The similarity between *Drosophila* and C. *elegans* early embryos extends beyond the parallels between *hunchback* and *glp-1* translational regulation. Both embryos contain cytoplasmic "granules" in the posterior region of the zygote that are segregated ultimately to germ cell precursors during embryogenesis—the polar granules of *Drosophila* (*14*) and the P granules of C. *elegans* (*15*) (see figure). In *Drosophila*, maternal *nanos* RNA is associated with polar granules; perhaps in C. *elegans*, a homolog of *nanos* is associated with P granules.

What about vertebrates? Does translational repression in the posterior cytoplasm establish embryonic polarity in these "higher" animals? A hint that this mechanism may indeed function in vertebrates comes from the identification of a maternal transcript that encodes a nanos-like protein called Xcat-2 in *Xenopus* embryos (*16*). Although the function of Xcat-2 is unknown, its location at the vegetal pole suggests a role in early pattern formation. Furthermore, a "germ plasm" exists in the vegetal cytoplasm of amphibian embryos that may be analogous to P granules and polar granules of worms and flies (*17*). Over the past decade, a handful of molecular mechanisms have been implicated in the patterning of *Drosophila*, C. *elegans*, and *Xenopus* embryos (*1*, *18*, *19*). On the basis of the diversity of these mechanisms, the prevailing view has been that each embryo has differentially employed a handful of common molecular mechanisms to create its own coordinate system. For example, localized transcriptional activators are utilized for patterning of both C. *elegans* and *Drosophila* early embryos (*20–23*), but the mechanisms for localization, types of DNA binding protein, and specified fates are not obviously similar.

By contrast, the molecular parallels between *hunchback* and *glp-1* regulation suggest the existence of an ancient mechanism for creating asymmetric patterns of gene expression in early embryos (see figure). This mechanism is predicted to depend on a trans-acting regulator similar to nanos and to act through cis-acting sequences similar to NREs in the 3'UTRs of maternal transcripts. If this molecular machinery regulates polarity in embryos as diverse as worms, flies, and frogs, it becomes plausible that it influences axis formation in all animal embryos, including mammals. "Molecular tinkering" (*24*) may then come into play to reinforce this primitive patterning control and to derive other axes from it.

Research in *Drosophila* has pioneered our understanding of the molecular mechanisms that can establish the body axes in an early embryo. Now, phylogenetic comparisons will tell us which mechanisms are primitive and which have evolved to reinforce, modify, or extend the underlying map. Are the controls that localize translational repression conserved? Are polar granules the ancient seat of pattern governance? What links the early controls of axis formation to the later controls of homeobox genes, a highly conserved system that specifies individual regions along the anterior-posterior axis of all known metazoa (*25*)? The *hunchback* protein is a transcriptional regulator that resides at the top of a cascade of transcriptional regulators, whereas the glp-1 protein is a membrane receptor that directs inductive interactions. Clearly, these distinct modes of regulation must converge to control expression of homeobox genes. How similar are the mechanisms of convergence? Answers to these questions, among the most fundamental of all developmental biology, may be waiting around the corner.

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The Embryonic Vertebrate Forebrain: The Prosomeric Model

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The mammalian forebrain—the cerebral cortex, basal ganglia, hypothalamus, and thalamus—is the seat of higher cognitive functions. How much of forebrain development and structure is controlled by a genetic program? Although at the later stages of development incoming synaptic information from the thalamus has been shown to influence patterning in the neocortex (*1*), at early embryological stages a specific set of newly discovered genes pattern the brain into a highly organized structure—before synaptic influences are present. Furthermore, the primordia of major structural elements, such as the thalamus, are segregated by cellular boundaries that are aligned parallel to the topologically transverse and longitudinal axes of the neural tube. Specific combinations of genes that are expressed in these domains direct the unique development of each region. Finally, the organization of the forebrain indicates that it is a segmental structure.

The basic morphogenetic unit of embryonic insects is a transverse domain, or segment (*2*). The identity of each segment is determined by its position along the anterior-posterior axis and is controlled by the expression of the homeobox segment identity genes (*3*). These genes encode transcriptional regulators of specific sets of target genes, which define the unique developmental pathway of each individual segment.

