Sustainable Development Seminar Series:
History of Science and Sustainable Development

Molecular Biology: the Short Life of a New Field

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We are gathered to better understand the dynamics of the emergence of a new academic field, Sustainable Development. I am no expert on the sociology of academic subject demarcations but I have been around as a scientist for a long time. Perhaps the experience I have to share with you will shed some light on what we are facing, and will face, as we go forward.

I studied physics and math as an undergraduate here. My reasons were neither deeply intellectual nor career-oriented. My parents were poor, and Columbia's tuition of $400/semester loomed over them and me as a possible barrier to my attending. When the Soviet Union launched Sputnik, the New York state response included a doubling of the Regents' scholarship for winners who would promise to major in the hard sciences or engineering.

I set aside my dream of writing, and majored in physics. So did about a third of the entering class of 1961, but most of the rest of my classmates figured out in short order that no one was tracking them, so we graduated in 1961 with the usual hundreds of pre-meds and pre-laws, and only nine - as I recall – physics majors, myself in the middle of that small pack.

I knew no post-high-school biology beyond what I learned from my pre-med friends. They were learning their biology in the Zoology and Botany departments. Those two departments were the ancestors of the Botanical Garden and Zoological societies of New York; they were merged into the current department of Biological Sciences well after I graduated.

Much of what passed for "zoology" then was still descriptive; it was what my physics friends and I called "stamp-collecting." The same was not true of the chemistry pre-meds needed to know – organic in particular – nor of the physics they also needed. Both were of more general significance, and because of that both were quite divorced from their biology courses in content, and in scope.

I understood too that there was a big deal that had happened some five or ten years earlier, the discovery by Watson and Crick in 1953 that a chemical called DNA had interesting properties which made it a candidate to be the vehicle of genetic inheritance. That was what led me to apply to Brandeis University's new graduate program in biophysics, biochemistry and biology.

That program promised to uncover by experimental design the promise of DNA; that is, that biological characteristics could be traced to physical and chemical causes, and that disprovable testable models could encompass the seemingly impossible complexity of the living world. That promise, and another - an NIH training grant that allowed them to offer me a stipend as well as tuition remission – brought me to Brandeis.

The key insight of that new PhD program was not technical, but aesthetic: the insistence that a genetics question could best be answered only if one took the very simplest of systems to study it. This minimalist approach had emerged from the work of a small group of émigré physicists and chemists who had come to this country as fascism and Nazism overran their countries in the middle third of the last century. Two - Salvador Luria and Max Delbruck - pretty much established the field of molecular genetics all by themselves. Their application of the aesthetic was to study the patterns of inheritance of viruses that grew in bacteria. These viruses were genetically and chemically orders of magnitude simpler than their host bacteria, which were of course millions of times smaller than a single cell of any plant or animal big enough to see.

They studied the emergence and growth of a bacterium with resistance to a virus or a drug. They quickly showed that such genetically stable resistance was not induced by a drug's or a virus's presence, but rather was the result of a constant accumulation of genetic variation in a cloned population of bacteria, with the subsequent selection for the variant as the only subpopulation capable of survival under the new circumstance of a drug or virus.

This discovery brought the work of Darwin into sharp molecular focus at the smallest scales of life. Taken together, Luria-Delbruck and Darwin meant that the simplest explanation for any genetic difference appearing in any population over time, would be the emergence of a random genetic variant – a new DNA sequence arising by error of replication - followed by the overgrowth of it when the new sequence provided a greater chance at survival under the specific conditions in which it found itself.

My career as a molecular biologist began with the demonstration in 1967 that proper construction of selective conditions could permit the isolation in cell culture of genetically reverted normal tissue cells from a clone of lethally malignant cells. The revertants were not induced by any agent, but arose by the same sort of error-driven genetic variation. In this case the variant re-expressed normal growth control, and that spared it from a drug that killed all its malignant relatives. The next step then was obvious: isolate revertants and compare the DNA of them with their malignant relatives, and thereby find "genes for reversion." Understand how such genes worked, and you would perhaps be able to domesticate a tumor rather than killing it.

