PRINCIPLES OF NEURAL DEVELOPMENT

Dale Purves and Jeff W. Lichtman

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THE COVER: Halo response of an embryonic chick ganglion after incubation with nerve growth factor; see Chapter 7. (Courtesy of R. Levi-Montalcini.)

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Early Events in Neural Development

CHAPTER

1

INTRODUCTION

The development of the nervous system is difficult to separate, as a topic, from the development of the rest of the animal. The nervous system is ultimately the collection of cells that organizes an animal's behavior. But embryos do not behave, at least in the beginning, and there is really no reason to imagine that neural development is fundamentally different from the generation of other organ systems. Moreover, the nervous system does not, of course, develop in isolation: it both is influenced by and influences the motor and sensory organs that allow an animal to act and to react. Finally, the development of the nervous system depends on a metabolic and hormonal context. Thus, it is no more sensible to talk about neural development without reference to the general course of embryogenesis than it is to discuss the performance of a conductor without reference to the orchestra; it is often done, but not very usefully.

Throughout this account, then, we have tried to relate the development of the nervous system to development generally, and the views of neurobiologists to the ideas of experimental embryologists.

THE RISE OF EXPERIMENTAL EMBRYOLOGY

Although many historical controversies seem outdated in retrospect, surprisingly few fundamental issues in development have really been settled; they have simply taken on different guises as technical and intellectual styles have changed. "It is easy to sneer at our ancestors," wrote T. H. Huxley, ". . . but it is much more profitable to try to discover why they, who were not really one whit less sensible persons than our excellent selves, should have been led to entertain views which strike us as absurd" (Meyer, 1939).

Perhaps it was Aristotle who began what must surely be one of the most protracted debates in the history of science: Is the development of animals based on preformation, or is it the result of an initial plan operating in conjunction with "external" factors? The idea that the zygote is simply a miniature individual that grows seemed so cogent that many philosophers took this notion of development for granted.

"In the seed," the Roman philosopher Seneca declared about 2000 years ago, "are enclosed all the parts of the body of the man that shall be formed. The infant that is borne in his mother's wombe hath the rootes of the beard and hair that he shall weare one day. In this little masse likewise are all the lineaments of the bodie and all that which Posterity shall discover in him" (quoted from Needham, 1959). Even with the advent of the microscope, the appeal of preformation was so strong that biologists claimed to see a homunculus in the head of a human sperm and a microscopic horse in equine semen. There were, of course, arguments against preformation (Meyer, 1939; Needham, 1959; Oppenheimer, 1967). For example, this view logically requires the inclusion of all humanity in a single ancestral homunculus. In spite of such counter arguments, the thrust of developmental inquiry well into the nineteenth century was not so much to question preformation but to decide whether the key element in this scheme was the egg or the sperm.

By the middle of the nineteenth century, the idea of preformation was in decline, largely as a result of the observations and arguments of C. F. Wolff and K. E. von Baer. In particular, von Baer's *Entwicklungsgeschichte der Thiere* (roughly *Developmental History of the Animals*), published in 1828, convinced many people that embryos simply did not look like miniature replicas of the adults they would become. In fact, embryos, regardless of species, resembled the embryos of other animals much more than they resembled the adults of their own kind (Figure 1). As concern shifted from homunculi to heritability, debates about development took on a decidedly more modern ring; it seemed that gametes might contain information needed to *create* an organism rather than animal rudiments in miniature form (Wilson, 1911; Jacob, 1982). A major proponent of this new view was W. Roux, who is generally credited with founding the discipline of experimental embryology and, indirectly, the more specialized field of neuroembryology (Hamburger, 1981).

Roux, who lived from 1850 to 1924, was the son of the fencing master at the University of Jena, where he became a student of the biologist and philosopher E. Haeckel. Haeckel was the foremost exponent of the biological approach to embryonic development in the late nineteenth century: the key to ontogeny, he argued, lay in phylogeny (see Box A). Haeckel's teachings apparently impressed Roux in two ways. On the one hand, Roux found Haeckel's emphasis on phylogeny unsatisfactory and metaphysical; on the other hand, he was intrigued by Haeckel's interest in the physicochemical basis of development (Gould, 1977). Roux did not accept Haeckel's verdict that phylogeny is a sufficient cause for ontogeny; he realized that proximate causes had to be analyzed. In consequence, he emphasized the importance of discovering a causal scheme of embryogenesis; he called this scheme "Developmental Mechanics" (in an analogy to Newton's laws of mechanics).

