INSTITUTE FOR ENERGY AND ENVIRONMENTAL RESEARCH

6935 Laurel Avenue, Suite 201
Takoma Park, MD 20912

Phone: (301) 270-5500
FAX: (301) 270-3029
e-mail: ieer@ieer.org
http://www.ieer.org

Comments by Richard Strohman on the monograph entitled *Ecology and Genetics: An Essay on the Nature of Life and the Problem of Genetic Engineering* by Arjun Makhijani

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In the May 17, 2001 issue of Nature the editors issued a "Call To Arms" to scientists to involve themselves in the debate over biological weapons and made clear that, our topic today -- the engineering of agricultural plants -- bears a clear and close relationship to the problem of bioweapons, a point discussed by Arjun Makhijani in his report. In any case, I am glad to be involved in a debate on these matters and I see the event today, and Arjun's report, as part of an extended the call to arms urged by Nature editors.

I want to address briefly some fundamentals of cell/molecular and evolutionary biology that may be useful background for framing Arjun's important and urgent arguments concerning the possible threats inherent in the present rush to move into full scale industrial production and dissemination of GEOs. [Note: I prefer the identification GEO (genetically engineered organism) to GMO (genetically modified organism) to make clear that we are talking about an engineering project and not some modification that is substantially equivalent to what happens in nature.]

Evolution of phenotypes

Internalization

Arjun states that organisms recreate internal representations of their environment as "genetic structures". This is a more imaginative and heuristically useful way of saying what population geneticists say: "that evolution of populations proceeds via a process whereby certain favorable gene combinations/recombinations are selected over many generations. What is actually selected, of course, is the phenotype of the organism itself ... its behavior in nature. And phenotypic change is generated not by the genome alone but by self organizing, regulative developmental processes that are able to take identical genomes and, in a context-dependent manner, produce individuals of widely different appearances and behavior. Thus, phenotype at all levels is the product of interaction between genome and environment and new phenotypes are the proximal materials with which natural selection has to work. The great unanswered question in evolution is "how do organisms internalize their environment in the form of genetic representations?" Most biologists continue to ignore this question assuming that random genetic change (mutation) is the only avenue to novelty.

Actually, over the past ten or more years biologists with a more dynamic view of life and of evolution: one that goes beyond random gene mutation and genetic determinism, have realized a new model and have completed the first stages of its development. This model is represented in Figure II and is compared with the model of a linear genetic determinism in Figure I. The differences between the two are major and may be summarized by the statement: Rather than simple linear and closed causal relationship between genotype and phenotype, we now see evidence that nature, so to speak, has placed between the genome and the phenome a complex non-linear (open) regulatory apparatus that connects the genome to the outside world and thus provides a working mechanism for what Arjun, and others before him, have called "internalization" of the ecosystem into genetic structures. This concept has for many years now been suppressed by the major paradigm, not only of molecular biology, but of biology as a whole: genetic determinism.

The conclusion drawn by many thoughtful biologists is that genetics alone and evolutionary theory alone, as powerful and as useful as they have been, cannot yet explain how organisms develop in a species specific manner or how one species gives rise to another. In spite of this, modern molecular biology, and especially biotechnology, is pushing ahead with programs to genetically engineer organisms and create new forms of organisms in a single generation. The role of development in biology continues to be ignored and instead there is clearly asserted the hegemony of genetic determinism: phenotype flows directly (somehow) from genotype (Fig I). I think it fair to say that my colleagues in molecular biology know all about the genes that are important, critical, aspects of development (homeotic genes), but are just scratching the surface of the processes that serve to integrate these genes in development itself.

Arjun's point throughout his essay focuses, not on single genes, but on a broader aspect of the classical view of population genetics. In the classical picture of the genetic basis of evolution, shaped largely by the American physiological geneticist (and population biologist) Sewall Wright, it is not selection of single gene mutations that is the prime operator, but the selection for entire genomes in which there is gene-gene interaction at a high level and where rare favorable mutations, when they do occur, become integrated with the ongoing developmental dynamics of organisms already engaged in interactive process with their local environments.