But at that time, in the late 1960s and early 1970s, there were no tools for isolating and quickly sequencing stretches of DNA from cells, as there are now. So, as a practical matter, I was reduced to explicating my initial insight in a string of papers to confirm and extend my work, and to keep my lab going, first at Cold Spring Harbor, then Stony Brook, then – in 1978 – back here at Columbia. As the new technologies of recombinant DNA and DNA sequencing emerged, I found myself running a lab that was keeping up, but still not able to follow through on the promise of our earlier work.

That all ground to a halt in terms of my running a lab in the early 1990s when, after a seven-year stint as the Dean of Columbia College, I decided to follow up my old interest in writing, to address a set of issues which involved subjective emotional states as well as facts of nature.

But I have never ceased to be a biologist, and am happy to say that today many labs and also many companies are searching the genomes of normal malignant and revertant

cells for the DNA sequence differences encoding small RNAs and other regulatory molecules that may be responsible for maintaining the revertant state.

In thinking about the future of Sustainable Development the point to remember is this: regardless of its funding source, most of the work that began as molecular biology is now connected with what is called translational research. In other words, it is being carried out in the hopes of selling a patent once preliminary results make a sequence particularly interesting. In that sense, it is no longer molecular biology at all, as its founders understood the notion.

That field's first golden stake went in in the 1960s, marked by the merger of zoology and botany into biology, of biology and chemistry into biochemistry, and the merger of them all into molecular biology. Then the second stake that bookended the field went in in the 1990s with the emergence of translational research.

Another way to approach the emergence and passing of molecular biology as a field is to look at the history of the publication of its founding textbook, "The Molecular Biology of the Gene." The first edition, by James Watson himself, came out in 1967, and it codified what departments of Chemistry, Zoology, Botany, Biology and Biochemistry already knew, that is, that DNA and its properties had changed the intersect of their fields forever. That edition went through many printings until the second edition came out in 1970; the rate of change in the field pushed Watson to a third edition in half the time, in 1976. By then though molecular biology itself was already beginning to speciate.

We can see this by the fact that it took a decade before the third edition emerged and when it did, it had fissioned into two volumes. The first volume was another update of the original by Watson; the second was a sort of commentary and compendium of wholly new technologies by him along with four of his acolytes from MIT and the Ivies. Nancy Hopkins, one of the four, had been a postdoc in my lab; you will perhaps know of her as the MIT professor who got her President to pay the same salaries to women as to men faculty.

The fifth edition in 2003 was also in two volumes, but the second one was now far more replete with new applications than with new ideas. The sixth and last edition to date came out in 2007 and there is no sign of any more to come. This book, in its many iterations by Watson himself at first and even when elaborated with the contributions of many others, defined the field of molecular biology for that period. So we can say the textbook spikes of this era of molecular biology per se went in at 1967 and 2007, a longer period of forty years, but no more.

The book had brought together the physics of energy conservation and information quantification, the chemistry of the exchange of kinetic for potential energy of covalent bonds, and the biochemistry of enzymatic construction of molecules, with the classic genetics of Mendel, the phage genetics of Delbruck, and the crystallography of double-helical DNA and of hugely complex proteins and small RNAs.

Then, in the latter half of those forty years, Recombinant-DNA technologies, informatics, cheap DNA sequencing technologies, powerful parallel processors of digital information, and pattern recognition algorithms had all departed from molecular biology to make wholly disparate and incommensurate uses of the technologies that had emerged

from the initial work in that field. These technologies then reconverged for a time in a new understanding wholly different from anything in the first edition of Watson's text, closing of an informational feedback loop by the synthesis and testing of new, unnatural sequences for characteristics of novel genetic activity.

These descendent technologies have themselves in turn speciated in the past twenty years into bioinformatics, drug development, forensic science, gene-mapping, and a re-emergence of embryonic development as the stage for understanding the construction and genetic complexity of the earliest stages in our formation. These, once again, have recently speciated, this time into stem-cell research, assisted reproductive technology, and the construction of trans-genic species hybrids.

