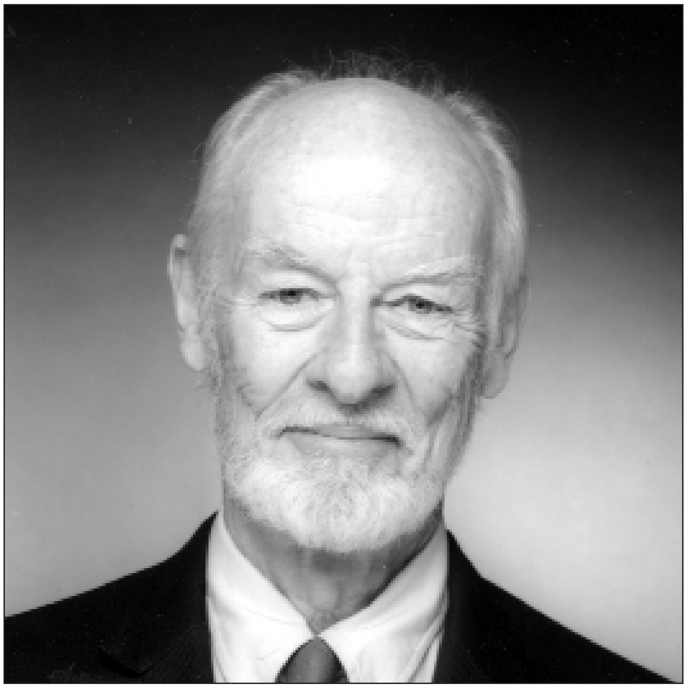
The Upcoming Biological Revolution

An Interview with Richard Strohman



Richard Strohman *is Emeritus Professor of Molecular and Cell Biology at UC Berkeley; with a Ph.D. from Columbia University. On leave from UCB in 1990, he was Research Director for the Muscular Dystrophy Association's international effort to combat genetic neuromuscular diseases; earlier he coauthored Gene Expression in Muscle. During 1992-93, he was "Distinguished Wellness Lecturer" at UCB. He continues to teach courses and publish articles, and is currently writing a book on the growing crises in theoretical biology. He has received wide acclaim as one of the leading figures thinking and writing on opportunities for a new, holistic scientific theory of living systems.*

Casey Walker: Will you begin by describing the properties of a scientific Kuhnian Revolution, and why Kuhn's understanding of paradigmatic shifts is key to a deeper critique of current developments in biogenetic engineering?

Richard Strohman: A scientific revolution is one in which a prevailing, dominant paradigm–one that defines a scientific worldview, together with the methods of achieving research-based understanding and technological utility–is replaced by a contending paradigm. The revolution, according to Kuhn, has several properties. One is *incommensurability*, where the scientists on either side of the paradigmatic divide experience great difficulty in understanding the other's point of view or reasons for adopting it. Second is the *accumulation of anomalies*, wherein "normal science" of the current paradigm unintentionally generates a body of observations which not only fails to support that paradigm, but also points to glaring weaknesses in its method and theoretical outlook. The paradigm, under the weight of accumulated anomalies loses the confidence of scientists in a minority sector and is ripe for overthrow. Third, paradigm shifts encounter *resistance to change* from the old guard, which is based not only upon a scientific incommensurability but on traditional ways of teaching and training the new generations in the (old) ways of research. Finally, there is enormous *inertia* based on the inability of a challenging paradigm to be fully capable of assimilating the accumulated anomalies and to provide a thoroughgoing scientific analysis and methodology capable of spelling out future programs of research and technology. The old paradigm may be a "scandal" of mistaken assumptions and failed predictions but if there is no fully competent paradigm ready to take its place, the scientific establishment must, by definition, remain loyal to it. As Kuhn compassionately noted, scientists cannot at the same time practice and renounce the paradigm under which they work. Thus, because of incommensurability, resistance to change, and inertia, the discovered accumulation of anomalies will be ignored until a new and competent paradigm is capable of replacing it.

