Inside development

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AT THE very least, this is yet another outstanding volume to arise from the annual Cold Spring Harbor Symposium, now in its fiftieth year. The papers — over 100 of them — come from leading molecular biological and genetic laboratories; they cover the subjects of nucleo-cytoplasmic interactions, cell lineage, segmentation, homoeotic mutants, homoeoboxes, tissue-specific gene expression, sex determination, cellular differentiation and developmental neurobiology. There is probably no book on the molecular biology of development to match this one, not only in the comprehensiveness of the coverage, but also in the care of preparation of individual papers, an indication of the authors' high regard for the occasion of a Cold Spring Harbor meeting. Most of the contributions are no-nonsense research accounts which assume a technical background and discuss only the immediate implications of results. Broader orientation is available by way of a general introduction by John Gurdon, and a summary of symposium highlights by Gerald Rubin. In this rapidly changing field, the papers cannot be expected to remain current for very long; the volume should be studied forthwith.

What is the molecular biology of development, as revealed in this volume? Joe Sambrook writes in his foreword:

> Developmental biologists are an audacious breed. Their ambition is to provide an intellectually satisfying account of the forces that guide development of multicellular organisms around the circle from fertilized egg to adult to gamete. These processes, however, lie close to the border beyond which genetics may not be feasible nor necessarily useful; furthermore, meaningful biochemical studies pose extraordinary challenges because of the small amounts of material that are available and the general rapidity of events in the early embryo. In the face of these difficulties it is not surprising that for many years developmental biology was essentially a branch of anatomy, in that it was exclusively descriptive in nature. Accurate and elegant though these descriptions were, they led to an understanding of developmental processes less frequently than to an amazement at their beauty.
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> In recent years, however, developmental biology has undergone a dramatic change and has matured from a descriptive to an analytical science. There is no doubt in my mind that this change stems almost entirely from two technical advances — the ability to use molecular cloning to isolate and characterize mutant and wild-type versions of genes that control or are expressed at specific developmental stages and second, the ability to generate transgenic organisms in which the expression of the introduced gene(s) is correct both spatially and temporally. In consequence, the developmental biologist has not only the capacity to describe but also now to analyze and influence the events that guide a fertilized egg to its destiny.

In the book, it seemed to me that the excellent description by I. Herskowitz of the mating-type locus in yeast approaches most closely the kind of "intellectually satisfying account" now aspired to by molecular biologists studying development (for example those working on sex determination, segmentation and homoeosis in *Drosophila*). Herskowitz indicates (1) how certain master regulatory genes encode DNA-binding proteins which directly control the expression of batteries of cell-type-specific genes, and (2) how these master regulatory genes are themselves regulated by products of the *HO* gene, which is activated within mother cells by the products of yet other genes of the *SWI* family. Finally he suggests (p. 572),

> returning to the egg, we can imagine that regulatory proteins such as the *SWI* products become asymmetrically distributed to sister blastomeres. They activate expression of genes analogous to *HO* that govern activity of a regulatory locus (analogous to *MAT*) that ultimately triggers cell specialization.

Several contributors trace similar thoughts to those of T. H. Morgan (*Embryology and Genetics*, 1934, p. 10):

> The initial differences in the protoplasmic regions [of the egg] may be supposed to affect the activity of genes. The genes will then in turn affect the protoplasm, which will start a new series of reciprocal interactions. In this way we can picture to ourselves the gradual elaboration and differentiation of the various regions of the embryo.

Thus, in scanning this volume, I sensed fair agreement among participants that new information on genetic regulatory hierarchies is compatible with the long-appreciated phenomenon of cytoplasmic localization (an *intra*cellular, lineage-specific phenomenon) and can be grafted on to it to give an intellectually satisfying account now identifiable as the molecular biology of development.

Is there more? As John Gurdon points out, vertebrate development is thought to depend primarily on arborizing cascades of ever more local inductive cell–cell interactions. The highly regulative nature of vertebrate embryos indicates the ongoing ability of individual cells to adapt their paths of development to *inter*cellular conditions. Imaginal disc regeneration and transdetermination also reveal the importance of continuous cell–cell interactions in invertebrate (*Drosophila*) development. These complex, multiple interactions, while mentioned in the volume, have an uncertain relationship to the genetic control of cell differentiation and to lineage-restricted cytoplasmic factors. If embryonic cells produce and respond to a great variety of *inter*cellular contexts, and if a cell's particular path of development (including its changing profile of gene expression) is highly adaptable to that context, then regulatory genes would themselves be subject to extensive regulation, and would seem to be rather less masterful in their control of development, even though they would function to control other genes and play an important inertial role in connecting the cell's past to its present. In organisms making use of cell–cell interactions to select developmental paths, gene-regulating genes might be elements of much larger intercellular regulatory circuits having many components, many inputs, multiple states and adaptability. (It's one thing to say that a gene controls other genes; it's another to say that a gene controls development.)

If this is the prospect, then with the help and stimulus of the exciting new analytical techniques, and with genetic dissection, we can look forward to a long period of amazement at the beauty of our enlarging description of development, as the molecular biology of development turns outwards from the nucleus. □

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