

Chapter 10

Metagenomic Metaphors: New Images of the Human from 'Translational' Genomic Research

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10.1 Introduction: The Context of the Human Microbiome Project (HMP)

In an article written in 1990 at the dawn of the US Human Genome Project, James Watson and Robert Cook-Deegan wrote something guaranteed to catch the eye of anyone interested in public engagement with biomedical science. They said that 'The major impact of the genome project will be a slow but steady conceptual evolution – a change in the way that we think about disease and normal physiology' (Watson & Cook-Deegan, 1990, p. 3322). Since the way we think about disease and normal physiology are fundamental to the public's interests in (and feelings about!) biomedical science, significant changes in how we think about these topics will be important to understand for any attempt to follow or facilitate democratic deliberations about genome science.

In their 1990 essay, Watson and Cook-Deegan go on to suggest the direction in which they think the Human Genome Project will take our thinking about disease:

A century ago, a revolution in medicine was in full stride following the discovery of infectious organisms and the dawn of bacteriology. Over the course of the century, the conceptual base of medicine has broadened from gross anatomy of organs to cellular biology to dissection of biochemical pathways. The next step is to study the most fundamental elements in biology – Mendel's hereditary factors, now known as 'genes'. This will not replace population biology, organismal biology, cellular physiology, or biochemistry, but will supplement them with a new and powerful foundation of knowledge. [...] Once this foundation is solid, the next stage will be to use the masses of information and new analytical techniques to understand disease and normal biology. (Watson & Cooke-Deegan, 1990, pp. 3322, 3324)

This is, in fact, a reasonable thumbnail sketch of how many genome scientists have seen their place in history: as laying the groundwork for the final phase of the reductionistic search for 'specific causes' of disease that revolutionized medicine a century ago, by focusing our understanding of human biology on dynamics of

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its 'most fundamental elements.'¹ With this vision comes the essentialistic suite of metaphors for genes and the genome that we have become familiar with in connection with the Human Genome Project, as the 'Holy Grail' and the 'Code of Codes' for human biology and as individual human beings' 'blueprints,' 'recipes,' 'templates,' and 'souls.' (cf. Van der Weele, 2005; Nelkin, 2001).

Now that the Human Genome Project has been completed, however, the genomic research enterprise has entered a new phase, and a new language is emerging to help interpret it. In this paper I will focus on one trio of metaphors from this new phase of genomic research, which are emerging from the planning of the Human Microbiome Project (HMP) at the US National Institutes of Health. The HMP is a 'metagenomic' initiative to sequence the genomes of all the microbiological flora collected from a variety of body sites from a variety of human volunteers, in order to pursue the interesting hypothesis that our indigenous microbial genome, or 'microbiome,' plays a vital and interactive role with our human genome in normal physiology and disease. Three metaphors are being widely used by the scientists promoting this initiative: (1) that the human *genome* should be understood as part of a larger sensory-motor organ, the human 'meta-genome', picking up and reacting to cues from its environment much like our nervous or immune systems; (2) that the human *body* should be understood as an ecosystem with multiple ecological niches and habitats in which a variety of cellular species collaborate and compete; and (3) that human *beings* should be understood as 'super-organisms' that incorporate multiple symbiotic cell species into a single individual with very blurry boundaries, like a colony of blue-green algae on a massive scale of complexity. Each of these metaphors carries interesting philosophical messages, which I shall conclude by pointing to as promising topics for future research. To the extent that they mark a departure from the essentialistic and reductionistic language that characterized the promotion of the Human Genome Project, they may contribute to a very different kind of scientific paradigm shift than the one Watson and Cook-Deegan described in 1990, and perhaps even one more conducive to democratic public engagement in science policy.

¹ There is no shortage of evidence that genome scientists have seen themselves as poised at the beginning of the 'end of history' for medical science. For example, Walter Gilbert writes that:

The genome project is not just an isolated effort on the part of molecular biologists. It is a natural development of the current themes of biology as a whole. [...] The information carried on the DNA, that genetic information passed down from our parents, is the most fundamental property of the body. To work out our DNA sequence is to achieve a historic step forward in knowledge. Even after we have made that step we will still need to refer back to the sequence, to try to unravel its secrets more and more completely. But there is no more basic or more fundamental information that could be available. (Gilbert, 1992, p. 83)

See also Guyer and Collins (1993) and Hood (1988) for similarly eschatological claims for genome research.

