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Introduction: On the Great Excitement in Cell Biology[1]

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As pointed out more than 60 years ago, "the key to every biological problem must finally be sought in the cell, for every living organism is, or at sometime has been, a cell" (Wilson, 1925). Careful studies of individual cells can make major contributions toward our understanding of the much more complex, multicellular organism. In fact, the relatively simple behaviors of individual cells has, in aggregate, a surprising power to explain even such sophisticated multicellular properties as the memory stored in nerve networks and the morphogenesis of a developing embryo (for a good example of the latter, see Foe and Odell, this symposium). Thus, cell biology is a very powerful discipline, which has many unique contributions to make to our understanding of multicellular organisms, including ourselves.

In this symposium, we have attempted to present a series of concise reviews of some of the major aspects of cell function. The reader will immediately notice that molecules play a central role in most of these discussions, whether an attempt is being made to explain cell membranes (Walter, this symposium), the orderly events of the cell cycle (Murray, this symposium), the separation of chromosomes on the mitotic spindle (Mitchison, this symposium), or the turning on of a specialized set of genes in a differentiated mammalian cell (Yamamoto, this symposium). The insistence that every biological phenomenon be explained in terms of the behavior of the molecules involved is a theme common to much of modern biology, and it reflects the belief of today's biologists that the tools are in hand to achieve such a detailed, mechanistic explanation.

Is the preoccupation with molecules in biology merely a fad—as some have claimed—or is there a good reason for the current widespread emphasis on cell chemistry? As I see it, modern cell biology draws its strength from a combination of three major developments, none of which were foreseen as little as 15 years ago:

1) The most obvious of the new developments stems from powerful new techniques that make it possible to answer almost any question about the cell, given sufficient effort. When I entered this field in the early 1960s, the cell seemed incomprehensibly complex. Moreover, there was no obvious way of deciphering this complexity. Most of the tens of thousands of different protein molecules in a higher eukaryotic cell were known to be present in such small amounts that is seemed beyond reach to ever know their structure. In recent years, this situation has entirely changed. With gene cloning and the ability to manipulate the cloned genes so as to produce any gene product in huge amounts, every protein in the cell is potentially accessible in virtually unlimited quantity. Like the first settlers to arrive in California for the Gold Rush, today's biologist faces an easy harvest of riches. For the next twenty years or so, one need not be especially clever or wise to make major contributions to biology. With luck, even the random cloning of a new gene—which requires little skill and no insight—can turn out to be exciting.

This situation in molecular cell biology should be contrasted with that in more traditional fields like descriptive cell anatomy and physiology, where one needs to have some special genius to outdo one's predecessors—who have already "mined" the research area well, using many of the same techniques and approaches for twenty years. Since the main goal of most scientists is to contribute to important new discoveries, many outstanding young biologists

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are naturally attracted to the newer techniques and approaches that make possible a molecular analysis.

2) At the cellular level, we now realize that there is a surprising uniformity among living things. Our understanding of the biology of plants and higher animals is benefitting greatly from the recent discovery—from comparative RNA structure analyses—that these organisms are closely related, not only to each other, but to relatively simple single-celled organisms such as yeast (Sogin, this symposium). The cells are so similar in their structure and function that new findings made with the cells of any one of these organisms can often be quickly extended to the others, and the proteins even interchanged from one organism to another. For example, yeast cells, which can be grown in huge numbers and easily manipulated by genetic techniques, share many of the central molecules that regulate their cell cycle with human cells—to the extent that several such human proteins will substitute in the yeast cell for their yeast equivalents (Murray, this symposium). Because different aspects of the same biological problem are best revealed in different types of cells, observations made in one organism can often be best understood by reference to what is known in another. This fact explains how yeast cells can be useful as models for human disease (Rine, this symposium).

3) Cells and organisms are very complex. But because they have evolved to this complexity by a repeated process of DNA sequence duplication and divergence, each cell is composed of parts that are closely related to other parts in their structure and function. This fact greatly simplifies the task of understanding the tens of thousands of proteins that make a human being. Each protein is formed as a string of small modules (called protein domains) that have tens if not hundreds of relatives in the same cell (Doolittle, 1985). To a first approximation, we can get a grasp on most of the cell's proteins by detailed studies of the structure and reactivities of the protein domains—numbering perhaps several hundred—that have been used repeatedly to form larger proteins.

THE CELL AS A PUZZLE

Scientists who have devoted their lives to studying cells view the cell as a large and elegant puzzle. Each biological macromolecule (protein, nucleic acid, or polysaccharide) that is discovered and studied in detail represents a small piece of the puzzle, which will only be satisfactorily understood when it has been adequately connected to all of the other "pieces" in the cell with which it interacts. Ten years ago, the total amount of information about cells was so small that nearly all of the interconnections between the known pieces were missing. In the last few years, we seem to have reached the point where enough of the puzzle has been filled in that the new pieces analyzed (most often a new protein) can often be connected to several others to provide some new insight. In terms of the puzzle analogy, we are still far from seeing the final picture, but we can often glimpse part of a tree, or recognize a familiar face in an otherwise chaotic jumble of partial information about the cell.

