



A new paradigm for life

Illustration by Stuart Bradford

BEYOND GENETIC DETERMINISM

By Richard Strohman

WHEN THE HIGHLY ANTICIPATED SEQUENCING OF THE human genome was completed in February, a headline in the *San Francisco Chronicle* announced: "Genome Discovery Shocks Scientists." Only some 30,000 genes were found in the human genome where scientists had expected 100,000; a further discovery was that we humans have only 300 unique genes distinguishing us from a mouse. News articles also made much of the fact that genes could work together to produce many proteins—far more than most scientists had previously thought. Discussion everywhere focused on the shock, the surprise, the wonder of it all.

But none of this should have been shocking, none of these discoveries was really new. We have seen suggestions of 30,000 to 40,000 genes for at least a year; we have known for some time that different species have highly similar genomes—humans and chimps, for example; and scientists have, for years, been investigating the number and range of proteins resulting from gene interactions.

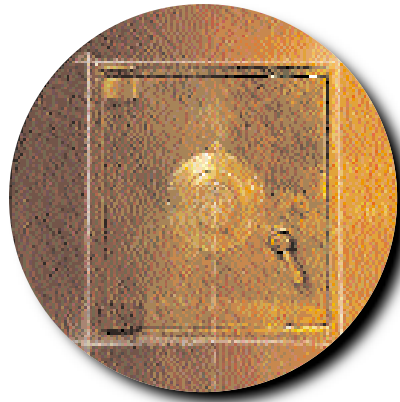
In fact, many biologists—myself included—have suspected for decades that genetics alone would not be sufficient to explain life's complexity, and that something more must be present.

Even Craig Venter, president of Celera, the corporate arm of the DNA sequencing effort, commented: "This tells me that genes can't possibly explain all of what makes us what we are." I would go further. I interpret Venter's comment as suggesting nothing less than the failure of genetic determinism—the biological theory that the complex characteristics of human beings are caused by specific genes.

But after almost a century of life sciences dominated by this theory, and after ten years of the Human Genome Project (HGP) dedicated to finding the genes which cause human diseases, with the human genome finally sequenced and biotechnologists and drug companies standing by—after all that, to announce that the entire project was based on an incomplete and flawed theory would have been much more than "shocking." It would have been a scandal.

So, instead, Venter and his colleagues went on to describe how they would develop new technologies that would enable researchers to read the "Book of Life" and thereby describe the most complex diseases and behaviors in terms of causal genes. In other words, the HGP leaders were saying that, in spite of the surprises, genetic explanations would be found as promised.

Most observers commenting on the sequencing of the human genome, after their shock and surprise, fell back to genetic determinism. One exception was the distinguished Harvard biologist Stephen Jay Gould, who wrote in the *New York Times*: "The collapse of the doctrine of one gene for one protein, and one direc-



tion of causal flow from basic codes to elaborate totality, marks the failure of [genetic] reductionism for the complex system we call cell biology.”

So, reading between the lines of the news reports and press conferences with the HGP leadership last February, we may say that the theory behind the technology that is now beginning to be applied to living cells is flawed. While the theory does tell us much about our genome, it tells us little about who we are and how we got that way.

Where is the program for life?

If Gould and Venter are correct in saying that genes alone cannot tell us who we are, then what will tell us? If the program for life is not in our genes, then where is it? Many of us have been saying for years that there is no program in the sense of an inherited, pre-existing script waiting to be read. Rather, inside each cell there are regulatory networks of proteins that sense or measure changes in the cellular environment and interpret those signals so that the cell can make an appropriate response.

What, then, is the role of genes? Genes specify information necessary to make proteins, and the genome as a whole provides a collective informational source. However, by itself a genome is passive: DNA, for example, cannot make itself, and cannot construct a protein, never mind perform an actual cellular function. DNA has been called the Book of Life by HGP scientists, but many other biologists consider DNA to be simply a random collection of words from which a meaningful story of life may be assembled.

In order to assemble that meaningful story, a living cell uses a second informational system. For example, let's say you have 100 genes related to heart disease or cancer. These genes code for at least 100 proteins, including some enzymes, so you have a dynamic-epigenetic network, consisting of 100-plus proteins and their many biochemical reactions and reaction products. It is “dynamic” because it regulates changes in products over time, and it is “epigenetic” because it is above genetics in level of organization. And some of these changed products feed back to DNA to regulate gene expression. The key concept here is that these dynamic-epigenetic networks have a life of their own—they follow network rules not specified by DNA. And we do not fully understand these rules.

In short, genetics alone does not tell us who we are, or who we can be. While, as Gould says, the reductionist theory of genetics

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has collapsed, the dynamic-epigenetic point of view still retains genetics as part of a new paradigm for life, one that has striking implications for the future of the life sciences.