A central question that absorbed Roux's interest was the cause of embryonic differentiation: How do cells that develop from a single fertilized egg become so different in form and function? To attack this

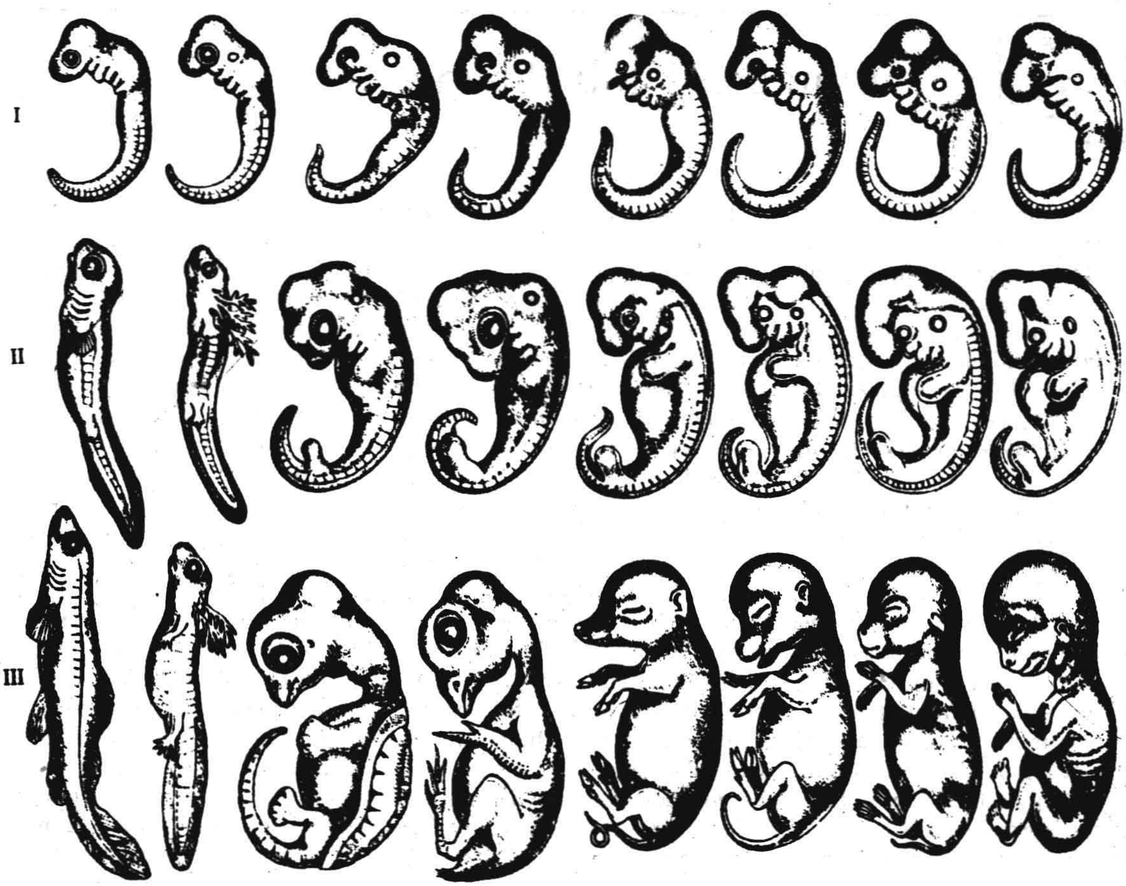

FIGURE 1. *The appearance of vertebrate embryos at various stages of development. The similarity of different embryos during early development is striking; this fundamental observation suggests that these different animals share both a common ancestor and the same basic mechanisms of development.* (From Romanes, 1901.)

problem Roux took up an experiment initially performed by Haeckel in 1869. Haeckel had tried to kill one of the first two cells produced by the cleavage of a fertilized frog egg, but he met with little success. Roux realized that the embryo arising from the remaining cell should indicate whether each cell generates a unique part or whether individual cells have a broader potential. In 1888 Roux published the results of experiments in which he succeeded in killing one blastomere at the 2-cell stage (Roux, 1888). The structures that grew from the residual cell appeared to constitute half an embryo, and Roux therefore concluded that each blastomere develops independently. On the basis of this result he proposed a mosaic theory of development that held that the fate of cells is preordained: each cell was regarded as having only the information necessary to create a particular part of the embryo.