In the present climate of biogenetic engineering, which is based on the dominant paradigm of molecular-genetic determinism, Kuhn's critical analysis allows us to recognize features of the paradigm's relative success and failure over time. These features might not otherwise be noticed or, if noticed, might be forgiven for a host of reasons having to do with the belief that science is always an accumulative process, and, presumably, given enough time, any anomalies would be assimilated by progress within a "more of the same" pattern of research development. But in today's setting, where vast sums of intellectual and monetary resources and power are devoted to the genetic determinist paradigm and its application in fundamental biology, in biomedicine, in agriculture, and biowarfare, we need to exert every opportunity to examine our paradigm lest it be found, too late, to harbor anomalies that may turn out to be irreversible in the long run. Granted, it is not always a good idea to prejudge the performance of an ongoing paradigm since it may indeed be self-correcting. But our dominant paradigm in biology has accumulated many anomalies, errant predictions, proven false assumptions and outright errors of application in basic research and in biotech application in medicine and agriculture. The question is, Can biogenetic engineering in its present mode be dangerous to the public health?

Kuhn's normal science in today's biology discovers its own flawed assumptions but this does not lead to further insight. It reveals a complexity more grand than that imagined–but a complexity revealed is not the same as a complexity understood. The fact that we have discovered more than we understand–including the overwhelming databases of the various genome projects–suggests that our present paradigm is missing something essential. We need to recognize this incompleteness before going further with genetic engineering that will also produce unforeseen events in the Earth's populations of animals and plants.

In "The Coming Kuhnian Revolution in Biology," you wrote "[W]e have taken a successful and extremely useful theory and paradigm of the gene and have illegitimately extended it as a paradigm of life." How did this illegitimate extension occur? Why did genetic determinism win out over systems theory, holistic biology, or areas of research in the complexity and non-linearity of life?

The revolution in biology is all about the failed theory of genetic determinism. At the level of coded information in DNA–of replication, inheritance, and decoding of DNA messages–the theory of the gene is elegant in a simplicity accurately captured by what has come to be known as the central dogma of molecular biology:

DNA–>>RNA–>>Proteins––//–>>Functions

At this level the gene theory is complete or nearly so. However, this theory of what genes do and why genes are important has been extended to a theory of life which states that genes determine more than local function defined by individual proteins (and even this is exaggerated). Extended, the theory of the gene is a theory in search of ways in which genes determine complex functions like normal or super intelligence, disease states, psychological states, and so on. It is this extension–from understanding inherited DNA as determinative of local protein functions to DNA as determinative of complex functions–not only of cells but of organisms of trillions of cells–that is illegitimate. It is this extended theory and paradigm of the gene that is in trouble, and where the revolution in biology is brewing.

It is easy to see how this illegitimate function was assigned. The structure of DNA as given by Watson and Crick was such a powerful insight about biological information and generated such a productive wave of discovery and understanding at the molecular level, there was every reason to think that this information somehow extended beyond proteins to programs of behavior. However, no genetic programs have ever been found, and here is our dilemma. We organisms are certainly "programmed" in some sense of that word, but if the program is not in our genes, then where is the program? We have no answer to this question and, according to Kuhn, without a paradigm capable of addressing the mystery of the missing program, we will have to hang on to our incomplete paradigm of genetic determinism. Current references to non-linear dynamics or complexity theory or chaos are all interesting starts at contributions to a new theory, but they remain as starts. That is our situation as we enter the new century. Our view of life is incomplete by half–at best.

> *This is the first time in the history of the life sciences that a single generation has been able to live through the rise and fall of a single dominant paradigm. It is a deeply disturbing experience, especially for those who have followed the radical change from a distance, and especially given the enormous investment our culture has made in ideas tied to a hopelessly ineffective, linear causality and determinism.*

For now, we adopt the shorthand expression for these alternative approaches and group them under the heading of "dynamics," the science that studies time- and context-dependent change in simple and in complex systems. In life, both genetics and dynamics are essential. They are also irreducible, meaning that one cannot be derived from the other in any formal way. In life, genetics and dynamics are irreducibly complementary. In the last 100 years we have had science based mostly in genetics, but mostly without dynamics. Dynamical systems science offers many possible approaches in which genetics may be complemented so as to provide understanding of complex organisms.