10.2 The Context of the Human Microbiome Project (HMP)

Before we get to the HMP and its metaphors, there are two more generic pieces of the new genomic language that are important to notice: the metaphor of ‘translation’ and the concept of ‘metagenomic’ research. Together, these provide the rationale and conceptual context for the HMP, and for its own interesting suggestions for what genomics teaches us about ourselves.

10.2.1 Translational Genomic Research

After floundering a bit with the infelicity (and inaccuracy) of entering a ‘post-genomic era,’ the genome research community in the US now universally calls its new phase that of ‘translational genomic research,’ to capture its goal of using genomic science to develop specific interventions that can be used in clinical and public health settings to benefit human health.² ‘Translation’ itself is open to interpretation here, of course. Some still seem to see it as a relatively mechanistic process of moving through a ‘pipeline’ or ‘translational pathway’ ‘from the bench to the bedside,’ more or less like the stepwise translation of RNA molecules into functional proteins within a cell’s ribosomes. The trans-NIH ‘Roadmap’ initiatives of the last several years, aimed at accelerating the process through which laboratory research leads to beneficial health outcomes, subscribes to this rather linear interpretation of translation. This interpretation still echoes the older metaphors of blueprints and codebooks, as if best route to health benefits need only be ‘read off’ the information genomics provides. But it at least suggests that genomics still has some distance to travel before it revolutionizes medicine, even after achieving the Holy Grail of a complete human DNA sequence. This in itself opens an opportunity for the public to line the roads and watch the genomic parade – or, more ominously, to ‘constrict the translational pipeline’ with undue regulatory governance.

Equally common, however, (and more interesting for our purposes) is to interpret ‘translation’ in this context linguistically, as if basic genomic research findings and medical diagnoses, prognoses and prescriptions described the same things in different languages and merely required a translator – or at most, ‘translational research’ – to be usefully interpreted in either direction. This interpretation has the heuristic advantage of signaling that there are human challenges in doing translational research: it involves communication across multiple disciplinary and professional boundaries (and the subcultures they define), and the process is not mechanical. Linguistic translations are capable of being better or worse, more or less useful, depending on the skill and discernment of the translator. This interpretation also opens up the notion to the idea that, in part, translational research should involve translating the insights of science into language that the public can appreciate as

²Thirty years ago, this would have been called ‘applied’ as opposed to ‘basic’ genomic research, and it would be interesting to study why that formulation no longer works.

well. In order for that to be true, of course, those doing the translating will need to know the public's languages, providing a role for public voices (and those who study them) in the translational research process itself, as critical insiders rather than external critics.³

The HMP is an example of 'translational genomic research' because it attempts to use genomic tools to address a problem of medical interest, by improving our understanding of the role of bacteria in human physiology and disease. Ultimately, the proponents hope to be able to provide both diagnostic tools, using DNA screening to assess a patient's bacterial needs, and more effective and 'individualized' pro-biotic therapies to address microbial imbalances. Genetically engineering the bacteria we include in these therapies could provide a useful new avenue for delivering pharmaceuticals as well, or even for replicating, in a reversible and safer way, what we might attempt to achieve through somatic cell gene therapy. The HMP will also be 'translational' in that it will involve a number of disparate scientific fields – microbial evolution, infectious disease epidemiology, human somatic cell genetics, DNA sequencing, dermatology, gastroenterology, gynecology and dentistry, for example – in collaborative efforts on a large scale. This, of course, makes the need for useful ordinary language metaphors critical to the effort simply to improve communication amongst those involved, even before the public is engaged.

10.2.2 'Metagenomic' DNA Sequencing Research

The second generic concept framing the HMP is the notion of 'metagenomic' research.⁴ Unlike 'epigenomic' research, this does not refer to the study of cellular environmental forces above and beyond the genome itself in the regulation and expression of genes. Rather, metagenomic research involves projects in which mixed samples of DNA from multiple species are sequenced, in order to identify all the organisms involved and study their molecular interactions (cf. Riesenfeld, Schloss, & Handelsman, 2004). For example, Coque, Oliver, Perez-Diaz, Baquero, and Canton (2002) studied the metagenome of an entire hospital in Madrid over an 11-year period, and found that bacterial resistance to several antimicrobial agents persisted despite the ephemeral nature of the bacterial species responsible for producing these enzymes. They concluded that genes coding for ESBLs were housed

³Just behind these molecular and linguistic readings lurks another old theological definition of 'translation' that also sometimes seems reflected in the way the term is used by promoters of translational genomic research: the miraculous ascension of some special saints directly to heaven before they have actually died. If only we could translate the findings of genomic research directly into medicine without the need for their death as basic science discoveries and their tedious epidemiological and clinical research interrogation before the gates of the clinical setting! Unfortunately, even most saints have had to die (often under torture) to get beyond this world, and in the real world research results face similar thresholds and challenges.

