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**John Tyler Bonner: First Signals: The Evolution of Multicellular Development** □ □

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## 1 *Introduction*

SINCE the 1940s, I have been thinking about how animals and plants and other organisms develop. As I look back over the many years, I see that the problem remains in some ways much the same, but in other ways it has changed to an extraordinary extent. The latter is entirely due to the fact that there has been such vast progress in the very nature of biology due to the eruption of molecular biology at midcentury. There has been a certain amount of tension between classical developmental biology and its modern molecular form, largely because the techniques are so different. But that is slowly changing with the present-day realization that the molecular developmental biologist is in fact pursuing the same goals that were first staked out by embryologists in the nineteenth century. They are pursuing two different ways of looking at the same problem; they are not opposed—they complement one another.

The premolecular biologists sought the immediate causes of the steps of development, the sequences of stimuli and responses that were responsible for the evolving of the embryo. They fully realized that ultimately those stimuli and responses were chemical in nature, but it seemed beyond the abilities of the times to find out what those chemicals might be. To give an example, in the early 1900s

Hans Spemann and Hilda Mangold (see Hamburger, 1988) discovered that the dorsal lip of the blastopore could, when transplanted to another embryo, cause the surrounding tissue to produce an extra embryonic axis. They called the dorsal lip region an “organizer,” fully realizing the obvious fact that it sent out a stimulus and that the response to that stimulus was the formation of a second embryo, with all its complex tissues. There followed many years of research in many distinguished laboratories to find what chemical substances might be responsible for this “embryonic induction.” The results were quite confusing and unsatisfactory, and it was not until the eclosion of molecular biology that it became possible to begin to analyze the molecular basis of Spemann and Mangold’s experiment. Now we know many of the substances involved—not only the specific proteins, but the genes that are responsible for their production. In fact, the level of detail of our present knowledge is quite staggering. But today those molecular details can easily cloud the underlying fundamental biological questions.

There are presently numerous and rapidly evolving reviews and books of this wonderful progress in molecular development, and it is not my intention to pursue here this exciting field of knowledge. Rather, I want to take a different approach.

In the case of the molecular biology of development, the explanation of even the smallest step has become enormously complex, a complexity that increases directly with the zest for digging. I am not criticizing this approach; in fact, I think it is essential and important and has produced stunning advances. However, I worry that all the wonderful

detail will make the fundamental principles harder to see, and that perhaps one might also get illuminating insights by examining the development of simpler organisms—by which I mean simpler than those workhorses of molecular biology, the fly and the worm. Of course, what one finds is that even with “simple” organisms, the more one delves into their developmental mechanisms, the more complexity emerges; the difference is only a matter of degree.

How can one simplify the mechanism of development? How can one cut through the details and get to the core of how organisms develop? One might argue that the details *are* development, but I will take a different tack. It seems to me there are some basic principles that underlie all the details. It is upon them that the details rest, and this essay is about how to find those principles and what they might be.

Here I will consider three ways one could pursue this quest for simplicity. One is the straightforward, descriptive biological approach where the mechanisms are at least superficially exposed.

Another way is to look for the beginnings of multicellular development, where one might assume that at first only the minimum steps necessary were present. What happens inside a cell is incredibly complex despite its small size, but with the evolutionary origin of multicellularity there must have occurred some minimal signals between cells, and that was the origin of multicellular development. Those extracellular beginnings were simple and were only subsequently followed by an increase in complexity.

The third way to seek simplicity is through mathematical modeling. One can ask what is the simplest way to achieve

some developmental change in form. This is an approach to which I shall return periodically to see how it fits in with my more central message of what might have been the nature of the first cell signaling when multicellular development arose in early evolution.

I do not mean to imply that these are the only ways of achieving simplicity, for there are others as well. To give a well-known example, the foundations of molecular genetics are achieved by Max Delbrück and Salvador Luria using viruses (bacteriophages), and by the very simplicity of these naked, parasitic genes (and their rapid rate of reproduction) it was possible to gain an extraordinarily deep understanding into the fundamental nature of mutations. The use of viruses to solve important biological problems remains important today, as shown recently by Birch and Chao (1999), who have elucidated some basic questions of population genetics, again by taking advantage of the molecular simplicity of viruses.

As indicated above, I want to use a different “simplicity” approach here. My plan is to get at the essentials of developmental biology by piecing together how the development of multicellular organisms might have arisen in the first place. This will be my window to finding the underlying core of development without interference from the obscuring details. But another equally important evolutionary theme runs in parallel. There is a constant selection pressure for size change: this is a major driving force in evolution. In a complex environment such as exists today for every category of organism, a complete array of size niches is present, and should any one be vacant, there will be a selection for a slightly larger or slightly smaller

species or variants to fill it. In early geological times, when the world consisted solely of single-cell organisms, the selection pressure for size increase must have been great, and the easiest way to achieve it was by becoming multicellular. The unicellular size niche was filled; expansion could only be in the larger direction. This explains why there were so many independent (or convergent) inventions of multicellularity.

What we have, then, is the evolutionary origin of multicellular development. First, there was a selection for an increase in size by becoming multicellular, and once achieved there was a selection for a better integration, a better coordination of the adhering cells to compete effectively for energy and for a way to reproduce successfully. Then, with each successive step of size increase, propelled always by the fact that the uppermost size niche is never filled, there has been a further selection pressure for integration and coordination, often by new and innovative devices to accommodate the newly created larger organism.

We will examine these themes in the following way. After a bit of history of developmental biology as a discipline (chapter 2), our starting point will be a natural history of present-day simple multicellular organisms to provide a basis for speculation of how they might have arisen in the first place (chapter 3). Next, we must look into the matter of size and size niches, and in particular how it affects microorganisms (chapter 4). What are the physical properties of small clumps of cells? There are the chemical properties to consider as well: how can the cells start to communicate with one another, and what are the beginnings of the signal-response system (chapter 5)? This leads

directly into the central chapter of the book, which examines the beginnings of multicellular development as a way to reveal the simplest elements of development (chapter 6). I use the cellular slime molds to show how the development of one organism can be analyzed from a classical developmental point of view and from the point of view of molecular development, and see to what extent the mathematical modeling of development might be helpful (chapter 7).

When I first began thinking about these problems, I imagined myself bucking the trend, for so many people are working on the mathematics of “complexity theory” these days; instead I was after “simplicity theory.” But clearly our goals are the same, and the point of complexity theory is to simplify, to untangle the tangle. The complexity people are grappling directly with the complexity, while I am doing an end run by looking at the underlying problem before it becomes complex.