Neither genes nor environments "cause" complex traits. If a word be needed here then "cell" will name the cause. It is the cell, and the body of cells as a whole, that selects from the dynamical interactions inherent in its physical and chemical pathways and responds formatively and adaptively to the external environment. We have mistakenly replaced the concept and reality of the cell as a dynamical center of integrative activity with the concept of gene causality.

Will you describe the anomalies discovered for genetic determinism? What doesn't genetic sequencing or complexity alone account for?

At all levels of life's organization–the evolution of populations, individual development, physiology, cell and molecular biology–and in applications in biotechnology and biomedicine experimental and field studies, we are discovering new facts that cannot be explained easily and sometimes not at all by the current theory. In many ways these discoveries are merely modern versions of old but forgotten aspects of elementary (non-linear) dynamic genetic processes, such as epistasis (gene interactions) and pleiotropy (one gene or protein with multiple effects). At all levels, one detects lack of correlation of genetic complexity with morphological complexity (an organism's structure and behavior). So, for example, differences in genome size and complexity between species are often much smaller than the differences in structure and behavior of those species (humans and chimps, for example, have DNA that is roughly 98 percent identical). Errant predictions based on genetics and the notion of specific cause and effect are turning up everywhere.

Development is a process in which identical genomes produce, in the case of humans, over 250 different cell types! In molecular and cell biology, one can delete genes with no apparent noticeable effect even though the deleted genes were thought to be essential. Once again, genetics alone fails to predict the correct outcome in these experimental settings. There are many other examples of anomalies.

On the other hand, complex dynamic processes do not account for the discrete informational bits in DNA and the syntax rules by which that information is encoded and manipulated. Genetics and dynamics are complementary–both are needed.

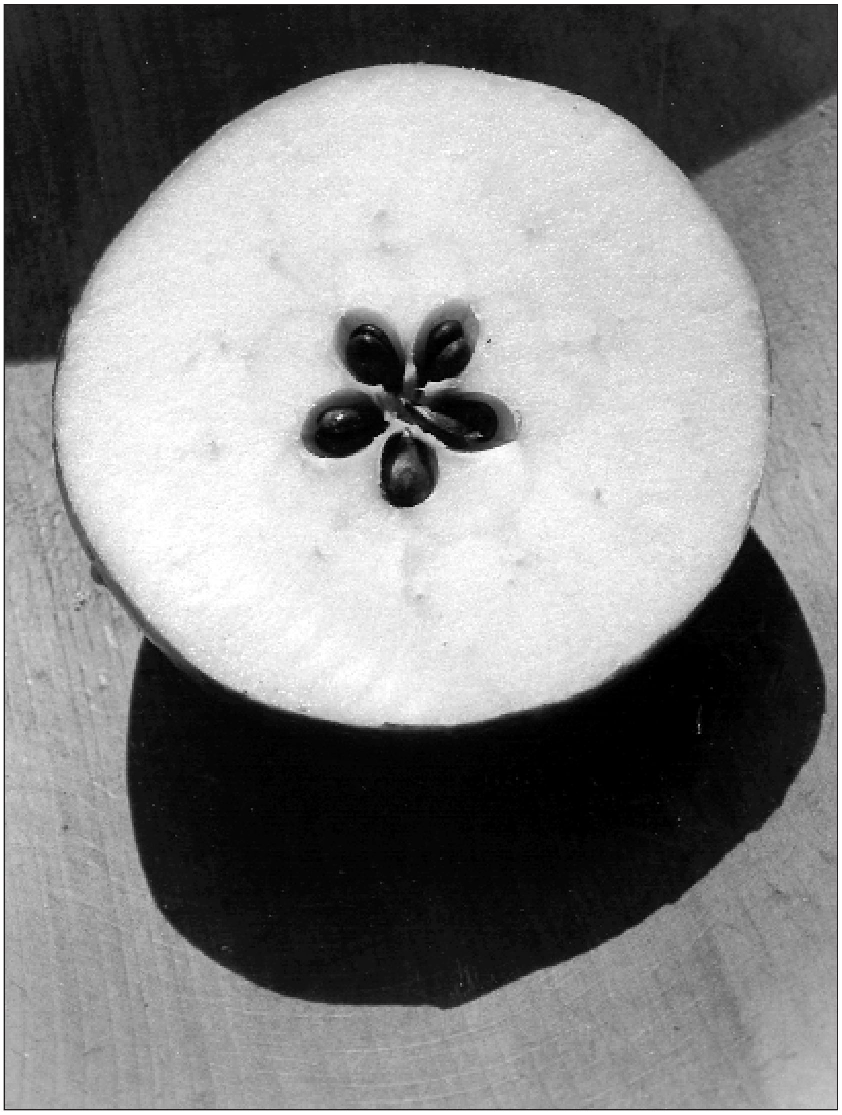
Is it possible that the scientific proof for a new paradigm will not come from any kind of determinism but from a description of motive, strategy, interactive will? If so, would theories along the lines of complex adaptive systems, epigenesis and non-linear dynamics, chaos, or self-organized criticality be grounded in scientific proof?