The ancestral species of science encoded in Molecular Biology of the Gene is now a fossil, of interest to historians and scientists of a certain age, but no longer the subject of many grants or companies, nor of even one freestanding course.

A few implications.

First,

ideas matter, and they matter quickly. You will appreciate that the notion of speciation of a field in a decade, with a species lifetime for that field then measured also in decades, is a play on Darwinian DNA-based natural selection. It speeds the process by about 10^5-fold.

That is no coincidence. As the one thinking, self-aware, social species capable of abstract symbolic thought we are increasing in numbers at a rate many-fold faster than other species our size; we are using up in less than 10^3 years, carbon sources that took 10^9 years to lay down, an even greater relative velocity of mental over physical processes.

Not even a decade has passed since the Faculty of the Earth Institute began to consider itself enough of a faculty in the classic sense to create its own curriculum for undergraduates and graduate students. Making ideas that matter stay for longer than a few decades, is the challenge we face in dealing with the idea of sustainable development.

Second,

We can predict from this experience that as the field of Sustainable Development emerges, its success will raise the likelihood of its being subsumed and overcome by new fields based on its insights but no longer committed to its agenda. To my eye, we are not yet there, but the speciating horizon can be seen.

Third,

We still lack a single textbook for the field, and more importantly we also lack a single informing insight into nature or society that has withstood testing well enough to justify our confidence that we are on the right track in our own expectations. What have we got to tell our students and each other, let alone our more distant colleagues in Chemistry, Engineering, Physics, Philosophy, Computer science, Economics, History, Political science, Earth science, Biology, Psychology and Anthropology, that has the scope and depth of Watson's mechanism linked to Mendel's data?

Fourth, and finally,

We should ask ourselves whether, like the zoologist and botanists of the 1950s who ignored Watson's discovery, we might be ignoring a model, an insight, an idea that would in fact bring us together in a new field. The current science that has emerged from what began fifty years ago as the new field of Molecular Biology has something to contribute to our discussion of this question.

We have learned a great deal in the past decade about what each of us is capable of as a thinking individual. We have assembled a rich database of human DNA variation. We are beginning to understand how those capabilities are expressed in molecular terms, through the interaction of encoded and inherited genetic information, with experience-driven modulation of that information in our bodies and brains.

Though the neurobiology of consciousness is in its earliest stages, we can conclude that the social barriers of language and economic development – what Professor Jim Cone has called the maldistribution of suffering – are not "in our genes." Rather, they occur within a species population of seven billion all of whom share the same capacity for thought, for feelings, and for making choices based on ideas and feelings as well as instincts.

Put another way, we are beginning to understand the genetic differences between us and all other species, and we are finding that our ancient notions of free will are surviving molecular mechanistic analysis.

Molecular Biology in its short life has thereby given us the green light to pursue an agenda for the new field of Sustainable Development, which would be to model the diminishment of the maldistribution of suffering in a new language of ideas that can and will be shared with and understood by not only ourselves and our students, but also by all seven billion other beings with whom we share a human genome.

As co-Director of the Center for the Study of Science and Religion – the CSSR – I'll close with this idea as articulated in 1978 by Vaclav Havel, who stood up to the Soviet controllers of his country when it was the Czech Soviet Socialist Republic, that is, the first CSSR. In his essay "The Power of the Powerless," he wrote:

> "If a better economic and political model is to be created, then perhaps more than ever before it must derive from profound existential and moral changes in society. This is not something that can be designed and introduced like a new car. If it is to be more than just a new variation of the old degeneration, it must above all be an expression of life in the process of transforming itself. A better system will not automatically assure a better life. In fact, the opposite is true: only by creating a better life can a better system be developed."

If that were our guiding idea I suspect we would be seeing a new field, uniquely defined as one that learns not only from its practitioners but also from its subjects, which I would call the field of Just and Sustainable Development.