It is widely held that this paradigm may apply to the organization of the somitic mesoderm (the vertebral column), the rhombencephalon (hindbrain), and the branchial arches of vertebrates. This view is based on the existence of homologs of the homeobox segment identity genes in vertebrates (the *Hox* genes) (*3*) as well as the metameric (segmental) morphological and histological features of these structures. This hypothesis has been confirmed in part by the use of genetic manipulations that al-

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ter the expression of homeobox genes. For instance, null mutations in *Hox-a2*, *Hox-b4*, *Hox-c8*, and *Hox-d3* and ectopic expression of *Hox-a7* and *Hox-d4* change the identity of vertebral and cranial bones (homeotic transformations) (*4*). In the central nervous system, overt morphological segmentation of the hindbrain is transiently apparent during embryogenesis when it is subdivided into seven or eight discrete units (rhombomeres) by constrictions in the wall of the neural tube (*5*). These constrictions correspond to boundaries that partially restrict the intersegmental mixing of neuroepithelial cells (*6*) as well as the intercellular movement of molecules whose molecular mass is greater than approximately 300 daltons (*7*). As in the *Drosophila* embryo, the expression of homeobox and other candidate regulatory genes is delimited by segment boundaries (*8*). Moreover, a null mutation in one of these genes (*Hox-a1*) alters the development of the anteriormost segments in which it is expressed (*9*, *10*).

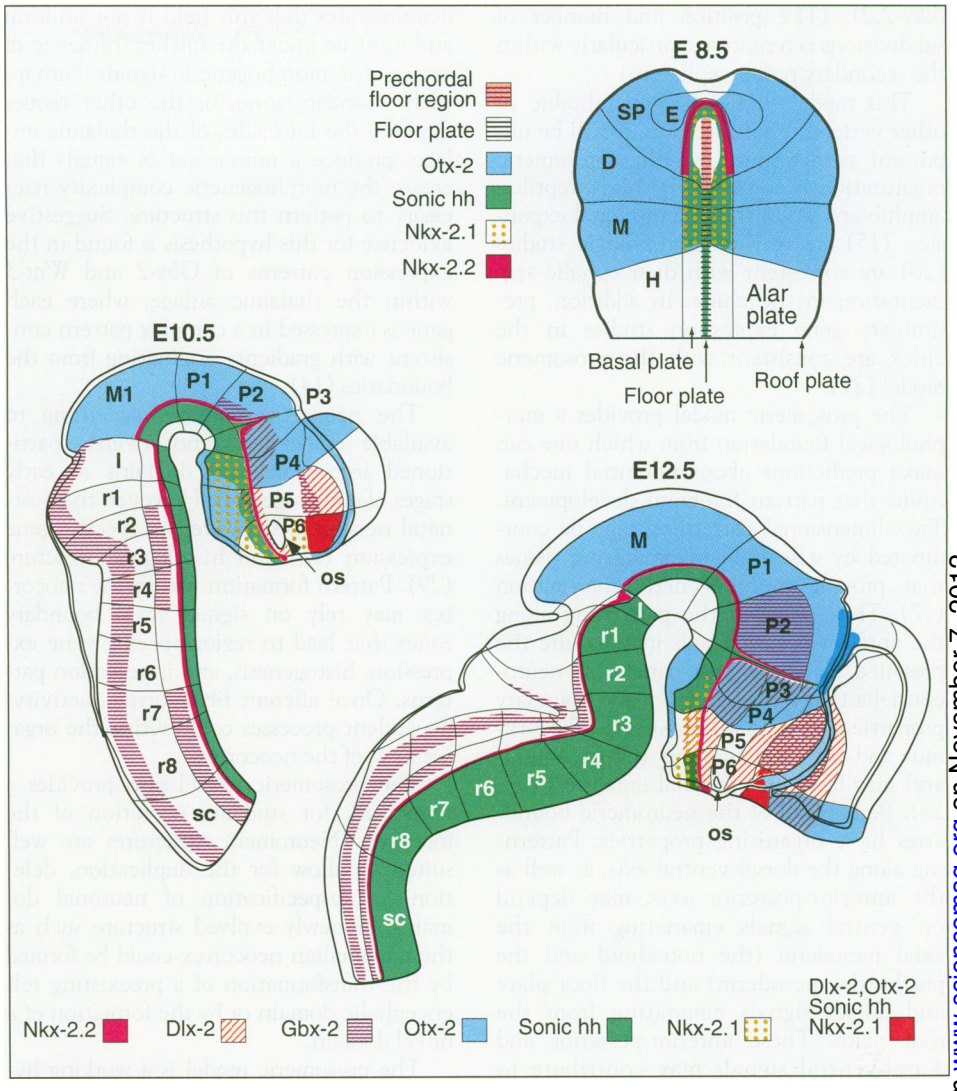
Are the more anterior parts of the vertebrate central nervous system also segmentally organized? The complex morphology and histology of the forebrain have led to divergent views about its embryologic organization. A century-old school of neuroembryology has postulated that segmentation contributes to subdividing functionally distinct domains of the central nervous system (*11*). However, the generally accepted anatomical viewpoint is based on an alternative model of forebrain organization—the "columnar model" of Herrick and Kuhlenbeck [see (*11*) for a comparison of the neuromeric and columnar models]. Recently, a number of publications have revived efforts to elucidate the organization of the embryonic forebrain. This renewed interest was stimulated in part by the discovery of a large number of regulatory genes that are expressed in regionally restricted patterns in the forebrain. Among these are at least 30 homeobox genes, some of which—such as members of the *Dlx*, *Emx*, and *Otx* families—are related to the *Drosophila* genes *Dll*, *Ems*, and *Otd* (*12*). These genes direct the pattern of head development in *Drosophila* (*13*).

