527–533 (1970)
Harris, R.E.: Viral teratogenesis: a review with experimental and clinical perspectives. Am. J. Obstet. Gynecol. **119**, 996–1008 (1974)
Hicks, S.P., D'Amato, C.J., Lowe, M.J.: The development of the mammalian nervous system. I. Malformations of the brain especially the cerebral cortex, induced in rats by radiation. II. Some mechanisms of the malformations of the cortex. J. Comp. Neurol. **113**, 435–469 (1959)
Langman, J., Welch, G.W.: Effect of Vitamin A on development of the central nervous system. J. Comp. Neurol. **128**, 1–16 (1966)
Lemire, R.J., Loeser, J.D., Leech, R.W., Alford, Jr., E.C.: Normal and abnormal development of the human nervous system. New York: Harper and Row 1975
Mall, F.P.: Determination of the age of human embryos and fetuses. In: Manual of human embryology (F. Keibel and F.P. Mall, eds.), vol. 1, pp. 180–201. Philadelphia: Lippincott 1910
Mann, Ida: Developmental abnormalities of the eye, pp. 50–55. London: British Medical Assn. 1957
Marin-Padilla, M.: Morphogenesis of anencephaly and related malformations. In: Current topics in pathology, vol. 51, pp. 145–174. Berlin: Springer 1970
Menashi, M., Ornoy, A., Cohen, M.M.: Anencephaly in trisomy 18: related or unrelated? Teratology **15**, 325–328 (1977)
Naggan, L.: Anencephaly and spina bifida in Israel. Pediatrics **47**, 577–586 (1971)
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. EntwGesch **134**, 1–12 (1971)
Ornoy, A., Segal, S., Nishmi, M., Simcha, A., Polishuk, W.Z.: Fetal and placental pathology in gestational rubella. Am. J. Obstet. Gynecol. **116**, 949–956 (1973)
Patten, B.M.: Embryological stages in the establishing of myeloschisis with spina bifida. Amer. J. Anat. **93**, 365–395 (1953)
Patten, B.M.: Human embryology. New York: McGraw-Hill 1968
Rugh, R., Grupp, E.: Exencephalia following X-irradiation of the pre-implantation mammalian embryo. J. Neuropath. Exp. Neurol. **18**, 468–481 (1959)
Sabato, S.: Anencephaly, a congenital malformation of the central nervous system, as demonstrated by two infants born at the Hadassah Medical Center in 1971. M.D. Thesis, unpublished (1973)
de Vries, E.: Description of a young anencephalic and amyelic embryo. Anat. Rec. **36**, 293–317 (1927)
Warkany, J.: Congenital malformations. Chicago: Year Book Medical Publishers, Inc. 1971
Warren, H.S.: Acrania induced by anencephaly. Anat. Rec. **111**, 653–667 (1951)
Washburn, W.W.: Wound healing as a problem of growth. In: Fundamental aspects of normal and malignant growth (W.W. Nowinski, ed.), pp. 664–711. New York: Elsevier Publ. 1960
Willis, R.A.: The borderland of embryology and pathology, pp. 147–163. London: Butterworths 1962

Received March 17, 1979