⁴For a very useful summary and conceptual analysis of metagenomics science, see Dupré and O' Malley (2007).

in transposable genetic elements as a minority gene population in the hospital metagenome. Residing in the hospital metagenome, these 'jumping genes' persist in a variety of bacterial species that themselves are not persistent. The HMP is metagenomic because it seeks to do bulk DNA sequencing of multiple bacterial species, like other metagenomic research projects. Unlike its predecessors, however, the HMP aspires to go further to support studies that include human somatic cell genomes in the metagenomic mix, in order to understand our inter-species interactions at the molecular level. As the US National Research Council explains in its ringing endorsement of the Human Microbiome Project,

The human 'metagenome' might be considered an amalgamation of the genes contained in the *Homo sapiens* genome and in the microbial communities that colonize the body inside and out. The organisms within these communities are collectively known as the human 'microbiome.' The metagenome of these communities encodes physiological traits that humans have not had to evolve, including the ability to harvest nutrients and energy from food that would otherwise be lost because we lack the necessary digestive enzymes. Without understanding the inhabitants of the human microbiome and the mutualistic human-microbial interactions that it supports, our portrait of human biology will remain incomplete. (National Research Council, 2007, p. 38)

10.3 Metagenomic Metaphors

If the architects of the Human Genome Project hoped to achieve a 'slow but steady conceptual evolution' in biomedicine, the proponents of the Human Microbiome Project have much grander ambitions: they to seek to spark nothing short of Kuhnian scientific revolution in our understanding of human biology. They argue that as the 'new science' of metagenomics emerges,

Basic ideas that organize biologists understanding of the living world may need refinement in the fact of greater understanding of [microbial] community function. New concepts of genomes, species, evolution, and ecosystem robustness will have effects beyond the specific field of microbiology. The questions that must be asked are 'deep' ones [...]. (National Research Council, 2007, p. 33)

The basis for these ambitious claims lies in the radical way in which metagenomics reconceives biological individuality. Traditionally, the individual mammalian organism – the horse or the human – has been the paradigm for both folk and scientific concepts of biological individuality (Wilson, 1999). In spite of the fact that we mammals are rather atypical of living beings generally, this vision of individuality has structured both our biomedical science and our social practices. Health and disease are paradigmatically conditions of individual patients, and only by extension their parts or the larger wholes to which they belong. Similarly, our society's ethics and political systems are famously built around the agency and needs of the human individual. In both spheres bodily boundaries make up critical demarcations, and as a result carry significant psychological weight, giving tangible meanings to our notions of 'purity,' 'integrity,' and 'wholeness,' on one hand, and 'infection,' 'contagion' and 'corruption' on the other. By using metagenomics to

study human physiology, the HMP challenges these boundaries methodologically, and, by extension, the ontological categories we use to 'carve nature at its joints.' Far from helping genomics realize the modern scientific project of reducing the ills of human individuals to their specific causes, metagenomics and the HMP seem poised to bring genomics to a post-modern understanding of the individual itself, as pragmatic construction that we project upon on a much more complex system (cf. Hauskeller, 2004).

To explain the implications of this conceptual shift – and to promote their project – the architects of the HMP have resorted to three metaphors I previewed in the introduction. First, they describe the human genome as only one contributing part of a larger functional genetic system, the human metagenome that interacts with its environment like a sensory-motor organ in maintaining a human individual's health. Second, they describe the individual human body as itself an ecosystem, casting 'health' in ecological terms as a homeostatic harmony between different interacting species and 'disease' as its imbalance. Third, they almost universally declare human beings to be 'super-organisms' rather than discrete biological individuals, rendering our personal boundaries fluid and flexible. Each of these metaphors has interesting philosophical implications, which I will suggest as I take them up in turn below.

