EPIGENESIS AND COMPLEXITY

Should you hire an epistemologist?

William Bains

Richard Strohman's impassioned appeal[1] to look again at genetic determinism and the cult of the gene must have worried investors and scientific directors across our eclectic industry. It may even have concerned a cloner or two. The majority of effort in academic research and biotechnology industrial development is based around the idea that genes underlie life, that the double helix is the icon of knowledge and profit for our age. Beadle and Tatum's "One gene—one enzyme" has become the industry's "One gene—one drug target" with unprecedented unanimity. Can we have got it so wrong? I am sure we have, and am equally sure it does not matter.

Strohman's thesis is that the paradigm of genetic determinism—that differences in the genes are the main causes of differences between sick and well people, between humans and hamsters—is ready to fall apart, after dominating biology for 50 years. He forgets the wholesale abandonment of academic biology to environmental determinism in the 1960s, when any mention of genes and disease in the same sentence was decried as 'eugenics', and even the reality of organic disease was questioned in favor of talking about mismatches between infinitely flexible people and unforgiving environments[2]. But today it would be a brave biologist who applied for a grant that denied the centrality of genes, and biotechnology companies have mirrored the trend, as the values of genome companies stocks testify.

It is equally clear that genes do not determine everything. Many experiments—from the failure to map 'genes for' affective disorder to the apparent health of tumor suppressor gene knockout mice—confirm this. The fallacy of hunting down genes 'for' common diseases is now evident. People are systems whose levels of causality are complex and intermingled. Diseases, indeed different types of wellness such as intelligence or homosexuality, are features of those systems, not of one component of them. Saying that a gene 'causes' hypertension or depression is similar to saying that a flat tire 'causes' a car to slow down. In a few pathological situations the two are causally linked, but most cars traveling slowly do not have flat tires. A 'tire knockout car' would tell us little about traffic lights or driving skills or speed cameras. On this reading, the genome program at any philosophical level is a doomed exercise.

But should we care? Of course we should, but not to the extent that we give ourselves ulcers or sell all our share in genome company stocks. This is not "*Nature Philosophy*": All definitions of "biotechnology" share a pragmatism that comes from having to make things. We are concerned with results. For the reductionist Martian studying cars, the discovery of the wheel is a genuine breakthrough, allowing cars to be distinguished from telephone boxes for the first time. And although it is true that flat tires do not cause careful driving, it is indubitably the case that shooting out a car's tires will correct the 'disease' of speeding (albeit with a high rate of adverse reactions). If we are after practical results rather than philosophical absolutes, then we can use the genetic paradigm as a lever to open up the black box labeled 'life', allow us to glimpse some lever to pull, and hand us the tools to pull it. We may have a completely wrong idea about their function or their importance. Sometimes the lever will do nothing, as ciliary neurotrophic factor seemed to do nothing for ALS patients[3]. Sometimes it will work but for the wrong reasons, like most early antisense agents. Sometimes it will do more harm than good, like the antisepsis antibody, Centoxin, or whole virus RSV vaccines. But their observable effect is beyond dispute, and we can select those with effects we want. Our gamble, and it has paid off so far, is that the successes will more than pay for the failures.

Surely such pragmatism, based on the philosophical quicksand of a dying paradigm, can only lead to clinical trials failure, stock price collapse, and lawsuits all round?[4] History teaches us otherwise. No-one had the least idea how penicillin, aspirin, the sulfonamides, or the steroid antiinflammatory agents worked when they started to be used. The paradigms of the day threw them up, and the pragmatic world used them as it would. Does it matter that cortisol was originally synthesized because it was thought to protect fighter pilots from the effects of oxygen deprivation at high altitude? Does it matter whether steroid antiinflammatory agents work by replacing failing hormones (the 'monkey glands hypothesis' as we would now sneeringly call it) as they were thought to do in the 1950s, by stabilizing lysosomal membranes as the hypotheses of the 1970s suggested, or by altering steroid-responsive promoter function as they apparently do today? It does not. The lever has been pulled, the box opened, and new wonders unveiled. Genes and their deterministic products are tools, discovered by one of the most powerful tool-creating technologies biology has ever seen, and we gladly use them as such.

For philosophers, it is deeply worrying that such practical results can come from gross error, but technology is about function. For an engineer, the most beautiful car engine is not the one that is simplest, nor that with the most sophisticated theoretical underpinning, nor yet that which accurately models the working of muscle or bone. It is the one that purrs smoothly to 8000 rpm and hurls you down the freeway, whether your tires are shot or not.

Strohman's comments are completely valid. They are important to those who seek to understand what we are and how we came to be that way, which is itself one of the grandest and most exciting goals of the past three centuries of science. Strohman points the way to the future, and he is the first to comment that he is not a lone voice in calling for a version of biology that deals with systems rather than only with their isolated components: Commentators as diverse as an earlier editor of *Nature*[5] and the European Patent Office[6] agree that life is not genes. The new system biology will generate its own tools and, if it has the potential to displace the genetic paradigm, its tools will put to shame the rudimentary gene tinkering of the late 20th century. But we do not need to understand the nature of knowledge to recognize tools when (and if) they are created as the new paradigm starts to crystallize from the melting slush of the old. And in the meanwhile, the genome databases, cloned proteins and other paraphernalia of functional genetics will generate tools, products, insights, careers and stock options for us all.

William Bains assesses investment proposals for Merlin Ventures in London. He has held several posts as a consultant to biotechnology companies.

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