Much of the present excitement in cell biology stems from the sense that we are now starting to know enough about cells to make the missing connections—so that often the characterization of a new protein or process will begin to make conceptual sense of what seemed previously to be an inexplicable muddle of facts. Nowhere is this sense of excitement greater than in the coming together of what had previously been two separate fields of enquiry—the study of the altered genes in cancer cells that allow tumors to grow in an uncontrolled way (Bishop, this symposium) and the study of the proteins that regulate the normal cell cycle (Murray, this symposium). As illustrated by this example, there is no longer any distinction between good cancer biology and good basic cell biology. In fact, one can argue that we are learning as much about cancer from studies of the cell cycle in yeast cells and frog eggs as

from studies of tumor cells—and it is clear that both lines of enquiry will make essential contributions to human health.

UNDERSTANDING THE CELL

Before ending this brief introduction to the symposium, I would like to try to clarify what biologists mean when they state that they are trying in their research to "understand" cells. To biologists today, a cell is nothing more (or, much better, nothing less) than a special collection of complex molecules, enclosed by a membrane, that has the very special ability to reproduce itself from the much simpler molecules available in its surroundings. Speaking as a chemist, a cell is a self-replicating collection of catalysts—most of which are proteins. We know how this works in principle: the cell carries out a highly organized series of energetically-favorable coupled reactions in its interior, releasing heat to the environment to "pay for" the otherwise thermodynamically unfavorable increase in order that is required inside the cell (see Chapter 2 in Alberts *et al.,* 1989). However, a complete understanding of a living cell will require that we know every reaction that occurs in it, so as to be able to see how each component contributes to the self-replication of the entire unit. In my opinion, a strong argument can be made for pursuing a concerted effort on the simplest known cell, since complete information for this cell should greatly illuminate the basic principles for all of its more complex relatives. As argued elsewhere (Morowitz, 1984), the tiny bacteria known as *Mycoplasma* would seem to fill this role ideally. With a cell diameter of only 0.3 μm and a genome size of only about 750,000 nucleotide pairs, these bacteria have a volume that is only about one percent that of the most commonly studied bacterium, *Escherichia coli,* and a genome that is about one-sixth *Escherichia coli* size. A single *Mycoplasma* cell is thus estimated to contain only 40,000 protein molecules, of about 600 different kinds. The amino acid sequence of all of these proteins could in principle be obtained from the DNA sequence of the *Mycoplasma* genome, a task that is well within the reach of current DNA sequencing technology. However, relatively little research is currently carried out on these organisms, because the inherent interest and importance of such a project has been generally unrecognized.

Is the complete description of one particular living cell enough to provide us with a complete understanding? I would argue that it is a good start, but that something very important would still be missing. Even the simplest of today's cells has had a long evolutionary history, during which it evolved from even simpler, more primitive cells that are presumably extinct—having been outcompeted by their more advanced successors. As discussed in a previous SAAWOK symposium (Alberts, 1986), today's cells are not optimally designed, because they are forced to carry many relics of their past. The complete understanding of any present-day cell will require an appreciation of its evolution, for only in this way will we be able to understand many of its reaction pathways, structures, and mechanisms. A present-day cell cannot be any possible self-replicating collection of catalysts: it is constrained to be one that could be derived by a stepwide process from an extremely simple ancestor—one that presumably contained only RNA catalysts with no proteins (Alberts, 1986; Cech, 1986; Orgel, 1986).

That cells exist at all is a marvel. To speak about them as "simply a self-replicating collection of catalysts" in no way reduces the beauty and wonder of the living state. If we were to be visited by a being from outer space, this being would undoubtedly find even the simplest of the living cells on Earth far more fascinating than any human-made object. That our own teenagers are largely bored with the memorization of cell parts and the rest of biology—but fascinated by consumer electronics and automobiles—is a great tragedy, and it reflects how far we have to go in changing science education for our young people. If this *Science as a Way of*

Knowing symposium can make some small contribution to bringing an appreciation of the beauty of cells to others, the great efforts made by John A. Moore in promulgating this series over the years—and the much lesser efforts made by the rest of us to help—will have been very well rewarded.

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Some of the *Science as a Way of Knowing VI—Cell and Molecular Biology* participants: Back row, left to right: W. V. Mayer, M. L. Sogin, J. M. Bishop, C. Guthrie, P. Walter, V. E. Foe, J. Rine, C. D. Laird, N. H. Hart, J. A. Moore. Front row, kneeling: B. M. Alberts; standing, left to right: K. R. Yamamoto, I. Deyrup-Olsen, B. Moore.