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VIEWPOINT

If Genes Just Make Proteins and Our Proteins Are the Same, Then Why Are We So Different?

" 'There's no use trying,' [Alice] *said: 'One* can't *believe impossible things.' 'I daresay you haven't had much practice,' said the Queen. 'When I was your age I always did it for half-an-hour a day. Why, sometimes I believed as many as six impossible things before breakfast.' " Lewis Carroll,* Through the Looking Glass.

Discussions of current biology often contain what is almost a mantra: "We are determined by genes and genes make proteins." There is an implied subtext that, like *truth is beauty,* ". . . this is all ye know on earth and all ye need to know." Inordinately simplistic and, at the core, indefensible, this proposal, nevertheless, has shown astonishing power.

The notion that genetics is little more than the inheritance of protein coding has a grip on the scientist's imagination, as witness the mega-Genome projects. These not only promise answers to the most profound biological questions, but (and here the mind boggles) will even explain the genetic basis of social ills. The idea that genes are simply codes for proteins dominates the presentation of biology in the media, in current textbooks, and in agencies that, by allocating funds, determine scientific direction. Yet, without the White Queen's ability, we know from everyday experience that biology must be much more than merely protein coding.

A simple example: Each person differs markedly from another, yet our proteins, except for the histocompatibility antigens, are essentially identical. For that matter, human proteins differ infinitesimally from those of apes, but the great dissimilarity in the organisms hardly needs noting. Also, the protein coding genes make up an embarrassingly small portion of the genome. Even genome project enthusiasts estimate them to amount to, at most, a few percent of the total. The project champions suggest the remainder of the genome to be some kind of "junk," an accident that metazoans have been carrying around for perhaps one-half billion years. Looking for the specification of animal and plant architecture in the protein coding genes is like looking in a brickyard for the design of a building. Brickyards make bricks, the architect's blueprints are elsewhere.

That forms are contained in the constituent materials, such as proteins, and need only be liberated is curiously redolent of medieval scholasticism. However, proteins, for all their profound importance to the biochemistry and structure of the organisms, cannot, of themselves, specify design and pattern. Mammals have taken on staggering variety of forms, while the family of anurans or frogs all resemble each other approximately. We might expect the proteins of mammals to differ markedly and those of frogs to be closely similar. Exactly the opposite is true. This apparently reflects the fact that mammals are relatively recent arrivals, while amphibians belong to a truly ancient order and the proteins indicate evolutionary age, not form.

Since biochemistry is, largely, unchanging, what then has changed during evolution? Evolution is in essence the study of the change of organismic form through time. Of course, form is all that can be deduced from fossils. However, there is little reason to think that biochemistry has changed much, at least since the Cambrian boundary. The biochemical pathways are almost universal. The changes in amino acids in proteins can serve as clocks; ticking, it seems, at a slow but surprisingly constant rate. They can position the organisms in evolutionary time: that they can so serve certainly precludes their also determining plant and animal form.

Ironically, we are much more sophisticated in considering simple, manmade systems. No one would suggest that structures, such as bridges, be fashioned merely by prescribing constituent parts. Such, if they stood up at all, would best be avoided. Digital computers and telephone exchanges are examples of dynamic systems composed of active elements, such as transistors. Specifying the transistors and their physics does not inform us at all of the deep, arcane mysteries of multilayered operating systems and appli-

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cations software. Operating systems care not one whit whether or not the computer is executed in silicon chips, germanium, gallium arsenide, vacuum tubes, or even, as Babbage proposed long ago, steam driven machinery.

Apart from a few notable exceptions, biologists think little about the nature and importance of organismic design. True, there was D'Arcy Thompson, but he, while admired from a distance, is little read and even less understood. As a result, we have the bizarre proposal dominating biology that the incredibly complex living systems are described entirely by component proteins and their coding sequences. Where is the genetic information that executes the design of an organism? We do not have to look far for a candidate. There is plenty of information in the more than 95% of the genome that is devoid of open reading frames. These sequences, heavily transcribed in all cells, appear to have little, if anything, to do with making proteins.