As Jay Forrester, the urban engineer at MIT, has said of attempts to engineer complex urban systems: "Compensating counteractions can be disastrous if the applied programs are expensive. The external financing may be impossible to sustain. ... Probably no active, externally imposed program is superior to a system of modification that changes internal incentives and leaves the burden of system improvement to internal processes. This point Arjun has made in giving examples of cases where genetic modification of plants takes control away from the system's own internal processes. The results are disastrous counteractions in the plant and in the ecology. And there are other such examples now showing up in the literature in the form of research reports from scientists critical of the GEO approach, at least in the form that has now become operational.

Think of compensating counteractions in a complex ecological system in the widest context and you can see what Forrester means when, for example, you genetically engineer corn (Starlink) to do one thing but it also unpredictably produces a product that may be allergic in humans and has

to be recalled at great cost, not to the producer of the product but to the taxpayer. This 'unfortunate' event was permitted because the US government, the FDA and the EPA have said that GEOs are substantially equivalent to wild type organisms.

Cell and molecular aspects of internalization-externalization

A second point emphasized in the monograph, not sufficiently acknowledged by most biologists, is the one of externalization: that organisms recreate their environments through these inherited genetic structures that include, in addition to DNA structures that are certainly critical, self organizing structures of regulatory networks of proteins. These proteins are, of course, specified by DNA sequences but the laws that regulate and constrain protein networks are not reducible to the laws of genetics. The science of genetic symbols (DNA sequences) and the science of the dynamics of these controlling networks are irreducibly complementary. Both are needed but to date most of the research in the molecular biology of GEOs has emphasized genetics to the near exclusion of dynamics.

Thus, the internal representation of the outer world is constantly being fine tuned through the internalization process. Most mutations in this view are seen as harmful or neutral to the organism and are selected against. We now know the mechanisms behind some of this neutrality. They include redundancy where more than one gene may carry out the same function, and gene silencing where complex signaling pathways repress mutant genes and where they serve to "mark" both DNA (by methylation) and chromosomal proteins (by acetylation) so that patterns of gene expression are altered in a context dependent manner. The genome is thus an open and dynamic (fluid) structure composed of interactive units connecting the organism to the outside world. (see Figure II).

SHOW OVERHEAD OF FIGURE II

It is the feedback loop from Function to Environment (in Figure II) that represents the process of externalization. As Arjun argues from his theoretical background and his experience as an ecological engineer, this feedback loop is critical.

However, until recently, this has not beenthe view of most molecular biologists, nor is it the view of most medical and behavioral geneticists who emphasize the importance of single gene causality whether it be for pesticide resistance in plants, or for cancer (oncogenes) or for manic depression (bi-polar disease for which no real candidate gene has yet stood up to scientific scrutiny) in humans. And it is decidedly not the view of Human Genome Project leadership one of whom, Craig Venter the President of Celera, has admitted: "We don't know anything about biology." This remark came after enough of the human DNA data were known so that he realized they could not contain what many of the other leaders had been wrongly telling him and us for years. We all remember statements to the effect that in these sequences we would find the Holy Grail, The Book of Life, the program for development, and so on, of human existence. In February of this year, following the publication of the human genome sequences in Nature and Science, to his credit, Venter said, "This tells me genes can't possibly explain all of what makes us what we are." And the distinguished Harvard biologist, Stephen Jay Gould, who does know more than most of us about biology, wrote in the *New York Times*:, "The collapse of the one gene

for one protein, and one direction for causal flow from basic codes to elaborate totality, marks the failure of [genetic] reductionism for the complex system we call cell biology."

For the HGP scientists there was profound shock at what had not been disclosed by their sequences. Why? Because their basic assumption was that gene-gene and gene-environment interaction is unimportant or minimal. And once this interaction is ignored then, in theory, the search for specific genes that have a one to one relationship to a phenotype (pesticide resistance, cancer, bipolar disease, etc.) becomes rationalized.