We are at the beginning of a Kuhnian revolution, and, as Kuhn said, a scientist cannot remain a scientist and at the same time be without a paradigm. The result would be complete confusion. All or most of the candidate theories that I have gathered under the heading of dynamics do contain references to motive, purpose (telos), and will as needing to be included as essential irreducible facts of life, and all, in one way or another, address this necessity without needing to throw out reductionism or genetics, but to complement these with dynamics. It is much too early in the game to even guess how this is going to work out.

For now, pragmatics dictate a loosening of the theory of genetics to include dynamics. Biology needs more work, not less. While calls to abandon biotechnical applications based on incomplete science are not only pertinent but essential, such calls should not be misunderstood as being anti-scientific–it is quite the reverse.

Will you explain epigenesis as an alternative to genetic determinism and describe the levels of dynamic organization it contends with? Further, will you speculate on the full import of understanding boundary conditions as key to the laws of living matter?

Epigenesis is the historical alternative to biological (genetic) determinism. It emphasizes a science of processes over objects, of order over heterogeneity and has, from the beginning, talked about the necessity of developing a science of qualities, purpose, and intentionality. The telos emphasized here has nothing to do with metaphysics or vitalism but everything to do with finding scientific laws unique to these qualities of life. Epigenetic process has been ignored for hundreds of years but has now been thoroughly revived–first as a necessary assumption to explain anomalies, and now as a description of regulatory (dynamical) processes that serve to regulate patterns of gene expression in a context-dependent manner. These networks are open to the world and provide the sought-after link between the environment, experience, and management of genetic information.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I wrote about boundary conditions as key to laws of life and I also spoke about epigenesis as able to provide only partial answers. Epigenetic processes are a class of dynamical processes operating in living systems. For example, they operate at the level of the genome to regulate patterns of gene expression–how signals from the world are integrated to turn genes on and off in an adaptive manner. But this is only one level of epigenetic regulation. There is a kind of infinite regress here since we now have to ask, What controls the control of gene regulation? The answer we might have to settle for is the cell. Then what controls the cell? And so on...Here we have to talk about boundary conditions. Michael Polanyi, the late, great professor of physical chemistry and of social studies at the University of Manchester (those were the days!) said the following: “Live mechanisms and information in DNA are boundary conditions with a sequence of boundaries above them.” (see *Science*,160:1308-1312 for 1968) He means that, in life, there is a continuous complementary relationship between genetics and dynamics from which comes the adaptive qualities of life. If we start with DNA, then the first, innermost, of a sequence of boundaries moving out to the cell as a whole is the epigenetic control of gene expression, and this boundary moves outward to populations of cells, to the whole organism and beyond to communities, populations, and, of course, to the world, natural or otherwise. They are all connected. And the idea of boundary conditions gives us a scientific way of understanding the connections. As Polanyi put it, “...The outer boundary harnesses the laws of the next inner one.” To which one might add, “Or is it the other way around?” By partial answers from epigenesis, I mean that at some point we have to stop calling these levels epigenetic and call them something else. Polanyi’s discussion reminds me of Wendell Berry’s essay on the “system of systems” in *Standing by Words*.

