create; then as Kay so clearly shows, we are badly misled by applying these measures to DNA. But, as she says, "code," "language," and "information" are themselves metaphors, terms appropriated by science and technology and given special content for special purposes. For an old-fashioned epistemologist, to say that DNA contains determinative information about amino acid sequences is simply to say that a knowledge of the DNA sequence is sufficient to provide knowledge of the amino acid sequence but not vice versa. The best way to protect ourselves against the damage of metaphors is to allow the models on which they are based to have as little specific content as possible while still allowing them to serve a constructive purpose. As Arturo Rosenblueth and Norbert Wiener once noted, "The price of metaphor is eternal vigilance."

The real damage done by the idea of DNA as "The Book of Life" is laid out in the last chapters of Kay's book. It is the elevation of DNA to the status of a master molecule, one which determines in some autonomous way the very nature of living organisms. The erroneous description of DNA as "self-replicating," as "making" proteins, and as "determining" organisms is repeated over and over in service of the hegemony of the gene. But DNA is not self-replicating any more than a letter put into a photocopier is self-replicating. DNA sequence does not specify protein, but only the amino acid sequence. The protein is one of a number of minimum free-energy foldings of the same amino acid chain, and the cellular milieu together with the translation process influences which of these foldings occurs. (Even Kay sometimes writes "protein" when she means "amino acid sequence.") And organisms are not determined by their DNA but by an interaction of genes and the environment, modified by random cellular events. Kay ascribes most of the fetishism of DNA as the ultimate information on which life is built to the tremendous prestige that technology acquired during World War II, to the immense amounts of money poured into biological research by technology-oriented government agencies, and to the impetus given to technology by the appearance of Sputnik. I would add that the notion of the primary role of the DNA "blueprint" and the merely mechanical, secondary role of the cell machinery that uses that blueprint for production is another form of the deep cultural prejudice (characteristic of modern capitalism) that mental labor is superior to mere physical labor, a prejudice that is replicated in the entire structure of laboratory life.

Biologists skeptical of the poststructuralist theories of a mere historian like Lily Kay might do well to consider the opinion of François Jacob on the matter:

> But science is enclosed in its explanatory system, and cannot escape from it. Today the world is message, codes and information. Tomorrow what analysis will break down our objects to reconstitute them in a new space? What new "Russian doll" will emerge? [*The Logic of Life*, (Pantheon, New York, 1973).]

But then again, what can you expect from a Frenchman?

BOOK REVIEWS: GENETICS

Communication Breakdown?

Sean B. Carroll

> And it's whispered that soon
> If we all call the tune
> Then the piper will lead us to reason
> – *Led Zeppelin, "Stairway to Heaven"*

Framed by the rediscovery of Mendel's studies in 1900 and the determination of the sequence of the human genome in 2000, the 20th century, it can be argued, was "the century of the gene." Over its span, genetics rose from obscurity to form a cornerstone of evolutionary biology's Modern Synthesis, and the physical and chemical bases of inheritance and mutation were explained, the genetic code deciphered, the riddle of antibody diversity solved, a several hundred billion dollar industry born, and new tools invented that have revolutionized fields from forensic science to paleoanthropology.

The Century of the Gene
by Evelyn Fox Keller
Harvard University Press, Cambridge, MA, 2000. 190 pp. $22.95, £15.95. ISBN 0-674-00372-1.

Now seems a fitting time to look back upon this parade of great achievements and to ponder what the future may bring. In her new book, noted science historian Evelyn Fox Keller ventures in both directions; she covers a few highlights in the history of genetics and offers a bit of crystal ball–gazing. But *The Century of the Gene* is less a celebration of the triumphs of genetics than an appeal to biologists to shed their gene-centric mindset so as to usher in a new "Cambrian Period" of biological reason.

Keller explains that one major impetus for the book was "the call for functional genomics," a recent buzzword for the functional analysis of genes defined by genomic sequencing instead of classical genetics. In this new era, Keller sees "at least tacit acknowledgment of how large a gap between genetic 'information' and biological meaning really is" and "an acknowledgement of the limitations of the most extreme forms of reductionism that had earlier held sway." In a fairly short, very readable text, Keller develops the theme that both current genetic parlance and the reductionist approach are inadequate for explaining our expanding biological knowledge. She finds that they threaten to limit the future intellectual growth and public understanding of the discipline. And she suggests that new concepts, terms, and ways of thinking will be necessary to loosen the grip that genes have held on the imaginations of life scientists.

Keller perceives "ever-widening gaps between our starting assumptions and the actual data that the new molecular tools are now making available." For starters, she tackles no less than "the gene" as an outmoded term and concept. She alleges that the "prowess of new analytic techniques and the sheer weight of the findings they have enabled have brought the concept of the gene to the verge of collapse." Yet we are never really told which techniques and what mass of findings have precipitated this supposed crisis. To be sure, the analysis of eukaryotic genes has revealed that more structural features (introns, dispersed cis-regulatory elements, alternative splice sites) are involved in the regulation of the transcription and processing of RNA transcripts than for typical bacterial genes. And, in multicellular organisms, genes do encode products that function in more than one place and at more than one time (although pleiotropy, a perfectly well-understood term and concept, is not mentioned). But structural complexity or multifunctionality do not disable the term "gene" anymore than the range of architectural complexity or variety of uses of "buildings," from shacks to palaces, renders that noun obsolete.

"Genetic program" is another term that draws Keller's fire. She traces its origin to the pioneering work of Jacques Monod and François Jacob in the early 1960s, which extrapolated from the principles of enzyme induction in bacteria to metazoan development. Keller objects to the notion that there is a program contained within the genome. She rejects model descriptions such as a "genetic switching network" on the grounds that this phrase "harbors a potentially treacherous ambiguity" that fails to distinguish between genes as the source of the program

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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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