Three years later, in 1891, H. Driesch tested Roux's conclusion more

BOX A

Ontogeny and Phylogeny

An important controversy that bears on the modern view of development is the relationship of embryogenesis to the obvious hierarchy of animal species (Gould, 1977). Although the argument can be traced earlier, the modern portion of the story begins with K. E. von Baer (1792–1876). A popular idea in the eighteenth century was that the embryos of higher animals recapitulate the *adult* features of lower forms. Von Baer (who figured in the discovery of the mammalian ovum, put forward the germ-layer theory and discovered the notochord in chick embryos, among other accomplishments) vigorously attacked this notion of recapitulation (von Baer, 1828). He suggested instead that the more general features of animals appear earlier than special features and that developing embryos of different species simply depart more and more from an early form common to all (see Figure 1). This sensible argument was temporarily eclipsed by E. Haeckel's assertion that the normal events of early development are a recapitulation of biological history (Haeckel, by the way, coined the terms *ontogeny* and *phylogeny*). For Haeckel, development was simply an accelerated version of evolution. However, Haeckel's idea that development proceeds through a series of adult stages of lower forms (a human embryo is first a fish) simply did not fit the facts. Embryonic men are not really like fish at some point; rather, human embryos and fish embryos are at early times very similar.

The similarity of early embryos is relevant to theories of evolution because it implies that more complex forms arose from a common ancestor—evidently the strategy of early development is highly conserved. In accord with this idea is the fact that the genes of closely related species (man and monkey, for instance) differ very little. This presumably means that the profound differences between the two species do not arise from major differences in genetic programs. One view of speciation is that many differences between animals arise from

carefully with sea urchin eggs at the Zoological Station in Naples (Figure 2). Instead of killing one of the first two blastomeres, Driesch separated them so that each cell could develop independently. In this circumstance Driesch found that the isolated blastomeres developed into fully formed, if smaller, larvae (Driesch, 1892). Subsequently, H. Spemann and others confirmed Driesch's work in vertebrates, thus invalidating Roux's major experimental contribution. The reason for Roux's misinterpretation was probably that the damaged cell, which remained in contact with the other blastomere, caused development to proceed abnormally.

In the end, however, it was Driesch who gave up science after a few years to become a professor of philosophy; in this post he argued that the "harmonious equipotential system" that the embryo represents is beyond analysis. He felt that no system of mechanics could explain how a part could be transformed into a whole. Roux, on the other hand, became a leader of German science, lectured widely, and continued to promote experimental embryology. Not the least of his achievements was founding the *Archiv für Entwicklungsmechanik* (Archives of Developmental Mechanics) in 1894 (now *Wilhelm Roux's Archives*). Influenced

A juvenile and an adult chimpanzee. The resemblance of the juvenile chimp to an adult man suggests that differences in the duration of development produce major differences in form. (From A. Naef, 1926.)

modulations of the regulatory systems that govern quite general aspects of development, such as rate. S. J. Gould and others have argued that humans and primates may differ because of the more protracted development of humans (Gould, 1977). For instance, by the criterion of ossification, a newborn infant (40 weeks) is comparable to an 18-week monkey fetus (macaque), and the bones of a macaque at birth (24 weeks) are similar in their development to a child of several years! Indeed, the physiognomy of an adult human bears a much greater resemblance to a baby chimp than to a full-grown ape (see figure).