Various studies have concluded that at least part of the forebrain is segmentally organized (*11*, *12*, *14*–*20*). Our conclusion that the forebrain is made up of segments is based on morphological considerations (for example, the presence of transverse constrictions in the wall of the neural tube in several species), on the expression patterns of candidate regulatory genes in mouse and chicken embryos (*14*, *21*), and on experimental embryological results (*22*, *23*).

We have proposed (*11*, *12*, *14*) that the forebrain is subdivided into six transverse domains (forebrain segments) named prosomeres [by the terminology of Vaage (*24*)] (see figure). The prosomeres can be grouped into two large transverse subdivisions: The diencephalon (which includes prosomeres p1 to p3) and the secondary prosencephalon (p4 to p6). The ventral region of the secondary prosencephalon consists of the hypothalamus; the telencephalic vesicles constitute its dorsal aspect.

Furthermore, according to this "prosomeric model" the forebrain is also organized into longitudinal domains, nonoverlapping regions parallel to the longitudinal axis of the neural tube. These domains are analogous to the roof, alar, basal, and floor plates of the spinal cord, and each of the prosomeres is subdivided by them. The model rests on our definition of the longitudinal axis of the forebrain, which follows the ventral and the dorsal midlines. The prosomeric and columnar models largely differ in their definitions of the longitudinal axis (*11*, *25*).

This model has been tested by examining the expression of some 30 different genes in mouse and chicken embryos at various stages of embryogenesis (*11*, *14*, *21*) (see figure). Each of the transverse (neuromeric) subdivisions coincides with the expression boundaries of several genes, some of which are shown in the figure (for example, *Gbx-2* is expressed in most of the alar plate of p2). Several genes are expressed in cells located in specific transverse boundary zones (*sonic hedgehog* in the p2-p3 boundary). In addition, the expression patterns have defined a number of longitudinal domains that extend across several or all of the brain segments (such as



Prosomeres defined by gene expression. The expression of six genes—*Dlx-2 14*, *Gbx-2 14*, *Nkx-2.119*, *Nkx-2.2 19*, *Otx-2 18*, and *sonic hedgehog* (*sonic hh*) (*31*)—in the neural plate (E8.5) and the neural tube (E10.5 and E12.5) of the embryonic mouse brain. The fate map of the neural plate is based on the studies of other workers [see references in (*11*)], and its relation to the expression patterns is hypothetical. The provisional transverse and longitudinal boundaries are indicated as thin black lines. D, diencephalon; E, eyes; H, rhombencephalon-hindbrain; I, isthmus; M, mesencephalon-midbrain; os, optic stalk; p, prosomere; r, rhombomere; sc, spinal cord; SP, secondary prosencephalon. [Data adapted from (*11*, *14*, *21*)]

Nkx-2.2). (The position and number of subdivisions is tentative, particularly within the secondary prosencephalon.)

