EPIGENESIS AND COMPLEXITY

Profit margins and epistemology

Richard C. Strohman

A response to two commentaries on *"The coming Kuhnian revolution in biology,"* published in *Nature Biotechnology.*

The response from William Bains[1] on my own commentary[2] describing epigenesis and complexity as characteristics of a coming scientific revolution was helpful. Bains, a biotechnology investment counselor in London, readily acknowledges the dominant role of a defective genetic determinism in academic and corporate research labs but maintains that ". . .it does not matter." It does not matter to the corporations or their investors that the grand design for increasing health and well being for all of us is, at its center, terribly flawed. And this is true, he implies, because the recipients of genes, proteins, drugs, and other medicines are as well served by a defective as by an efficient scientific analysis of how life works. We don't need to understand complex processes, we just need to discover new tools with which to fix these processes when they go wrong.

But, as Bains agrees, we are more than our genes; we are complex entities whose health, well being, and longevity are regulated by an interactive, multileveled arrangement of molecular networks whose rules are not specified by DNA. And in his factory analogy of genetic determinism, any part of the machine in production may turn out to be a redundant structure involved in functions never to be guessed at through our random process of mutating the assembly line. However, sometimes we are lucky and a unique genetic structure is found that may be used to engineer a useful product.

In helping to make this point, Bains provides a service. His description of the differences between fundamental and corporate (applied) research in biology could not be better stated, because essentially, or so it seems to me, he is saying that there aren't any differences. As I stated[2], corporate and academic research in biology have become "biotechnology." There are no organisms in either; there are no wholes but only mechanisms and parts, and the overriding concept guiding this research is "fundamental" or "basic" only in the futile hope that some day the parts and mechanisms will somehow add up to the whole.

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The ultimate agents in all of this are, of course, the genes but we have to be careful with that "ultimate." If you mean by it that genes "cause" diseases, for example, then by working on the former in order to understand the latter you are, in some sense, doing fundamental research. However, if by "ultimate" you take the epigenetic meaning that genes and their surrogate proteins are but instruments of a larger mechanism, if you now work on the instruments without regard to the larger mechanism, then something vital to the concept of basic research has been lost.

The revolution I was talking about is predicated on the idea that our concept of fundamental research is degraded. As Werner Heisenberg tells us, "Whenever one treats living organisms as physicochemical systems they must necessarily behave as such."[3]

It is the growing awareness of this confusion that defines our current dilemma and the possibility of a revolution within which we may recover some sense of "larger mechanism" that is coextensive with the organism itself. What then would be a proper relationship between an applied (tool-oriented) biotechnology and a separate basic research entity focused on the organism?

One useful aspect of this relationship would be a return to the idea of "organism-in-the-world." What Bains does not acknowledge is the degree to which regulatory networks lying at the center of our lives are inextricably connected to the world in which we live. His reference to "environmental determinism" also misses the epigenetic view that has historically opposed the myth of a quantifiable and isolated organism in which genetic functions and environments exist in separate domains.

Rather, complexity science seeks to provide scientific meaning for their interaction through the agency of a cell or multicelled organism. In this view profit margins would be based on biological "therapies" and "interventions" that improve, at once, both sides of the organism/environment interface so that we do not continue to generate effective individual cures only to discover we have at the same time failed to address the larger problem of collective risk.

What I'm talking about here is documented in the resurgence of tuberculosis, in the general phenomenon of bacterial resistance to antibiotics, in the long-term degradation of the land within the remarkable short-term successes of agribusiness, and in the continued pursuit of genes for rare diseases that comprise only a small fraction of our disease load while perpetuating the myth (parts=wholes) that those same genes will play important roles in the common forms of these diseases, and much more.

But the medical, ethical, social, and legal problems that arise from a narrow view of profitability and pragmatism in which human beings are seen as "treatable units" isolated from the larger community is a truly long story[4] and I thank Mr. Bains for his argument, which opens us to this complex discussion. It can show us that, while in the long term we can grow healthier through understanding the complexity of our interactive dependence on a viable world, it will also, predictably, be more difficult to preserve short-term profit margins. This is true since one cannot isolate, sequence, clone, and bottle complex interaction. The question is: How long can we afford a biotechnology that does not address both sides of the human disease/environmental community decay interface?