What perspective do you hope society will gain, finally, on the usefulness of biogenetic engineering?

Biogenetic engineering, when faced with the limits and dangers of an incomplete genetic science, will have to conclude that engineering the human genome is– for 98 percent of our problems– facing an overwhelming complexity. That is the message from recently discovered anomalies and from experiments pointing to epigenetic, context-dependent regulation of the genome.

What then? Is that the end of genetics or of biological engineering? Certainly not. Biological–not biogenetic– engineering, through dynamics will, or may, expand outward to include the organism and the natural world–the system of systems of the philosophers, poets, and scientists of the land, such as Wendell Berry, Wes Jackson, and many others. The human genome is ancient, conserved, difficult to improve upon most of the time and for most people. Biological engineering may use its databases not to engineer genomes but to understand the requirements of genetic agents and epigenetic processes in the world. Biotechnology and engineering would then be devoted to a restoration of the world to reflect the conserved genomes of organisms–human, non-human animals, and plants–that must occupy the land in common.

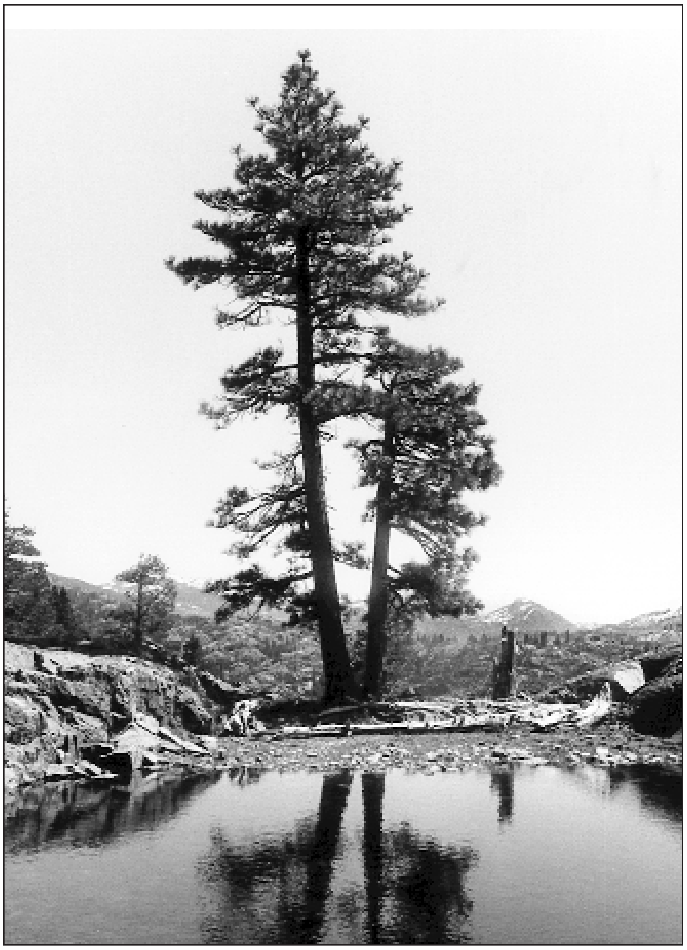
Biogenetic engineering assumes that organisms may be improved through genetic information almost exclusively. Biological engineering looks at the boundary conditions between genetic and other kinds of information and at the boundary conditions at all levels of living things, including the interface between the individual and the environment. As an example of the latter, elimination or reduction of human health risks (malnutrition, contaminated water and food, and tobacco smoking) has been the single most effective biological engineering in human history. We have already used it to gain 35 years of life expectancy just in the last 100 years. We have done this without engineering any genomes but have instead provided those embodied genomes with a proper world, one that reflects their evolved limits and capacities. In fact, further improvements in life expectancy are expected not from eliminating diseases associated with old age, or from genetic breakthroughs, but from further improvements in eliminating environmental risks and in greater access to improvements for those who suffer premature morbidity and mortality. For example, people suffer from their lack of access to the food we can provide, not from our lack of ability to provide that food. However, as our world continues to suffer the disasters of our other technologies (land, water, air degradation), and as we continue in the futile hope of being immunized to the consequences of this suffering by genetic engineering–of ourselves or of the animals and plants– we will surely begin to lose the gains in health and life expectancy we have achieved this century.