This model should be generalizable to other vertebrate species; thus, it will be important to determine whether prosomeric organization is conserved in birds, reptiles, amphibians, and fish. Recent clonal expansion (*15*) and earlier morphologic studies (*26*) are consistent with diencephalic segmentation in the chick. In addition, preliminary gene expression studies in the chick are consistent with the prosomeric model (*21*).

The prosomeric model provides a morphological foundation from which one can make predictions about potential mechanisms that pattern forebrain development. Two-dimensional patterning may be coordinated by a scaffold of organizing tissues that provide morphogenetic information (*27*). Thus, some of the patterning along the anterior-posterior axis may require the presence of transverse rings of neuroepithelia that have inductive and boundary properties (transverse organizers). The isthmus and the zona limitans (p2-p3 boundary) may be neuroepithelial organizers (*22*, *23*). Perhaps all of the neuromeric boundaries have organizing properties. Patterning along the dorsal-ventral axis, as well as the anterior-posterior axis, may depend on ventral signals emanating from the axial mesoderm (the notochord and the prechordal mesoderm) and the floor plate and dorsal signals emanating from the roof plate. These anterior-posterior and dorsal-ventral signals may contribute to the progressive parcellation of the neuroepithelium into a grid-like arrangement of histogenic fields such as the thalamus.

The histogenic fields are patterned along three dimensions. Patterning along the medio-lateral axis involves differential migration of neuronal populations to sequentially form deep and superficial nuclei or layers. Patterning along the anterior-posterior and dorsal-ventral axes may be regulated by the boundary zones encasing the fields. For instance, the entire dorsal thalamus is derived from one alar longitudinal domain in p2 (see figure). That the thalamic anlage gives rise to multiple nuclei demonstrates that this field is not uniform and must be under the further influence of asymmetric morphogenetic signals. Perhaps each boundary zone, or the other tissues flanking the four sides of the thalamic anlage, produce a unique set of signals that create the morphogenetic complexity necessary to pattern this structure. Suggestive evidence for this hypothesis is found in the expression patterns of *Gbx-2* and *Wnt-3* within the thalamic anlage, where each gene is expressed in a complex pattern consistent with gradients originating from the boundaries (*14*).

The neocortical anlage, according to available evidence, is not overtly partitioned into transverse domains at early stages of embryogenesis. However, the postnatal neocortex shows region-specific gene expression (*28*) and histological structure (*29*). Pattern formation within the neocortex may rely on signals from boundary zones that lead to region-specific gene expression, histogenesis, and innervation patterns. Once afferent fibers arrive, activity-dependent processes could refine the organization of the neocortex.

The prosomeric model also provides a framework for studying evolution of the forebrain. Neuromeric structures are well suited to allow for the duplication, deletion, or respecification of neuronal domains. A newly evolved structure such as the mammalian neocortex could be formed by the transformation of a preexisting telencephalic domain or by the formation of a novel domain.

The prosomeric model is a working hypothesis that should facilitate future studies of forebrain development, but that must still be refined. The model may prove useful, for example, in examining whether growing axon pathways derive positional information from signals encoded in the scaffold of domains and boundaries (*30*). However, many key questions remain: How are the neural plate and neural tube patterned? How are the boundaries formed? What cellular interactions are involved? Where are the sources for the patterning signals and what are the signals? What are the transcription factors that specify regional identity? Many developmentally important genes have been discovered; now their functions need to be assessed. Such studies will not only elucidate the blueprint of forebrain organization but will also ultimately aid in efforts to understand abnormal neural development.

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