The problem is part science and part philosophy

We must now ask: where did the Human Genome Project go wrong? That is, where did the mistaken idea originate that complex human diseases could be traced to one or a few major genes?

Early on we found that there are indeed some diseases that are traceable to single genes. I worked on one, muscular dystrophy, for 25 years. These monogenetic diseases provided a simple model: one gene leads to one disease.

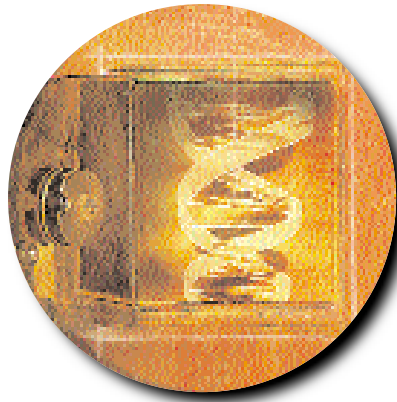
But that model is wrong because it has limited application: Muscular dystrophy is one of the few clear cases where it works. In these relatively simple diseases, a single defective gene finds no redundancy, or back-up information, in the cell, and therefore the gene may be said to be the single cause. But these diseases are rare; in fact they account for only 2 percent of our disease load.

The mistake of the HGP was to use that simplified model to attack all diseases, including diseases such as most cancers, heart disease, and bipolar disorder (manic depression). Together, those diseases account for over 70 percent of our disease load.

The vast majority of human diseases are multifactorial: They are influenced by many genes interacting with one another and by a vast array of signals within the cellular environment (including nutrient supply, hormones, and electrical signals from other cells), and all of these are in turn influenced by the external world of the organism as a whole. Thus, mutations in specific genes in one human body, given its genetic background (all other interacting genes), might produce a disease; but in any other human body there might be little or no disease because each human being has a unique genetic background.

For diseases involving many genes, the effect of each gene is small, and loss of function for one may be compensated by gene interaction and by environmental conditions. In addition, many diseases will be altered when the conditions of life are altered, especially in early life.

A telling example is spina bifida, one of several potentially fatal neural tube diseases in which there is failure of the spinal cord or



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brain to close or develop. Long thought to be a multifactorial genetic disease, spina bifida is now actually known to be due to a deficiency of a B vitamin (folic acid). If the 70 million women capable of becoming pregnant were to take folic acid one month prior to conception, many of these neural tube diseases would disappear. And lung cancer is an obvious example of environmental impact: Even for long-term smokers, life expectancy is vastly improved for those who give up the habit.

But HGP scientists thought, and still do, that they could find a small number of genes that are the key to these diseases. However, this strategy is flawed because for most multifactorial diseases affected by many genes, these genes have small, not large, effects. And genes with small effects are very hard to find. Even when found, one would have no way of predicting the disease outcome unless one also knew all the initial conditions surrounding the developmental history of the individual. In addition, most multifactorial diseases like cancer take many years, even a lifetime, to develop, so one would also have to know all the historical details to make predictions. Finally, the strategy is further flawed because it traces all causality back to genes rather than to genes coupled with dynamics, the duration of exposure to changing environments. Here again lung cancer is instructive since the disease is dependent on the dose (number of cigarettes) and the duration (number of years) of exposure.

We must also ask: Why is the alternative to genetics—the dynamic-epigenetic management of complex diseases—not in the news? The answer has as much to do with philosophy and sociology as it does with science.

Right now, this new view of life is being tested in laboratories around the world, and scientific journals bring weekly news of its progress. However, the full extent of cellular regulatory networks is not understood, nor do we have knowledge of how the cell as a whole integrates the output of these systems to produce an adaptive response to a complex set of ever-changing external signals.

The transition from a genetic-determinist paradigm to a new, more complex regulatory paradigm will take much more time. The Human Genome Project has been devoted to a determinist, gene-based view of life, and has spent ten years sequencing the genome. But, along the way, scientists outside the HGP tested various predictions, and the community of science and technology

arrived at a much more complex picture of life and of the genome than it started out with.

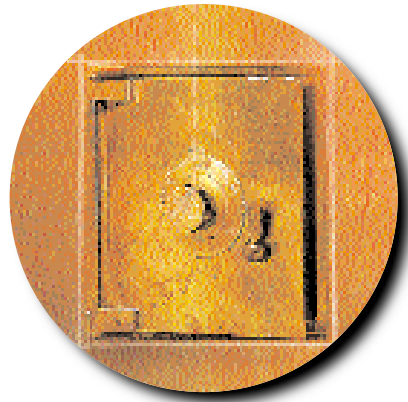
Until we have a theory, or a paradigm, of life that is able to assimilate the contradictions generated by the HGP and by the experimental community at large—one that is able to explain what genetics alone cannot—we will have to move ahead with caution and with every effort to put the dynamic-regulatory science in place alongside the more familiar genetics. But moving ahead with caution, and with an incomplete theory of life, is not exactly newsworthy in today's atmosphere of certainty and instant rewards.