The revolution against a preordained genetic determinism has discovered a complexity from which there is no turning back.

In sum, several conclusions concerning the future of biotechnology seem inescapable. First, in the science of molecular genetics the fundamental assumptions about specific genes and their specific “causal” effects on organisms are deeply flawed. As one recent paper in a major journal noted, there is now every reason to believe that it will not be possible to carry out genetic engineering (transfer of specific genes to a host cell) in the hope of achieving a specific effect. The normal complex interactions between genes and molecules in cells will be distorted by the presence of even a single transferred gene yielding unpredictable and therefore potentially dangerous results of unknown dimensions.

Therefore, biogenetic engineering of humans and of plants where unanticipated results could cause damage to individuals or to millions of acres of cropland will have to cease except under tightly controlled laboratory conditions and until the time when the complexities are understood and the dangers eliminated. Controls here would include concerns of ethical, legal, and social dimensions. These concerns must reflect the “ethics of the unknown” of the incompleteness of the science being applied, and not just the ethical concerns growing out of a “successful” technology.

There is, after all, an ethical component built into the structure of science itself, one that is often ignored by governmental and corporate structures as funders of research. This component includes the imperatives to seek evidence for disproving one’s hypothesis (Popper), and to consider all, and not just selective evidence (Whitehead). It includes also



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the historical record showing the capability of "normal science" to uncover the flaws and misconceptions of a prevailing paradigm (Kuhn). These imperatives and demonstrated long-run capacities are inconsistent with modern corporate technology, which is based on the need to produce marketable results in a cost- and time-effective manner and in a manner that deflects anomalies from consideration. Government support of "basic" research is all too often heavy-handed in insisting that all efforts be "sold" under the heading of being able to solve key problems or address other issues reflected, as Whitehead pointed out, "...in the fluctuating extremes of fashionable opinion." Science is mostly a long range affair while technology is not. The question remains: Who will pay for the long-range need to know?

Second, the flagship of biogenetic science is the human genome project, and similar projects involving other animal and plant genomes are themselves squarely facing the anomalies discovered by their own scientists. Leaders of these projects are now increasingly aware of the flawed assumptions just discussed, and these projects are all now actively seeking to place their genetic findings within a wider physiological and ecological context. The search is on for the "meaning" of life that is now acknowledged not to be simply genetic in nature. The context has progressively shifted from epigenetic levels of genome control to a hierarchy of control extending to the cell as a whole and beyond the cell to cell populations, to organisms, and to the interactive and mutually dependent communities of life. The revolution against a preordained genetic determinism has discovered a complexity from which there is no turning back. However, without a fully developed paradigm of complexity as robust at the higher levels of biological organization as the Watson Crick theory has been at the level of the gene, further progress will, predictably, be ruled by conservative forces. Therefore, in the interim, all caution must be exerted to guarantee that those forces also tightly regulate the old incomplete paradigm while we await its complementation with a science we have here called simply "dynamics."

This is the first time in the history of the life sciences that a single generation has been able to live through the rise and fall of a single dominant paradigm. It is a deeply disturbing experience, especially for those who have followed the radical change from a distance, and especially given the enormous investment our culture has made in ideas tied to a hopelessly ineffective, linear causality and determinism. Of course, from my perspective as a biologist, all this is wonderfully exciting: science can and does work in a free society. As the great astronomer and cosmologist Sir Arthur Eddington has said of basic science, "We must follow science for its own sake whether it leads to the hill of vision or the tunnel of obscurity." Today, with the obvious link of science and society, there are many opportunities ahead–having to do with those as yet unexplored boundary conditions and mysterious spaces between hierarchical levels where "emergent" qualitative features arise from quantitative interactions below–to understand biology as the most complex of all sciences, and to understand the equally complex impacts of its applied technologies.

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