We might well ask: How did such a truncated view of genetic instructions come to prevail? Perhaps the answer would enable us to envision a biology that includes a rigorous study of the genetic specifications of form.

The notion that genes are simply proteins stems from Beadle and Tatum's proposal in the 1930s that "one gene = one enzyme." The current statement is "one gene = one protein." This is a seductive statement indeed, promising to cut through much complexity and myriad irrelevancies to a simple core of gene function. However, the actual experiments simply did not support this global deduction. Rather, they showed only that in a lowly eukaryote, one with little higher order structure, heritable altered enzymes did have a corresponding Mendelian gene. That every protein is encoded by a genetically identifiable sequence is the accurate statement of the Beadle and Tatum findings, one that is much narrower and less exciting. Most important, it does not tell us about the non-protein coding genomic information. There has been little effort to test the "one gene = one protein" proposal and the question of what else is encoded by the genome has been left unconsidered.

Why was the backwards statement of Beadle and Tatum so widely and unquestioningly accepted? Possibly because, at the time, biochemistry was becoming a dominant influence in biology. Naively interpreted, biochemistry seemed to say that knowledge of chemical reactions was all that was important in the organism. Unfortunately, this misapplication of biochemistry was reinforced by the seemingly amorphous cell interior seen by conventional electron microscopy. In such an unstructured milieu, little besides soluble chemicals could be important. This picture we now know to be dreadfully misleading and the cell interior is full of complex scaffolds and machinery.

Every science has an implicit agreement as to what constitutes knowing. All share the criteria of Francis Bacon, who set the ground rules for empirical natural philosophy. However, what different disciplines consider to be significant can be very dissimilar. Much of biological research practiced today is grounded in the chemistry that occurs in solution; little else is considered of equivalent significance. Until now, the approach has served biology and medicine well. Not surprising then that biologists tend to look for causation in materials such as soluble factors, nutrients, and the like, and not in physical organization. Cancer may well prove to be fundamentally a disease of structural disorganization of the cell, but the hunt continues for altered proteins from mutant genes and inappropriate regulatory factors.

Why consider methods of inquiry? If molecular sequencing will not, of itself, answer the mysteries of life, why not just get on with what will? Alas, there is a normal human propensity, not unknown amongst biologists, to find comfort in knowing the single, sure road to truth. Once seemingly found, the road is staunchly defended, as attested to by the ferocity of religious and ideological wars. Biology, more than any other experimental sciences, wrestles with epistemology angst. Physicists and chemists are phlegmatic, by comparison, about methodology, differing only occasionally over philosophy and scientific method. Biologists have been at it, hammer and tongs, over what is correct science harking back to Aristotle.

Today, self styled "reductionists" hold the high ground in biological arguments. They posit that rigorous science is only that which yields a protein sequence or, at the very least, bands on a gel electropherogram. All other experimental studies, even if possessed of ingenuity and subtlety, risk being contemptuously labeled "descriptive."

There's nothing new here; Darwin had to endure similar carping at the "descriptive" nature of the theory of evolution. The "Origin" failed to follow the prescription for inductive

science set forth by Bacon and exemplified by Newton. Bacon was actually arguing with the scholastics and not writing laboratory manuals and Newton no more followed Bacon's dictates than does any contemporary scientist. Darwin remains difficult to fit to any methodological category. This should warn us of the dangers of trying to dictate methods.

The purview of biology is living things and no single approach can possibly explain such complex systems. Understanding the daunting intricacy of a living entity requires marshalling every discipline at our command, including some, such as fractal geometries and chaotic systems, that are just being born. As now conceived, molecular genetics, for all of its unquestioned power, can never penetrate the deepest questions of form and its function locked in DNA currently referred to as "junk."

