Brooklyn Law Review

Volume 67
Issue 1
SYMPOSIUM:
DNA Lessons From the Past - Problems For the Future

Article 2

9-1-2001

Keynote Address: Beyond the Genome

Joshua Lederberg

KEYNOTE ADDRESS

BEYOND THE GENOME*

Joshua Lederberg†

What can genetics tell us about what is entailed in being human? Is human identity all in the genes? Among the most important questions that biology is confronting today, this issue is being pursued in a very aggressive fashion. The "human genome" has just been "published" in its entirety. However, this is obviously just the very beginning of genomic research. The most challenging prospect is the opening of comparative genomics: the comparison of individual to individual within the same species. Equally provocative is the contrast of Homo sapiens with other primate species. Here, we can begin to ask in some detail what was involved in the evolution of the human brain. What is the genetic basis of the distinction between the brain of the human vis-a-vis our closest relatives, the chimpanzee, the gorilla, and the orangutan? The DNA disparity among these primates and ourselves is no more than 1%; whereas the diversity among the human species may approach 0.2%. Further research about how we relate to other species and what is unique about human beings may help us better understand ourselves.

Should we look only in the DNA? How much of our nature is in the genes? This is not to get into the nature versus nurture controversy, a well-worn discussion. Rather, the issue is how much biology and how much, if any, "nature" is there

---

 The current text is based on remarks given as a luncheon address at the Brooklyn Law School Symposium, *DNA: Lessons from the Past—Problems for the Future*, on March 9, 2001. A calculated diversion from the main theme, the address bore the dual title: "Beyond The Genome" and "Whose Germs Are They Anyhow?"

† Joshua Lederberg is the Sackler Foundation Scholar at Rockefeller University and a Nobel Laureate.

beyond the genome, beyond the instructions inscribed in the chromosomal DNA. This takes us back to controversies beginning in the 1930s. Most or all of the variation seen within the species was controlled by Mendelian markers located in the chromosomes and could be tested by cross-breeding. That method obviously broke down when it was applied to non-hybridizable species. Some then argued that different protoplasms perhaps provided the context in which these genes operate; that the essence of species-to-species differences might rest beyond the genomes. Direct refutation of this hypothesis is all but impossible. However, the proposition has been greatly weakened by: (a) the ever-widening domain of traits that are directly gene controlled, essentially the primary structure of every protein (fiber, enzyme, antibody, hormone) so far examined; and (b) the unhindered functionality of DNA segments when these are transferred from one cell to another, regardless of species. It would be bolstered if some cytoplasmic constituent, outside the nucleus, could be transferred to, for example, a foreign egg, and modify the quality of the offspring. Conversely, when nuclei are transplanted from one setting to another, that might probe the completeness with which they dominate the "nature" of the offspring. This test is complicated by other incompatibilities between the sperm and egg of diverse species, resulting in embryos that just do not work at all—but that is another matter.

There is one outstanding exception: the mitochondria. These are another set of tiny DNA particles in the cytoplasm, outside the nucleus. They may be thought of as multiple replicas of a "47th chromosome," making up another five parts per million of the total DNA. The mitochondrial DNA has been forensically useful because it is transmitted almost exclusively through the (maternal) egg and can help rectify confused family relationships or the affinities of otherwise unidentifiable remains. A handful of disease syndromes, such as susceptibility to antibiotic side effects leading to deafness, have been traced to mitochondrial idiosyncrasies. We should not be surprised at this connection to antibiotics. It is further testimony to the hypothesis that mitochondria are ultimately derived from a microbe that had invaded ancestral cells many aeons ago. They are now indispensable to our body functions, particularly in the domain of cellular respiration. These aerobic

bacteria have evolved into the furnaces that energize every cell of our body. It is not absolutely excluded that some or all of us still carry other intracellular passengers, as do a host of invertebrate species, such as the luminescent bacteria in the headlamps of deep-sea squid.

In any case, we must look at the comparative genomics of mitochondria to compare humans with other mammals. Although mitochondria live in the cytoplasm, their biological functionality mimics that of the nuclear DNA; their information content is that of the sequence of bases, read three by three down the helical chain. I call that, simply, nucleic information. The mitochondria then add a tiny supplement to the content of the twenty-three chromosome pairs.

When we look more closely at the different expression of the same DNA, comparing, for example, a neuron and a fat cell from the same individual, some further complexities emerge. At least to a close approximation, in a DNA sequence the nucleic information is identical in these cells. Yet in cell heredity, in tissue cultures, or during the development of the organism, the fat cell and the neuron retain their specific appearance, their repertoire of proteins, and their functions during cell generation after cell generation. These are called "epigenetic" traits, in view of their connection with embryonic development. But that epithet is no explanation of the mechanism! Upon further enquiry some developmental changes (unlike fat cell versus neurone) have turned out to be nucleic. Defying much prior dogma on the uniformity of somatic cell genomes, the diversification of immune cells can be attributed to a special kind of near randomization of some nucleic sequences so some white cells will have a DNA different from others. Then the progressive shortening of life span of some cells in cultures can be related to the shortening of their telomeres, the DNA at the very tips of each chromosome. So these are epigenetic changes which are nucleic.

