Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by James F. Crow and William F. Dove

Learning the Common Language of Genetics

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This article is based on Spradling (2004).

TODAY the Earth hosts millions of species of multicellular organisms, whose individuals may contain trillions of interacting cells comprising thousands of distinct cell types, arrayed in intricate three-dimensional patterns and directed by tens of thousands of differentially expressed genes. Now comes the complicated part: Unlike the fundamental entities of the physical sciences that follow simple laws, cells and their contents have been shaped by billions of years of shifting evolutionary pressures, ensuring that their behavior belies ordinary and reasonable expectation. Current species and genomes represent only a snapshot in the continuum of now extinct forms, adapted to now extinct environments, stretching back to the first organized groupings of biomolecules on the young Earth. Consequently, each cellular component still partly reflects the obliterated history of countless ancient crises, beyond prediction, never to be revealed. In short, it is no exaggeration that the story of life on Earth comprises by far the most complex phenomenon known in the universe.

Despite these seemingly insuperable obstacles, biological research has thrived. During the 75 years since the founding of the Genetics Society of America (GSA), the field of genetics has passed through four successive "revolutionary" eras: classical genetics, molecular genetics, molecular cloning, and now genomics. Each era has corresponded to a quantum leap in our ability to understand and manipulate genomes. Each has broadened the general interest of the field and attracted new participants from formerly separate areas of biology and from the physical sciences. Each has increased the medical relevance, commercial value, and public interest in what geneticists do. Genetics is no longer practiced by a small group of devotees, but now touches almost all areas of biological research and increasingly affects society at large.

These achievements are bringing changes in the way in which genetics research is carried out. During the last 75 years, independent scientists, working with small groups of trainees, have driven advances in the field. Now, genome projects and biotechnology have demonstrated the value of a larger scale and a more industrial style of biological research. The newest influx of scientists trained in the physical sciences are not planning to simply become outstanding biologists, like many of their intellectual forebears, but hope to open new physico-mathematical frontiers on some of the great questions in biology under the rubric of "systems biology." Clearly, genetics research is thriving as never before. But questions abound regarding the appropriate style and direction in which it should be going.

In considering our future, a little history is helpful. Overcoming the seemingly insurmountable scientific challenges inherent in biological research is thrilling. Perhaps this is why major biological advances have often engendered a kind of exuberance that has blinded even leading researchers to the immensity of what remains. In the 1960s, after discovering the first molecular gene regulatory circuit using the intestinal bacterium *Escherichia coli*, Jacques Monod, famously remarked that "*E. coli* is like an elephant." Following the advent of molecular cloning, some scientists seriously believed it would be possible to easily transfer major functional capabilities, such as nitrogen fixation, to distant species. Others expected that we would soon engineer fantastic new creatures, such as "alligators with fur," to quote a "conservative prediction" from a typical newspaper account. Today's genomic era, so reminiscent of those following previous revolutions in genetics, has likewise generated considerable exuberance. How many times have you heard: "I will use this approach to define *all* the genes involved in (fill in the process)." How many times has the underlying assumption become: "we basically understand this process; now we just have to compute how it works."

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But why not? A little exuberance, perhaps even a lot of exuberance, can be a good thing. Exuberance can drive one to contemplate what should seem impossible, but turns out to be pathbreaking. Time and the scientific process, if left to operate openly and competitively, can sort out the prophetic from the overly hopeful. Unfortunately, however, we must currently confront the fact that too much exuberance, especially highly expensive exuberance, in a time of limited resources and diminishing career prospects, can damage the research enterprise. Human and financial research resources remain precious and limited. Every avenue pursued closes off, at least for the while, an alternative possibility.

So where does genetics research really stand in this post-genomic era? When we look around our Society and the biological community generally, it is striking how much we still resemble a collection of tribes. Researchers who speak mouse can scarcely understand researchers who speak Drosophila or Arabidopsis, and few of them can comprehend the arcane three-letter syntax of the "lower" family of languages, including *elegans*, spoken yeast, and the various prokaryotic dialects. The Rosetta stone most of us would need to translate population genetics has yet to be found. Yet we have all been thrilled by the astonishing unity of life processes. Not only did life evolve only once (and survive) but so did Golgi, guts, and gonads. This underlying core of life processes, along with the thousands of shared genes on which it is based, should somehow be describable in a common genetic language. We need to become fluent in this tongue and to understand our favorite systems in terms of their particular departures from the common core. Then we can have a truly interesting conversation.

