GENOMICS:

An enduring mainstream of the social empowerment of bioscience , or a short-lived sexy sideshow?

Few can have missed the fanfares with which the part completion of the public and private human genome sequencing projects was announced earlier this year. The achievement was hailed as the embodiment of the book of life, a milestone in the improvement of the human condition, and as signaling a revolution in medical science and practice. Given the expenditure of dollars and the human time and effort committed to the projects, perhaps its not surprising that great enthusiasm was expressed by the project leaders and investors. It was hard not to be infected by this enthusiasm particularly when we heard, for instance, that the genomic changes leading to different types of cancer could now be fully defined, as could the genetic basis for individual susceptibility to the various diseases. This was reinforced by the intervention of state leaders who had declared, with a measure of chauvinistic euphoria, how important free access to genomic knowledge would be for the public good. Yet at the same time, no one yet can be entirely sure where the explosion of genomic knowledge will bring most value to society.

Some of us may be totally skeptical at yet more self-congratulatory theatre by scientists. Is this novelty just the toy of an elite cognoscenti?. Will broad access to the benefits be denied by the complexity of the subject itself or even by formalized intellectual property constraints and corporate greed? Will it not just lead to us spending more of our income on interventive health care when what we really need is to learn how to live less indulgently? Such questions are the subject of a healthy debate but a debate which is afflicted by a narrow body-centered mindset.

I would argue the perhaps the greater gift which genomics brings us, just as the Land Grant renaissance does, is the opportunity to explore more productively the wider goal of welfare in an inexorably changing world. I would also argue that it is the opportunity to engage with the complex issues of biological diversity, and biological interactions, which brings meaning and value the genomic approach.

In this context, less widely hailed has been the completion and disclosure of the genome sequences of 80 and more microbial species, and also flat-worms, insects, and plants. OK, 80 out of the total of known microbial species is not much in relation to biodiversity yet , but let's try coming at this from another direction.

The microbiology of the land , of the ocean and of our bodies has been predicated on techniques of cultivation of microorganisms on Petri plates, in fact it is reckoned that Louis Pasteur, one of the founders of microbiology, would be well accommodated to a modern microbiology lab. The practice and paradigm is still the same. However, we are beginning to learn just how small a part of the microbial biosphere we have yet explored via the "culture" approach (some estimates put this as low as 0.1%), and the term non-culturable either strikes terror into the average microbiologist, or gets their head well and truly buried in the sand (or in an even darker place). The culture approach has served us well in the discovery and classification of the colonizers of our bodies, but less well for the microbial flora of the land and ocean. But, for these unseens and unknowns their genomes are out there. So, the genomic approach says, forget the organisms, lets look at the genes in the environment. Let's tap biological diversity via genes and genomes. If we want to know what is going on in a digester or a water treatment plant or a river, let's

look at which genes are active and at work in it rather than trying to define operational states and environmental impacts by fluctuations in the populations of "representative" known organisms. This proposition is backed up by some very exciting genomic technologies. High thru-put sequencing coupled to the massively parallel procedures of microarray and the so-called gene chip technologies, are at the core of new capacity for exploration of the microbial biosphere or of the complex managed systems of bioremediation.

Lest this begin to sound like a grotesquely whimsical piece of special pleading, let us begin to flesh it out to demonstrate how social value can result.

Consider the predicament we find ourselves in with respect to clinically useful antibiotics. All our studies of anti-microbial compounds synthesized by culturable organisms has left us with a limited chemical arsenal of vanishing utility as, over time, under constant challenge, the population of pathogens acquires resistance. The current rate of discovery of new antibiotics to replace those which lose their utility, is alarmingly low. So, the approach these days might be to take slugs of anonymous genes from the environment and to transfer these into culturable organisms. We can then grow and examine such organisms for the elaboration of new compounds and examine these for the ability to moderate the growth of pathogens. Any positive leads can then take us back to the pot of random sequences from the environment and to start looking for the rest of the genome of the source organism and its relatives. This type of genome-centered approach will lead to the discovery of new biosynthetic capacities evolved out of sight, and definitely out of mind, in the competition of microorganisms for their special niches. Convincing progress has already been made with this type of approach (see www.diversa.com).

Besides such practical prospecting approaches to diversity, genomics is overwhelmingly a comparative pursuit . The tools of bioinformatics enable us to access the basis of genetic diversity at the DNA level, but also allow us to locate and quantify differences and similarities in genes across the range of organisms. Within-species the differences may be diagnostic of particular sensitivities or positive attributes, and may be used to inform provision for individual health care in humans, or breeding value or progeny selection in domesticated animals or crops. This sort of analysis is informed very often by accessing polymorphism at the level of single nucleotides, the so called SNPs. High through-put systems such as the aforementioned microarrays enable us to analyze many thousands of such polymorphisms in parallel. The difficulty will be in deciding just where the acceptable boundaries of the technology lie. How much do we want or expect to know about ourselves and our fellows. In the case of the human genome the technical issues are being overtaken by ethical ones, but for the species on which our continued occupation of the land depends, both the domesticated and the wild species of the environment, improved genomic knowledge will be a key tool of sustainable management practice.

I return to the question of genetic diversity in the biosphere. A recent study of genomic fragments recovered from Icelandic hot springs has revealed that of the 14 groups of sequences found, only 3 were affiliated to groups of previously known microorganisms. (Marteinsson et al, Applied and Environmental Microbiology 67,p4242, 2001). In the

context of environmental microbiology this is discovery! The invisible , unknown 99% is coming in sight.
Genomics, in the broad sense, puts on the shore of a new voyage of discovery. Each of us with a sequencer and a PCR machine and the desire to explore, can emulate Columbus, Magellan, or Da Gama.. The words of an ancient Chinese benefaction say “may you live in interesting times”. Now is the appropriate moment for us to echo Ronald Regan’s reply “ you ain’t seen nothin’ yet!”.

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