What of the other epigenetic phenomena, the ones not nucleic? Our best guess is that many of them, which I prefer to call epinucleic, are lateral modifications, like methylation, of some of the DNA bases. Think of them as diacritical marks—a cedilla, or an acute accent, modifying an alphabetic character. For the most part these modulators are erased in the germ

line, but here too are exceptions that blur the once rigorously enforced boundaries between heredity and epigenesis. These epinucleic modulators have everything to do with the success of nuclear transfer in cloning experiments, using nuclei from differentiated cells, and, are what makes stem cells distinctive; but this brings us to the very brink of our current knowledge.

Then in principle, we might harken to yesteryear's traditions and still expect to find cell differences that are extranucleic, have nothing to do with the DNA sequence, and are in some vague way imprints of historical protoplasm. I do not put much faith in this expectation; but, as stated above, it has not been quite excluded yet. So recall the typology of nucleic, epinucleic, and extranucleic and you will have achieved a semantic clarity that outdoes many contemporary researchers. Too many of them have assumed that epigenetic (developmental) means epinucleic.

	BIOLOGICAL SETTING	
LOCUS OF INFORMATION:	HEREDITY (genetic)	DEVELOPMENT (epigenetic)
Nucleic (chromosomes, plasmids, mitochondria)	germinal genome, sperm, eggs	somatic diversity, immune cells
Epinucleic (DNA-methylation, binding proteins)	imprinting (usually transient)	most embryogenesis
Extranucleic ("protoplasm")	?ancient speculation	?some embryogenesis

Table 1. Modalities of Cellular and Organismic Determination

We are still not quite finished with our contemplation of the sources of individual identity. I refer now to our microbiome. These are the microbes that share our body space and that inhabit our skin, our mucous membranes, and our gut. We are beginning to understand that they have a very

considerable bearing on our health through the regulation of pathogenic organisms. Each one of us is a small ecological community that operates in some balance with competitors within its various components. For example, forty percent of the people in a given room have Helicobacter pylori in their stomach lining. Every once in a while, this will predispose the carrier to a stomach ulcer. But Helicobacter secretes antibiotics that are protective against cholera! This makes ecological sense, since the Helicobacter's cozy home is compromised if its host succumbs to another disease. If we eradicate such symbionts, as we sometimes do with antibiotic treatment, we open the door to the entry of the wrong organisms, since they are no longer held in check by the habitual ecological neighbors that we have customarily acquired. This microbiome may envelop the genomes of one more or more different species of microbes involved in these communities.

These symbiotic phenomena are well ensconced in the rest of the living world. Legumes, like pea plants, could hardly survive without their root nodules containing nitrogen-fixing bacteria. Many insects grow a special organ, the mycetome, to harbor each species' well-adapted symbionts that enhance the nutrition of the host. Microbial communities in the soil have been studied longer than those in the human microbiome. They have opened the door to the discovery and exploitation of antibiotics, dating back to Fleming's penicillin and Waksman's streptomycin, which have changed the course of history. There is every expectation that similar benefits will flow from understanding our own microbiomal ecosystem.

So this raises some rather interesting questions under the headings of responsibility, privacy, and property. The law has been very slow to recognize the responsibility that we each have to keep our microbiomes to ourselves and to not impose them on others. Health regulations impose some standard of hygiene on food-handlers, but beyond that the law provides hardly any sanctions against those who carelessly plant their microbiomal clones in the somatic space of other citizens, even when this may have mortal consequences. Not only has the duty of hygiene all but evaporated; public facilities, even schools, offer serious deterrents to hygienic lifestyles.

To turn to the positive uses, ponder what is the legal status of your microbiome as property? I guess if you discard it in the garbage pail, or in the sewage system, you have abandoned it. Your microbiome is left for interested parties to mine those nuggets freely. But many governments are looking to retain property rights on bugs collected on their soil. Even the U.S. Park Service licenses prospectors looking for thermally resistant microbes at Yellowstone National Park.

I recall an Italian film called *A Matter of Property*. The dispute concerned two peasants' conflicting claims on the droppings of the donkey. Who has the better claim, the donkey's owner or the owner of the path? They were seeking manure for fertilizer. In this techno-age, how many valuable derivatives may come from equally unlikely sources? So I feel that this consideration of the microbiome is a successor to our genome discussions. Ten years from now we will be having a symposium on its uses, forensic and otherwise, property rights, and privacy, resembling how people talk about the genome today.[1]

[1] For further reading see FRANKLIN M. HAROLD, MOLECULES, ORGANISMS, AND THE ORDER OF LIFE (2001); EVA JABLONKA & MARION J. LAMB, EPIGENETIC INHERITANCE AND EVOLUTION: THE LAMARCKIAN DIMENSION 346 (1995); JAN SAPP, EVOLUTION BY ASSOCIATION: A HISTORY OF SYMBIOSIS 255 (1994); JAN SAPP, BEYOND THE GENE: CYTOPLASMIC INHERITANCE AND THE STRUGGLE FOR AUTHORITY IN GENETICS (1987); H. Warr Hurd & A. E. Polwart, *A Parasite that Increases Host Lifespan*, 268 PROCEEDINGS OF THE ROYAL SOCIETY OF LONDON SERIES B-BIOLOGICAL SCIENCES 1749 (2001); Joshua Lederberg, *Infectious History*, 288 SCI. 287 (2000); Hans L. Tillman et al., *Infection with GB Virus C and Reduced Mortality Among HIV-Infected Patients*, 345 NEW ENG. J. MED. 715 (2001).