Finally, Bains asks ". . .should we hire an epistemologist"? If that person is one who understands complexity as well as molecular genetics and who has an expanded vision of profitability and concern[4], then yes, hire an epistemologist to run the NIH, and to diversify our national research portfolio so as to encourage the new systems biology.

The second response to my commentary, from Streelman and Karl[5], is another kind of problem altogether. My colleagues in philosophy and history warned me that I should not "wrap" my analysis of genetic determinism in a Kuhnian package. . .that, in so doing, I was asking for trouble, and that I should just stick with the facts. But it was not until I read this answering commentary that I understood what those colleagues meant. I now can't imagine what possessed me to enter the arena of the philosophical controversy around Kuhn, and the "referential quality of paradigm" within which what I thought was a pretty straightforward definition supplied by Kuhn—"a paradigm is a major model guiding scientific research"—appears to have become lost. Where Bains provided clarity and sharpness, Streelman and Karl provide, for me, mostly obfuscation. Let me try to get back to an ordinary bench scientist's view of paradigm shifts.

First, they ask, ". . .if philosophers don't believe in paradigms, why do biologists?" The straight answer, already provided several paragraphs later by Streelman and Karl, is that scientists need research dollars. In attempting to obtain these dollars, they use their tacit knowledge of what a paradigm is—it's a research model. And the general idea in grant applications is to follow the agreed-upon working model. Research questions outside the model—systemic aspects of development, robust (nongenetic) features of cellular regulation, for example—are put on the back burner until such a time when the current model loses some of its rigidity.

As I tried to say, in these days where so much money and commitment are already invested in one model (genetic reductionism), other models having to do with regulatory levels above the gene tend to go from the stove to the deep freeze. That's pretty simple stuff; advanced philosophy is not required in the same way that advanced economic theory is not required to comprehend the relationship between doing research and having the money to do it.

In my nearly forty years of successful approach to NIH and other study sections I have witnessed a transformation of grantsmanship from a straightforward request to work on a particular problem in cell/molecular biology to one in which a full defense for the work is required in terms not only of how the work is going to prevent and cure diseases, produce a better tomato, or reverse an antisocial behavior, but how it is going to do all these things through understanding genetic causality. Every working biologist that I know, with rare exception, understands that unless the grant proposal deals directly or indirectly with genetic causality the chances of success are low.

Streelman and Karl protest that ". . .if molecular biologists are not extreme reductionists in practice, then what has led Strohman to this perspective?" The answer here, beyond the one given above, is found in reading the table of contents of any current journal of molecular and/or cell biology, which reveals precisely the overwhelming extent to which, despite all protestation, the research is based on genetic determinism.

If scientists do not really believe in genetic determinism, then why is roughly 90% of their practice precisely devoted to that subject? They do it because that is what they are trained to do and they must believe it; but they believe in Kuhn's sense that they cannot at the same time practice science and abandon the paradigm under which that science is carried out. And as I took pains to point out, most of this work is the best there is, needs to be done, and should be done. It's just that in too many ways it has forced to the margins approaches that, while they do not exclude genes, emphasize a more complex and long-term approach. We all do agree, evidently, that the virtual disappearance of organismic complexity from the phase space of basic research now presents our academic research institutions with formidable problems in planning for the revolution to come.

Streelman and Karl state that the popular press is the major source of the problem in which ". . .accounts often oversimplify the relationship between DNA mutations and disease" but it is outrageous for them not to acknowledge that press conferences are called by scientists and their institutions precisely for the purpose of expanding and encouraging the naive view of genetic determinism. And it is outrageous to forget that the "public press" includes the reporters and commentators from some of our most prestigious weekly science journals, who until quite recently often failed to raise appropriate questions. Streelman and Karl cover all this with the flimsy aside that "scientists sometimes do exaggerate the implications of their work."

