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DEVELOPMENTAL NEUROBIOLOGY OF THE FROG. Emanuel D. Pollack and Harold D. Bibb (eds.). 1988. Neurology and Neurobiology Series, Vol. 44, Alan R. Liss, New York, New York. 286 p., $55.00 (hardcover).—This book is a collection of 12 papers presented at the 1987 meeting of the American Society of Zoologists in a symposium to honor Jerry Kollros on the occasion of his retirement from the University of Iowa. Kollros' many contributions to developmental neurobiology are celebrated in this volume, which emphasizes the role that "the frog" has played in understanding mechanisms of neural development. The papers are grouped under three headings: 1) regulation of a neural population: the lateral motor column; 2) specificity in neural development and regeneration; and 3) neuronal order, differentiation, and population adjustments. Like most edited volumes, the quality of both writing and content varies widely among the authors.

The first three chapters use the frog's lateral motor column (LMC) to test current hypotheses on the functional significance of cell death in neural ontogeny. Pollack discusses the problem of differentiating between genetic (pre-programmed, non-interactive) and epigenetic (cell and tissue interactions) control of neuron numbers. Because prevailing dogma says that the

vertebrate nervous system is too complex to be under strict genetic control, much attention has been directed toward epigenetic processes. (For an especially clear statement of this argument, see Changeux, 1985. However a common error in logic seen in both Pollack and Changeux is not that neural development is controlled epigenetically, but that its complexity necessitates epigenetic mechanisms. In fact, the development of relatively simple systems can also be under strong epigenetic control.) Two epigenetic processes that Pollack discusses are control of cell proliferation and death by thyroxine and interaction of neurons with their targets in tissue culture.

Sperry tests the hypothesis that adequate innervation of a target of variable size is the reason for neuron over-production. His analyses suggest that, while environmental conditions strongly affect target size in developing amphibians, mechanisms controlling proliferation and death in motor neurons and their targets are largely independent (i.e., non-interactive). Cell death only reinforces patterns of variation in neuron number that are established during the proliferation phase. It appears that, in the frog LMC, neuron proliferation and death are epigenetic, not in the usual sense of interactions between embryonic cells and tissues, but rather in that proliferation of both neurons and targets is responsive to the external environment.

Lamb et al. discuss the hypothesis that cell death "selects" neurons that have made the best functional connections. Like Sperry, Lamb et al. also conclude that target size is not important in determining the final size of the neuron population. Their data suggest that the number of surviving neurons influences the number of secondary myotubes, rather than vice versa, leaving the question of what controls neuron numbers unanswered. Lamb (1976) showed that some inappropriate connections are removed by cell death, and the remaining chapter consists of several ad hoc arguments for why neuronal "selection" may be important despite the fact that a large number of studies have failed to demonstrate its importance. The basic problem is that many more cells die than (apparently) have inappropriate connections. More hypotheses are refuted than supported in these papers, but controversy makes interesting reading.

The second section concentrates on mechanisms for generating neuronal specificity, consisting mostly of fairly solid, non-controversial work on a variety of distantly related issues. Three of the five papers are on limb innervation, and repeat more than once basic descriptions of limb development that were also repeated in the first section. Muhlach discusses growth factor-directed substrate adhesion and chemokinesis (i.e., growth rates that increase as the appropriate target is approached), and Peng et al. discuss in vitro studies of ACh receptor clustering at developing neuromuscular junctions. Lee and Farel show that regeneration of motor neurons innervating hindlimb muscles is less specific than original innervation, and suggest that growth of regenerating axons is channelled by the connective tissue sheaths that were associated with the nerves before transection. Bibb's data suggest that the relationship between proliferation rates, death rates and target size may be stronger for sensory neurons than for motor neurons. More interesting are the experiments of Smith and Frank on sensory neuron specificity. Sensory neurons not only grow an axon from the cell body to the target, but also grow an axon into the brain. The central connections must be appropriate for whatever peripheral target is eventually innervated. Ramón y Cajal (1911) hypothesized that peripheral targets "instruct" sensory neurons to make central connections that are appropriate to the target, in contrast to pre-programming of both central and peripheral targets. Smith and Frank showed that sensory neurons can successfully innervate novel targets, and develop central connections appropriate to the new target. This is fairly strong support for Ramón y Cajal's hypothesis, but does not definitively rule out pre-programming because it is mostly (if not exclusively) newborn neurons, rather than ones that previously innervated a different target, that make the novel central connections. Thus, there is no evidence that an individual neuron respecifies its central connections when it innervates a new target (which would definitively rule out the pre-programming hypothesis).

The final section of the book deals with development of neurons of the brain and spinal cord. Roberts presents immunocytochemical studies of five CNS neuron populations which suggest, like so many other studies, that axonal growth is very precise even at the earliest developmental stages. Kollros provides new data showing that both the proliferation rate and the death rate of tectal cells are affected by the presence of ingrowing retinal afferents. The relative proliferation of glia vs neurons remains to be clarified, despite arguments to the con-

trary, because available evidence is not sufficiently stage-specific to resolve the issue. Constantine-Paton's work on tectal development in frogs with supernumerary eyes has provided a fascinating model for the development of topographic and columnar organization in the brain. The tecta of three-eyed frogs are binocular, and the synaptic fields of each eye are organized into stripes reminiscent of the ocular dominance columns of mammalian visual cortex. Reh and Constantine-Paton (1984) and others have shown that synapses between retinal afferents and tectal neurons are highly dynamic. Tectal neurons constantly change their synaptic connections during ontogeny, from heavily innervated, older afferents to weakly innervated, younger afferents. In the frog tectum, as in the cat visual cortex, neuronal activity is necessary for stripe development. Her data suggest that aggregation of cells with correlated synaptic activity produces the striped organization, and she reviews current models for the molecular basis of activity-dependent synapse formation. Lastly, Gona et al. provide a descriptive summary of proliferation, cell migration and the effects of thyroxine in the developing cerebellum.

The trend in the empirical studies presented here, as well as in studies of "higher" vertebrates (Tosney and Landmesser, 1985), is that both axonal growth and synapse formation are highly precise even at the earliest developmental stages, so that few inappropriate connections are formed during development. If development is as precise as all of these studies suggest, then it seems unlikely that cell death is necessary for the establishment of appropriate connections.

It is clear, as virtually all of the authors claim, that "the frog" has been a productive system for studying neural development. This book is a valuable, if somewhat repetitive, review of much that the frog has taught us, but provides disappointingly few glimpses at where the frog may lead us in the future.

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