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# The Prognosis for Research on Model Organisms

Though more than a million described species live on Earth, most basic knowledge about the properties of cells has come from study of just a few “model organisms,” including the bacterium *Escherichia coli*, the yeast*Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, the mustard plant *Arabidopsis thaliana*, the fruit fly *Drosophila melanogaster*, and the mouse *Mus musculus*. But investments in biomedical research often are justified through their potential applications to human disease. As researchers increasingly gain the ability to study diseases directly in humans, will research on model organisms decline?

That's unlikely, say Stanley Fields, a Howard Hughes Medical Institute investigator at the University of Washington, and Mark Johnston at Washington University School of Medicine in St. Louis, in an article published in the March 25, 2005, issue of *Science* entitled, “Whither Model Organism Research?”

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With that said, however, Fields and Johnston believe that within the next few decades, research into model organisms will reach a pivotal juncture. Starting with yeast and progressing through the more complex organisms, the basic biology of model organisms will be “solved,” they said. In other words, biologists will understand, at least in outline, all of the basic mechanisms of the cell, including the functions of nucleic acids and proteins, the signaling pathways by which cells communicate, and the selective expression of subsets of genes.

“Our contention is that at some point, no basic biological processes in these organisms will be obscure,” said Fields, who has spent much of his career studying genetic processes in yeast. “Within twenty to thirty years, for example, we predict that there won't be key biological processes in yeast that we don't understand, even if we don't know every detail of those processes. At that point, we will have to face the fact that we have been very successful in what we set out to do, and we'll have to move on.”

“Some people will say that to speak in terms of a `solution' is ridiculous, but I believe they are wrong,” said Johnston, also a specialist in yeast genetics. “Of course, you can always find more detailed questions to answer. But the basic biology of these organisms will be understood at a reasonable level of detail.”

Once that biology is understood, the character of model organism research inevitably will change. In some cases, the quantity of research on an organism may decline, as happened with *E. coli* in the 1980s. However, Fields and Johnston insist that model organisms will remain critical to future investigations of human biology, for five main reasons.

First, model organisms will continue to provide insights into basic cellular processes, even after the organisms' basic molecular mechanisms have been solved. For example, when a human gene involved in a disease is identified, researchers often will be able to examine the function of a homologous gene in model organisms. “For basic cellular processes, you want to work with the simplest organism that carries out that process,” said Fields.

Second, biologists will continue to use model organisms to examine disease processes more directly. For instance, Alzheimer's disease, Parkinson's disease, and Huntington's disease all involve misfolding or aggregation of proteins, and similar molecular malformations occur naturally or can be induced in yeast, worms, and flies. Model organisms have genes involved in aging that may play analogous roles in humans. Studies of yeast will shed light on diseases caused by single-celled organisms, just as studies of fruit flies could help control the mosquitoes that carry malaria.

Third, model organisms will be essential to understanding the complex biological networks that control life processes. Basic cellular processes such as DNA replication involve elaborate molecular mechanisms with many components acting in multiply connected ways. Studying how these networks operate “will bestow upon biologists the predictive powers and design capabilities long held by physicists and engineers,” Fields and Johnston write. In particular, study of molecular networks will be essential in understanding complex diseases, which result from the effects of many genes and environmental influences working together. “Model organisms will be the proving ground for studies of complex diseases, which is the frontier in biology," said Johnston.

Fourth, critical questions of biological variation and diversity will be investigated using model organisms. Biological traits can change depending on small differences in large numbers of genes. These relationships will need to be understood in model organisms before diversity in other organisms can be understood, said Fields and Johnston.

Fifth, model organisms will remain the proving ground for developing and testing new technologies. Already, model organism research has led to the ability to isolate and manipulate genes, purify and characterize proteins on a large scale, and profile and control gene expression. Indeed, the more that is known about model organisms, the more useful they will be in developing new technologies, and "the people who had the biggest impact on biology have been the people who have developed new tools," said Johnston.

"Ten or twenty years from now we probably wouldn't come up with the same list" of potential uses for model organisms, said Fields. "Other areas that we could have mentioned include infectious diseases, the development of immunity, and ecological systems—how organisms fill niches." As Fields and Johnston write in their paper, exploring these and other research areas, both in model organisms and in the great many largely unstudied organisms, "is certain to occupy [biologists] for a long time."

According to geneticist Maynard Olson at the University of Washington, Fields and Johnston's paper is "interesting, constructive, and provocative." It asks "new kinds of questions," which helps push biological research in new directions.