Can we envision a study of biological architecture firmly based on our molecular and genetic knowledge? Is there a need for a biological version of the "Novum Organum." Probably not, since there are many laboratories that have gone beyond the narrow molecular biology paradigm. No single rubric identifies their labors (Molecular patterning? Genetics of form?). Such studies are not yet considered fashionable science: They are not reported in the popular press or on public television and they often suffer from a lack of support. Yet, these laboratories are developing the future of biological science that we will turn to when deep problems prove intractable to the sequencing approach. They share a common interest in how biological things are arranged in space and why.

The "new" biology might be subdivided into learning the terrain (i.e., how cells are really constructed) and exploring the functions of architecture. The former has been given impetus by new techniques of electron microscopy. I remember being long baffled by conventional electron micrographs of cells that raised myriad disturbing questions. How did membranes curl into cisternae with no visible guides? How did polyribosomes cluster in Nissl substance with no visible supports? What guides spindle microtubules from pole to kinetochore? Where was the contractile apparatus in smooth muscle cells and why couldn't one see it? There were endless suggestions of things that must be present but which were invisible.

The cell as a bag of jelly suited the biochemical emphasis of research, but it is a false image, arising from the practice of embedding samples in dense, obscuring plastic. Keith Porter reintroduced a technique from the earliest days of electron microscopy, the embedment-free whole mount. His pictures were deeply revealing, but confusing for many. For the first time the soluble proteins, previously hidden by embedding plastic, were visible. These aggregated into dense, bewildering networks and it was difficult to discern the true skeletal structures of the cell. For once, Nature was kind and it proved easy to release soluble proteins, leaving an intact cytoskeleton in place.

Embedment-free micrographs of extracted cell structures are vastly more revealing than those of embedded sections. They show the cell interior to be filled with a veritable Eiffel Tower of complex scaffolding. These struts and braces of the cytoskeleton give shape to the cell and, connecting across cell boundaries, assemble tissue architecture. More techniques of cell dissection have followed, providing both microscopy and biochemical analysis of the nuclear matrix and its substructure of core filaments.

It is increasingly apparent that the scaffolding of the cell also serves to signal the cell nucleus regarding the cell environment. This brings us to the other category of investigation: the functions of cell structures. In a truly seminal report, Folkman and coworkers showed that cell shape regulates cell growth. There was an initial shock at learning that a basic cellular process was regulated by the physical rather than chemical state of the cell. Upon reflection the finding made good engineering sense. An architect cannot simply give instructions and then leave. Building anything requires constant examination of just what has been made and correcting the compounding inaccuracies of parts and assembly. This feedback process is universal and it seems likely that the cell shape response is the in vitro manifestation of a cell's function as a building block. Subsequent work has shown that not only growth, but also many differentiated functions depend on cell shape and external environment. This is a bustling area of research that promises deeper insights into developmental biology and, very possibly, neoplasia.

The "Prospect" articles in this compendium deal with the nucleus in new, non-canonical ways. For much too long the nucleus was thought to have an essentially formless interior. Managing the chromatin of a mammal is akin to stuffing 60 miles of wire into a basketball. The chroma-

tin must be separated into euchromatin and heterochromatin, replicated, and folded into neat packages at mitosis. All this seems implausible without a guiding scaffold. Nevertheless, the report of Berezney and Coffey (1974) of just such a scaffold met with long-standing, obdurate objections. Perhaps this was because the conventional electron micrographs, which there was no reason to doubt, showed no non-chromatin nuclear structure. It is also possible that many *did not* like the implications of such a structure. Its existence promised to complicate the existing models in which soluble factors regulate DNA in the manner of bacteria.

In the manner of true science, the study of the nuclear matrix has worn down or outlived its objectors. It has become, if not yet completely accepted, at least quite respectable. The articles presented here, dealing with the form and functions of nuclear architecture, offer new avenues to the understanding of cells and suggest the intellectual riches reached beyond conventional wisdom and attitudes.

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