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Editorial

A view of neurospinal dysraphism

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Knowledge of the role of growth factors in mesodermal induction, of homeobox genes in the determination of cephalocaudal gradients and of proto-oncogenes in induction has offered the tantalising prospect of a more readily comprehensible genetic mechanism for major malformations; indeed, some well-defined anomalies may be produced by alteration in homeobox expression (see Wolgemuth et al. 1989; Chisaka and Capecchi 1991). More recently, the so-called paired motif genes (e.g. *Pax-1*) have been shown to be altered in various mouse mutant alleles which are manifest as spinal anomalies (*undulated*) and variations in the *Pax-3* genes produce animals with well-defined neurospinal dysraphism (including exencephaly, meningomyelocele and spina bifida – see Balling et al. 1989). It is worth looking at the pathology of neurospinal dysraphism in the light of these new data, but it is of interest to note that accurate pathological studies have helped in the process of understanding.

This complex series of malformations is probably best considered in three categories: cranioschisis aperta (open cranium) with encephaloschisis (anencephaly), cranioschisis occulta with encephalocele, and the Chiari malformation with hind-brain, cerebellar and aqueductal developmental compression and deformity (Marin-Padilla 1991). The two classical theories of non-closure of the neural tube (von Recklinghausen) or rupture of a closed neural tube (Morgagni) are 100 and 200 years old respectively and experimental evidence has been adduced to support either in particular models. The vast literature on this subject is confused, displays wonderful examples of prejudice, unshakable commitment to untenable hypotheses and, importantly, ignorance of pathological findings.

Both cephalic and caudal anomalies may vary in extent and severity and in associations with other defects. These associations are clearly important in developing a view of pathogenesis; the valuable paper of Marin-Padilla (1991) has emphasized the necessity of considering neural anomalies in association with the accompanying skeletal and oropharyngeal defects in attempts to comprehend the embryogenesis of these malformations. He points out that the separately formed axial basicranium (skull base) the neurocranium (cranial vault) and the visceral cranium (the facial skeleton) are all affected differently in the different anomalies.

The basicranium is established before the closure of the anterior neuropore. Paraxial mesoderm accumulates around the anterior end of the notochord and forms much of the axial chrondrocranium, including the sphenoid bone. The occipital bone is part of this structure and it is now thought that a component of the segmented mesoderm may contribute to it; it is pointed out by Marin-Padilla and Marin-Padilla (1977) that the occipital bone behaves like vertebrae in certain of the chondrodystrophies. Altered development of the paraxial mesoderm in the genesis of the defects would affect the formation of the axial skeleton and the elevation of the neural folds and relate cranial and caudal defects.

The involvement of the viscerocranium is essentially secondary to basicranial (mainly sphenoid) anomalies. It is neural crest derived and all of its major components articulate with the sphenoid bone, the central component of the basicranium.

The neurocranium (cranial vault) is composed of membrane bones derived ultimately from the paraxial unsegmented and segmented mesoderm and from the neural crest. A primitive meninx splits into two layers giving rise to bones and to the meningeal coverings of the brain. In cephalic disorders, the neurocranial bones are only partly formed and the extent of the original defect indicates the extent of the original failure of closure of the cephalic neural folds.

More recently made assertions in this debate have centered around which tissues are initially affected in the developmental failure of the early CNS, although the pathological data indicate a vital role for mesoderm. The accepted embryological view has long been that the neuroepithelium is primarily affected and that associated mesenchymal (vertebral) anomalies are secondary, but some time ago Morriss (1972) suggested that hypervitaminosis-A-induced exencephaly is related to an effect

on mesenchyme. Alles and Sulik (1990) have shown that high doses of retinoic acid produce excessive cell death in the presumptive neural crest and in the tissues underlying the posterior neural plate. Eversion of the neural plate at the posterior neurophore occurs due to continued growth of the neural plate while there is delayed growth in the mesenchyme of the primitive streak and tail gut. In several experimental systems combined skeletal, neural and oropharyngeal defects are produced by vitamin A.

If these observations are related to the work of Marin-Padilla it is evidently plausible, as he suggests, that a primary paraxial mesodermal insufficiency prevents proper formation of the axial basicranium. The neural folds, if they fail to reach an appropriate elevation, will not close normally (note that the whole neural fold, not only the neural tube, is affected). The extent of any defect is dependent on the severity of the mesodermal defect – in severe anomalies the surface ectoderm, the neural crest cells, supporting paraxial segmented and unsegmented mesoderm and neurectoderm are affected and the neural folds fail to close altogether. Partial defects which allow the closure of the surface ectoderm and its supporting mesoderm while the neuroectoderm remains open, give rise to encephaloceles and meningomyeloceles. In this type of defect the neural folds could also close normally, as in the Chiari malformation. The Marin-Padilla account of this malformation emphasises that in the Chiari malformation the base of the skull is shortened with hypoplasia of the occipital bone and the posterior fossa. This produces a subtentorial space too small to accommodate the hindbrain and cerebellum with forced outgrowth of nervous tissue through the foramen magnum. The aqueduct compression produced results in hydrocephalus and further compression of the posterior fossa.

It is possible to see that failure of induction of neurectoderm by mesoderm might well be a major factor in the genesis of dysraphism. There are many possible mechanisms; in mouse defects paired-motif gene anomalies appear to be increasingly recognised – the *Pax 1* gene has a pattern of expression which is specific and limited to the developing somites in the region of the intervertebral discs, structures specifically affected in the *undulant* gene produced anomaly. The *Brachyury* gene (*T*) plays a direct role in mesoderm formation and in the formation of the notochord; in homozygous embryos there is gross disturbance of the primitive streak and death; heterozygotes may show abnormalities of the sacral vertebrae only. As Herrmann (1991) implies in his recent paper this gene, which appears to be expressed under the influence of peptide growth factors such as bFGF, may be the type of gene to study in unravelling the problems of early interactions between mesoderm formation and axial organisation. The enormously important early inductions in the pre-embryonic stages of development may be affected by many environmental factors, but increasingly the interaction of genes responsible for positional information, induction, and growth of anlage to sizes which permit morphogenetic movement are being defined.

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