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Another disagreement centers on the assertions, throughout their commentary, that ". . .there is no reason to believe that epigenetics or complexity theory conflicts with molecular biology. . ." and that new discovery in complexity is made ". . .safely in the domain of molecular biology." As I pointed out, and, again, as we evidently agree, molecular biology increasingly does discover anomalies in its paradigm of genetic determinism. But, in a manner strongly reminiscent of Kuhn's analysis, there is a persistent attempt to rescue genetic explanations (the *c*-value paradox is a case in point) in the face of anomalies that refuse to go away. This is now beginning to change as evidenced by a recent CIBA symposium on the limits of reductionism (genetic and otherwise) in biology reviewed in both *Nature*[6] and in *Science*[7].

It is a misreading of recent progress to contend that the new insights are within the domain of molecular biology. Molecular biologists are involved in leading us to a more profound view of complexity, but just as new studies in metabolic pathways lead to radical views like distributed control that are not contained in standard textbooks of biochemistry[8,9], so it is that new studies of generic properties of organisms are leading to a view of individual development that is irreducible to, but not independent of, genetic elements[10].

These new studies are decidedly not "safely" tucked into the domain of molecular biology, although, of course, molecular biology is included. For example, epigenetics, as defined by Robin Holiday[2] as the molecular control of genomic behavior, is only the simplest case of hierarchical regulation; as such, it does represent a continuum with molecular biology and is a first-rate example of genetic "distributed control." But there is nothing in molecular biology itself to suggest anything like robust generic properties of hierarchies above the genome, and we will need to make a place for these new insights to grow and bear fruit. The question here, as put by Max Perutz at the CIBA conference, is: "Will there be new laws of biology?"[7]

Finally, complexity studies go on, but not only at well-known and well-financed centers like the one at Santa Fe. For each of these, there are 10 startup attempts to bring complexity to the marketplace of ideas and to practical application in biotechnology. And there are many hundreds of individual researchers, in or out of universities—mostly physiologists practicing molecular biology without a license—who are trapped within the "romantic poverty and anonymity" of their holistic paradigm and struggling to find ways to go from the genome to complex function but who realize that you can't get there from genomic approaches alone. It's a catch twenty-two situation brought on by a triumphant molecularism that has been allowed to force aside perfectly sound alternative—holistic—scientific pursuits of complex organismic behavior. But as Streelman and Karl seem to agree, the pendulum is finally swinging back and we will have to wait and see what happens.

1. Bains, W. 1997. Should you hire an epistemologist? *Nature Biotechnology* **15**:396.
2. Strohman, R.C. 1997. *Nature Biotechnology* **15**:194–200.
3. Heisenberg, W. 1958. p. 104 in *Physics and Philosophy*, Harper and Brothers, New York.
4. Berry, W. 1983. pp. 25–63 in *Standing by Words*. North Point Press, San Francisco, CA. Wendell Berry has been called a prophet of the land informing us of the dire results to come from an agricultural use policy emphasizing an "internal accounting" (production) to the exclusion of understanding the effects of production on the land itself and on associated communities. It is only recently that scientists have begun the task of an "external accounting" where it becomes possible to attach a monetary value to the use and disuse of the world's ecological resources. See the article by Costanza et al. in *Nature* **387**:253–260 (1997).
5. Streelman, J.T. and Karl, S.A. 1997. *Nature Biotechnology* **15**:696–697.
6. Nurse, P. 1997. *Nature* **387**:657.
7. Williams, N. 1997. *Science* **277**:476–477.
8. Veech, R.L. and Fell, D.A. 1996. *Cell Biochem. Function* **14**:229–236.
9. Fell, D. 1997. *Understanding the control of metabolism*. Portland Press, London.
10. Webster, G. and Goodwin, B. 1996. *Form and Transformation: Generative and relational principles in biology.* Cambridge University Press, Cambridge, UK.