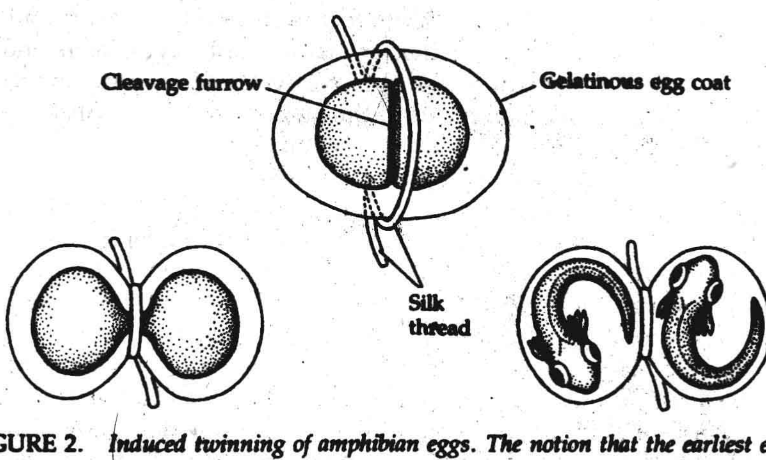

FIGURE 2. *Induced twinning of amphibian eggs. The notion that the earliest embryonic cells in every animal are preordained to give rise to only a part of the embryo had to be discarded when the German zoologist and philosopher H. Driesch showed that each of the first two blastomeres of the sea urchin egg could give rise to a complete larva. This point was confirmed in an experiment carried out by H. Spemann in which a salamander egg was constricted by a fine thread in the plane of the first cleavage furrow, as illustrated here. (After Hamburger, 1963.)*

by Roux's approach, T. H. Morgan, E. G. Conklin, H. Spemann, E. B. Wilson, F. R. Lillie, R. G. Harrison, and others rapidly provided a body of classic experiments in this field (Wilson, 1911; Morgan, 1927; Detwiler, 1936; Waddington, 1936). Before Roux, embryology as a discipline was either a philosophical or an entirely descriptive pursuit; Roux made it an experimental and analytical science. "In zoology," Spemann wrote in 1938, ". . . the speculations on evolution have, partly, perhaps for accidental . . . reasons, outweighed and overpowered every other interest for a number of decades. Here, the initiative of an original thinker was necessary to remind investigators of the fundamental principle [of strict causation]. We owe this achievement to Wilhelm Roux. He will always be honored as the founder of a new discipline in animal embryology" (Spemann, 1938).

In fact, the controversy about whether the fate of early embryonic cells is preordained or determined by interactions with other cells and the environment has never been fully resolved. A variety of observations and experiments indicate that both preordination and flexibility are important in different aspects of development (Chapter 2).

SOME MAJOR EVENTS IN EARLY EMBRYONIC DEVELOPMENT

Respective roles of nucleus and cytoplasm in the earliest stages of development

Development begins with the activation of the egg, usually stimulated by the penetration of a sperm. At the turn of the nineteenth century, the relative importance of the egg nucleus and cytoplasm in development was unclear. In the 1890s, T. Boveri, who later showed that chromosomes are qualitatively different from one another, found that fragments of sea urchin egg that contained only cytoplasm and the genetic material contributed by a sperm developed into an embryo, all parts of which were characteristic of the paternal species (Wilson, 1911). This observation suggested what is now taken for granted: the nuclear material rather than the cytoplasm carries the genetic information. These experiments were extended by I. J. Lorch and J. F. Danielli, who were able to remove (and subsequently reimplant) nuclei from amoebae (Lorch and Danielli, 1950). The enucleated cells failed to survive; they could, however, be rescued by subsequent nuclear implantation.

Other experiments, however, showed that the cytoplasm of the egg also plays a critical role in development. The egg cytoplasm has an uneven distribution of cytoplasmic inclusions such as lipid droplets and yolk granules; such asymmetries are the basis for describing eggs as having an animal pole and a vegetal pole (Figure 3). Different parts of the egg cytoplasm have special functions in development. A striking example is the egg of *Styela* (a sea squirt). Before fertilization the egg has three distinct regions: a peripheral layer that is yellow, a central mass of gray yolk, and a clear germinal vesicle. E. G. Conklin was one of the first embryologists to note that the egg cytoplasm is rearranged within a few minutes of fertilization (Conklin, 1905, 1932). The yellow