Such a dialogue remains largely for the future, and what geneticists do not like to do may be partly to blame. It has been said that classical geneticists felt no need to look at embryos and that molecular biologists disliked biochemistry. Well, genomicists seem to absolutely hate anatomy. They rarely talk about the intricate cellular makeup and precise three-dimensional architecture of tissues or marvel at their constant renewal as new cells are born, migrate, differentiate, communicate, and die. Indeed, today's genomics could be more accurately termed "single-cell genomics." The sciences of multicellular biology—anatomy, physiology, developmental biology, and neurobiology—seem not to exist. Instead, flying in the face of one billion years of evolutionary innovation, there is fervent striving to discover some clever mathematical computation on single-cell data that will make all the messiness of real tissues in real animals just magically go away. In effect, exuberant single-cell genomicists are saying, "yeast is like an elephant."

Paradoxically, systematic cellular anatomy cannot be done without genomics. Cell types, the key to understanding tissues, are ultimately defined by their chromatin organization and revealed by the genes that they express. To find them, one needs to map the expression of genes throughout the cellular anatomy during all developmental stages and environmental states. Then one needs the ability to alter these expression patterns in precise cellular groups so as to determine their functions. Even in model organisms or humans, the detailed expression of only a minority of genes has been studied, mostly at lower-than-single-cell resolution, and in just a few stages and situations. Many fewer genes have been functionally studied. Consequently, it should come as no surprise that many, perhaps most, cell types have yet to be discovered. Undiscovered cells may be the keys to understanding many currently perplexing aspects of tissue function.

In fact, a whole level of biological organization has largely been overlooked—a level larger than the single cell but smaller than a full-blown tissue. It consists of small, highly organized, interactive, supracellular modules made up of a few cell types. Some of these units have been recognized by classical anatomists and given such names as "crypts," "islets," "follicles," "niches," "cysts," etc. They likely constitute the basic building blocks of tissues and operate using mechanisms and genes conserved over long evolutionary periods. It is only by comparing gene function within the context of conserved cell types operating in conserved multicellular architectures that we can master the common language of genetics. We still know little of this language, because we do not yet have a genetics that is powerful enough to do the experiments that will teach a common language to us.

Such technology is being developed, however. We do not have to recoil from multicellular complexity; we can embrace it and thrive. We are closest to this in the case of the model genetic organisms whose utility has been advanced and applied by so many members of this Society. New model organisms are also being added to the collection, leapfrogging in their technology within just a few short years, what earlier took decades. Synergistic with technical advances are the ongoing efforts to understand every aspect of the biology of these organisms. Model genetic organisms will increasingly be the first in which novel aspects of metazoan biology can be understood at the level of a complete suite of relevant component cells. Increasingly, these organisms can be used to model detailed characteristics of human disease and to elucidate complex aspects of human biology (Spradling 2006). For understanding metazoans, "model organisms with powerful genetic tools are truly like an elephant."

The single most important aspect of genetic research has not changed at all in the last 75 years. That is the primary need for new knowledge and new ideas. Idea-free data is of limited value compared to a valid new mechanism. We have not yet discovered all of the basic biological processes that govern the genome and have barely

begun to explore biology's higher levels of organization. RNA interference (RNAi) was unknown just a few years ago, when genomic exuberance was already in full swing. Now, it appears that there may be more undiscovered RNA genes than all the protein-encoding genes put together. Just a few years ago we tried to imagine a long-lost "RNA world." Increasingly, it appears that we are still living in it.

Many more RNAi's remain to be discovered at every level of cellular function. These truly novel mechanisms are unlikely to be uncovered by large multi-disciplinary projects, by data-gathering exercises, or by road maps. They can be brought to light only by creative individuals following their own instincts. History teaches us that some of the most important future medical applications will also come from such discoveries. As we have repeatedly witnessed during the last 75 years, the most significant advances are nurtured by R01-style grants, but rarely by mission-oriented projects. No revolution has diminished the potency of giving new investigators adequate resources and independence at a young age. As a Society we need to rein in the exuberance of today's enthusiasts for central planning. Otherwise, we will set records for expenditure and hype, but end up with relatively little of lasting value to show for it.

The fact is that we are not at some unique turning point in genetic history, but rather at just one more garden variety, ho-hum revolution. We have climbed a peak, but at the top we found another much higher peak still ahead of us. So on this 75th anniversary of the GSA, we should raise our glasses in a toast. Genetics is more advanced, more understood, more important, more vibrant a science than ever before. But most of the needed work is still before us. Most of the knowledge, most of the concepts, and most of the mechanisms required to understand even a single organelle, much less a chromosome, much less a cell, much less a niche, much less a lobe, much less an organ, much less an organism, much less a population, remain to be discovered. We should continue to welcome every person who wants to join in this most rewarding quest to share our insights and to delight in truly new ideas and approaches. The era following the genomics one, an era that will open up the study of multicellular life and its evolution, can become reality only through the efforts of individuals who remain dissatisfied with the status quo and who dream of a better and more powerful biological science. There have always been many such individuals in the Genetics Society of America.

LITERATURE CITED

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