and as entities upon which the program acts.

Granted there is some sloppiness in the uses and connotations of terminology, but does this really threaten scientific communication or progress? Although there is no consensus definition of "program" or "networks," these terms are most often encountered and understood in the context of the regulatory interactions that link groups of genes and gene products in developmental processes. Many of these linkages have recently been elucidated in considerable detail for key events in a variety of species. Keller could have presented these new findings to illustrate concrete points about the formal logic and mechanisms underpinning the architecture of genetic regulatory systems. But she is less concerned with explaining empirical insights than with critiquing potential semantic ambiguities. The reader is left to weigh her argument without the benefit of understanding the substance of new discoveries.

This lack of scientific substance and a narrowness of explanations weakens Keller's overall case. In another example, Keller argues that the inadequacies of genetic methods and logic are laid bare by the existence of genetic redundancy. Quoting from sources now 7 to 10 years old, she makes much out of the frustrations of gene knockout studies in the mouse that yielded slight or no observable phenotypes. She suggests that genetic redundancy exposes a critical, insurmountable limit on genetic analysis. But in presenting only these earlier challenges and no subsequent solutions, the resulting message (that reductionism has hit a wall) is misleading. Keller offers a limited (and untestable) explanation for redundancy in computer and engineering terms, which indicates that redundancy is what we should expect evolution to produce. But the extent of redundancy is contingent upon the history of the particular group. Those lineages that have experienced genome-wide duplications (as occurred at the base of the vertebrates and again in some teleost fish) or polyploidy display greater redundancy and pose more obstacles to genetic analysis. Nevertheless, molecular biologists and geneticists have devised many ingenious ways to identify potentially redundant genes and to elucidate the biological roles of the products they encode. The lack of recognition of such efforts and the glaring omission of any mention of the expanding success of the genetic analyses of complex traits (in development, evolution, and medicine) leave an unbalanced picture of the intellectual and technical forces that now shape genetic and molecular approaches to challenging biological questions.

The call for functional genomics to which Keller has reacted is not an acknowledgment of the limitations of reductionism. On the contrary, it is a call for tools and technologies to practice reductionism systematically on a much larger, genome-wide scale. The dangers and demise of reductionist biology have been pronounced before, only to be mocked by waves of innovation and discovery. This piper's tune is likely to go unheeded.

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BOOK REVIEWS: GENOMICS

# Hunting the Metaphor

**Sydney Brenner**

The human genome has been called a Rosetta Stone, the Book of Man, the Code of Codes, and the Periodic Table. To some people it is a blueprint, to others, something more mundane like a cookbook. Richard Dawkins finds it a digital archive of the African Pliocene. Walter Gilbert calls the complete sequence the "grail of human genetics" and sees it as a tool to study biological function. It has also been viewed as a parts list and, judging from the U.S. title of Kevin Davies's new book, as a safe in which secret codes are stored. Best of all, President Clinton described the human genome as "the language in which God created Man." Perhaps now we can view the Bible as the language in which Man created God.

Davies, presently the editor-in-chief of Cell Press, tells the story of the sequencing of the human genome largely from the point of view of the last few years but with flashbacks to earlier times. So we are given glimpses of the histories of *Drosophila* genetics, the double helix, molecular biology, and even Mendel (he is mentioned a few times, although once only in noting that the geneticist Thomas Hunt Morgan was born the year Mendel published his work on inheritance in garden peas).

To comprehend why we want to sequence genomes, one must first understand what the science of genetics is about. Nowhere else in nature are there complex systems that carry within them an internal description of their construction and behavior. Understanding this has always been the central problem of biology. It was Mendel who put us on the right track by his assumption that there are factors inside organisms which specify the characters we observe. These factors become the genes of later years, and genetics has assiduously pursued the discovery of what genes are made of, how they are copied, and how they function in organisms. Classical genetics could not assert the existence of a normal gene until a mutant variant of it was discovered; Mendel could not say there was a factor for tallness until he found plants (dwarf mutants) suffering from a lack of tallness. Geneticists had to study genes by observing their phenotypes and how these phenotypes behaved in breeding experiments. For most organisms, such experiments were impractical or even impossible. The only complex animals that we could study were those like fruitflies and nematode worms, which had rapid life cycles and could be kept in large numbers in a laboratory. In the mid-1970s, two technical innovations changed the field. The first was DNA cloning, which let us make libraries that covered entire genomes. The second was the invention of DNA sequencing methods. For the first time, we could look at the bases directly instead of through the poorly focused spectacles of the phenotype. Genetics was freed from the tyranny of short breeding cycles, and all organisms became amenable to genetic analysis. We could now find genes by sequencing genomes, we could translate the DNA into amino acid sequences, and sometimes we could recognize the resulting proteins and say something about their function.