Nor does the HGP exist solely in the world of science. Over the past ten years, it has developed strong relationships with corporate, social, and economic interests, and has—willingly, I would say—become a tool of those interests. It has given itself over to a propaganda stream of unprecedented dimension and has made promises that play on the health aspirations of people everywhere. In addition, the corporate world of biotechnology has investments of billions of dollars in the pipeline, so withdrawal from the determinist position is extremely difficult. These are all clear facts, confirmed in our daily news.

Where do we go from here?

Along with many other scientists, I conclude that we are in the middle of a biological revolution. We have a failed or, at the least, an incomplete scientific paradigm called genetic determinism. At the same time, we have an alternative paradigm called dynamics-epigenetics, which is extremely interesting but also incomplete. Unfortunately, over the last 50 years our research portfolio has become unbalanced, heavily favoring genetics and ignoring dynamics. It will be difficult to change direction, if for no other reason than it will take a long time to train the next generation of scientists who understand both sides of the equation. And any change away from the genetic-determinist view will also be resisted by corporate forces that have huge economic investments at stake. This resistance grows stronger as a result of university alliances with the world of corporate biotechnology.

In the long run, the issue of genetic determinism will only be settled when something like the dynamic-epigenetic theory becomes complete enough to challenge the status quo. For now, the important issue before us is the technological problem of



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genetic engineering of organisms in the light of our imperfect understanding of how the living cell actually works. It must be emphasized that we simply do not understand how living cells respond over time to their manipulation through genetic engineering, and thus the error factor here remains large.

It seems to me that we must move ahead at several levels. First, we need the construction and imposition of scientific standards that would constrain attempts to genetically engineer or clone ourselves, our children, other animals, and the plants that constitute the basis of our agriculture and much more. If the announcements from the HGP tell us anything, they tell us that we do not know how organisms make themselves. As many developmental biologists have said, we are still in the dark ages about how organisms regulate their genomes to produce adults. While the scientific inquiry must go on, technological applications must stop—until we are assured that we may proceed without doing any harm.

Second, at the level of science itself, we must now ask what we want our life scientists to do next. Already they can measure and show us things far beyond our expectations of only a few years ago. But now we are reminded, once again, that the wider environment as well as complex cellular processes—not just genes—play important roles in shaping our lives. The work of corporate biotechnology will go on; as the *Wall Street Journal* reminds us, it is inevitable, as is human cloning, as is a future gene-based medicine for the wealthy few who hope to immunize themselves against premature diseases and death. But theirs will be a false hope. Premature disease and death will surely come if we allow a continued degradation of the very environment so necessary for the healthy expression of genes now present in all of us.

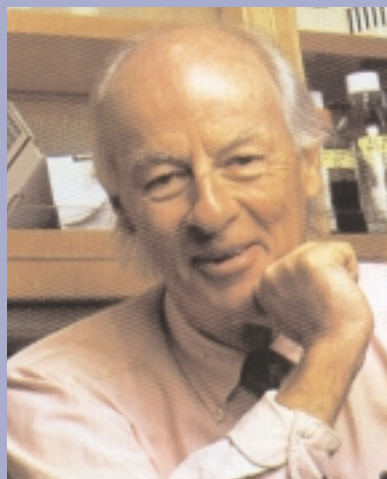
Emphasis on gene technology causes us to forget that a technology called public health has already provided a model for the future. Public health technology has given us nearly forty years of increased life expectancy in just the past 100 years—

without genetic engineering of any kind—proving that the genomes we have are already competent to provide us with a life expectancy at birth of 85 years.

The university and national (public) laboratories may now choose to take up the quest for new rules of the complex adaptive systems we call life. We can choose to support work that would allow us to discover constraints at the level of multi-cellular organisms, populations, and ecological settings. Violation of these constraints could bring great risk to individual health and to stable ecosystems.

We thought the program was in the genes, and then in the proteins encoded by genes. But knowing all the individual proteins will not reveal a program; for that one needs to know the rules of protein networks that are coextensive with the cell itself. The program location is the cell as a whole; and the cell, through signaling pathways, is connected to larger wholes and to the external world. If we could find the financial and other necessary inspiration, and the will to implement the additional research, we would have a science and a technology—a university-industrial complex—that everyone could invest in and benefit from. The real questions for all of us are: Who chooses, and who decides the future of life? ☹

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Richard Strohman is among the working retired Cal faculty, teaching freshman seminars and writing a book dealing with the issues in this article. He has been at Berkeley since 1959, serving as chair of the nation's top-ranked zoology department and director of the Health and Medical Sciences Program. In 1992, while on leave, he was research director for the Muscular Dystrophy Association's fight against neuromuscular disease. He is a frequent contributor to *Nature Biotechnology*, a leading journal in the biotech industry.