SHOW OVERHEAD OF FIGURE I

But, as the scientists who had been developing the model in Figure II realized, and as Professor Gould has suggested, the [single gene-->single phenotype] thesis has not paid off in either medical or behavioral genetics in spite of over 50 years of the persistent faith and billions of dollars of research devoted to it.

So what has all this to do with GMOs with the report issued by the Institute for Energy and Environment Research?

The promise in agricultural genetics is based on the Figure I model that we now know to be inadequate. How could we have come this far with such an inadequate model? First, because medical geneticists had discovered very early on that a [one gene--->> one disease] model did work for specific diseases. Cystic fibrosis, Duchenne muscular dystrophy (which I had worked on for over 20 years in addition to my work on the molecular and cell biology of development) are examples of single cell diseases of which there are over 1000. But such diseases are rare ... as one might expect. Why, after all, would nature devise a system as complex as a living thing in which so much would depend on a single gene unbuffered by protective alternatives when that gene went down: that is became mutant or deleted? The answer is that even Nature makes a mistake but rarely. In total these monogenic diseases constitute less than 2% of our disease load.

For our complex or sporadic diseases like common cancer and most coronary artery disease, hypertension, and behavioral diseases like manic depression accounting for well over 75% of premature morbidity and mortality, many genes and many alternative alleles of the same gene that interact with one another and with the environment to shape the disease are involved. For example, for heart disease and the common cancers there are hundreds of candidate genes already identified. Now the HGP scientists (fig. I) and the complexity scientists (Fig. II) take two different views of these facts. The Fig.I people look at hundreds of genes and see an opportunity for magic bullet discovery. After all 200 genes is much less than 30,000 and the odds for success are thus increased by focusing on these candidates. The Figure II scientists look at the same numbers but do the computations of hundreds of genes interacting with one another, with a host of environmental factors, with the unknown background factors of individual development and individual natural history, and conclude that genetic data alone will not provide the answers. We will also need to understand the regulatory pathways shown in bare outline in Figure II that stand between the genome and the phenotype of individual organisms.

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The second reason we say the science behind the model in Fig. I is incomplete even though the technology is suburb, is because the technology for moving genes from one organism to another and from one species to another is encouraging only when focus is on the *technological process* and not on the *product* which is the transposed gene in the plant, in the ground, under natural conditions that are impossible to replicate in the laboratory. And we now know, because of the work that has gone on under the Figure II model, that perhaps all transgenic products ... the actual genetically engineered organism (GEO) in the ground may be unstable in the long run.

The new model provides measurement capability and calls for new technology that can address directly the questions of substantial equivalence and potential genetic instability in GEOs. Transgenes in host cells may draw powerful compensating counteractions from the plants regulatory networks. These may include gene silencing through methylation of DNA and acetylation of DNA binding proteins, and many other changes in gene sequences in an around the transgene all of which point to a genetic instability.

So far the GEO industry has not taken advantage of these measurements and are not required to do so by our regulatory agencies even though they provide for the GEO industry the kinds of controls that Dr. Martha Herbert has called for, the equivalent of which are standard in the pharmaceutical industry and in clinical trials.

Finally, I conclude that the model in Fig. II represents a fundamental and even revolutionary shift in world view in biology. The shift away from a simple genetic determinism is becoming generally accepted by a majority of biologists but there is a clear hesitation over what will replace it. The concept of an irreducible complementarity of genetics with dynamics is not accepted generally and there is much work ahead before the new biology works its way to some new consensus concerning the the meaning of dynamics. In Fig II, the reference is to regulatory pathways connecting the environment to the genetic structure of DNA but there is much more involved about which we remain ignorant. In the presence of a theory of life dominated by an incomplete genocentric view it seems likely that the major effort will continue to be on straightforward genetic engineering. And this will be reinforced by the GEO industry that has billions of dollars in the pipeline awaiting the transition from laboratories to farmlands. Under these circumstances, it seems only prudent that any further broadcasting of GEOs into ecological settings must be stopped until a way is found to complete the kind of complementary science described in Fig II.