**Cracking the Genome**
**Inside the Race to Unlock Human DNA**
*by Kevin Davies*
Free Press, New York, 2001. 320 pp. $25. ISBN 0-7432-0479-4.

*released in the UK as*
**The Sequence**
**Inside the Race for the Human Genome**
Weidenfeld and Nicholson, London, 2001. 320 pp. £20. ISBN 0-297-64698-2.

**Venter, Clinton, and Collins at the finish.**

It is this possibility of extending genetics into every corner of the biological world that gives genome sequencing its great power. Everybody recognized this immediately during the early debates on the human genome project. I remember a meeting where there were three speakers, one against sequencing the human genome, one neutral, and one in favor (me). When my turn came, I began by asking: "Hands up all the graduate students who are sequencing genes for their professors!" One by one, hands were raised until eventually there was a forest. "I have come to liberate you," I said. "Graduate students should be learning how to do research and leave DNA

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sequencing to their elders." To me, it had become clear that it was not sequencing per se that people objected to, but the idea of having a "big science" factory project.

Davies sketches the early days of the human genome project from the first meetings in 1985 and 1986 to the important events in 1987, when the National Research Council panel chaired by Bruce Alberts concluded that the Genome Project should go ahead. Most of the panel's members were originally skeptical, but as their meetings proceeded they converted and became enthusiastic supporters. I did not believe that the technology existing at the time would be able to generate the information required for large genome sequences, and I thought my generation would be better off finding the important parts of the genomes and leaving the difficult parts to our younger, more energetic successors. Unlike several of my contemporaries, I was not interested in seeing the whole genome before I die (as most of it is junk), but I wanted to see all the genes.

The main part of Davies's book focuses on the rivalry between the two groups that finally finished running the whole race: Craig Venter with his company, Celera, and the international Human Genome Project, the publicly funded consortium led by Francis Collins at the NIH in the United States and John Sulston at the Wellcome Trust's Sanger Centre in the United Kingdom. The consortium included the laboratories of Robert Waterston (Washington University), Richard Gibbs (Baylor), and Eric Lander (the Whitehead Institute) as well as the Department of Energy's Joint Genome Institute. Other members of the originally loose alliance had to be ditched when the public project adopted a tighter organization to compete with the superior resources of Celera.

Venter emerges as the ogre of the piece. He is seen by many as someone who has sullied the human genome by trying to patent it and make money out of it; his critics view themselves as defenders of the just, Knights of the Grail. We read of the attempts to bring the parties together and how the original concept of a pristine sequence declined into a draft sequence (was it a first draft or a rough draft?). The pundits all claimed that it would be impossible to assemble a genome sequence using Venter's shotgun method and that such a sequence would have hundreds of thousands of gaps in it (the Holy Book of Man perhaps). They were proved wrong.

Do we have the complete sequence of the human genome? That depends on what you mean by complete. The sequence can only be asymptotically complete, much in the vein of W. C. Fields's remark that for the man who falls off a 300-foot building, it is only the last inch that really hurts.

How can something seen as being so valuable—a grail, a unique source of knowledge and understanding—have degenerated into a spitting match between the two groups? The answer is that everybody is human, probably because we share the same genome. Scientists, like mountaineers, want to get there first. The next human genome sequence might be suitable as a Ph.D. thesis. Everything in science is bound to be discovered, and those who discover it first get the credit. Genome sequencing is a field where it would be quite easy to find replacements for the people doing the actual work.

The book contains many references to Newton's famous phrase, "If I have seen further it is by standing on the shoulders of Giants." And there is quite a lot of shoulder-standing in the sequencing efforts. Somewhere I think I have read an alternative quotation, "I have stood on the shoulders of pygmies." It is a clever remark, and one that is applicable to the story Davies tells. There is, however, the sobering thought that in a land of giants and pygmies there is no point in standing on the shoulders of a pygmy if one is a pygmy oneself.