10.4 The Human Metagenome as a Sensory-Motor Organ

In its report promoting the HMP, the National Research Council argues that

Metagenomics will enable us to address a number of fundamental questions about ourselves. Is there an identifiable core microbiome shared by all humans? How is each individual's microbiome selected? What is the role of host genotype? Should differences in each individual's microbiome be viewed, with the immune and nervous systems, as features of our biology that are profoundly affected by individual environmental exposures? (National Research Council, 2007)

These questions point to the key aspirations of the HMP, which are ultimately to offer a positive (and biomedically useful) answer to each of them. The last question is of particular 'translational' interest, since if the human metagenome can be influenced by environmental exposures, it offers a window for medical manipulation that the 'primate-lineage component of the human genome' (Ley et al., 2007, p. 3) seems to resist. As the architects of the NIH HMP write in a background paper,

As twenty-first century medicine evolves its focus towards disease prevention, new and better ways of defining our health status are needed. The gut micro biota is an effector and a reporter of many aspects of our normal physiology. Comparisons of germ-free and colonized animals have shown that the micro biota helps regulate energy balance, both by extracting calories from otherwise inaccessible components of our diet and by controlling host genes that promote storage of the extracted energy in adipocytes (2–4). The micro biota directs myriad biotransformations, ranging from synthesis of essential vitamins to the metabolism of the xenobiotics that we ingest and the lipids that we produce. (Gordon et al., 2007, p. 1)

Moreover, as this list indicates, among these interesting microbiotic contributions to our physiology are interactions with our 'primate lineage' genes. Microbiota help regulate differential gene expression in different tissues and in response to environmental stimuli, effectively extending the capacity of our cells to differentiate and adapt. As humans and their bacteria have co-evolved, this has meant a role for the microbiome even in the 'internally programmed' process of normal growth and development. As Dupré and O' Malley point out in their review,

Particularly striking is the growing understanding that symbiotic bacteria are required for the proper development of many vertebrates. It was recently reported, for example, that environmentally acquired digestive tract bacteria in zebrafish regulate the expression of 212 genes (Rawls et al., 2004; Bates et al., 2006). In fact, for the majority of mammalian organism systems that interact with the external world – the integumentary (roughly speaking, the skin), respiratory, excretory, reproductive, immune, endocrine, and circulatory systems – there is strong evidence for the coevolution of microbial consortia in varying levels of functional association (McFall-Ngai, 2002). (Dupré & O' Malley, 2007, p. 840)

The key to the success of this shared system of genetic regulation is the wide variation that bacterial genomic plasticity provides, which allows the microbial lineages in our metagenome to evolve quickly in the face of selective pressures. As the National Research Council report explains, 'The mechanisms for rearranging coding elements within a genome serve as mutational switches, ensuring that as the environment changes due to shifts in chemical, physical or biological conditions, there will be variants in the cell population that can flourish' (National Research Council, 2007, p. 34). As our microbial genome evolves under environmental pressure, so do the messages that it conveys to the human genome, affecting the regulation and replication of our primate genes. At the level of the human organism, this rapid evolutionary change looks virtually mechanical, inspiring comparisons to other cybernetic organ systems. As one team writes, 'like an organ, a healthy microbiota consumes, stores and redistributes energy and mediates important chemical transformations that benefit the host. Communication among the cells that make up the microbiota enable replication and repair, and a set of feedback loops link host and microbiota' (Foxman, Goldberg, Murdock, Xi, & Gilsdorf, 2008).

10.5 Discussion: Implications for Genetic Determinism

One of the problems with the essentialistic genetic metaphors that animated the promotion of the Human Genome Project is that they were already outdated by the science they attempted to illustrate. In fact, casting genes in the role of specific causes for traits requires holding onto a strikingly old-fashioned form of genetic thinking which today was disparaged by Ernst Mayr in the mid-20th century as 'bean bag genetics.' Early Mendelians assumed that particular genes (or 'unit characters') were necessary and sufficient causes for their trademark traits: 'specific causes,' in medicine's terms. Mayr pointed out, however, that unlike colored beans drawn from a bag, genes rarely have only one phenotypic effect, and are never entirely disconnected from each other (Mayr, 1963, p. 263). Since then, the phenomena to

which he referred – pleiotropy, heterogeneity, and linkage – have become foundational for much of modern genetics, and were crucial to the basic ‘positional cloning’ strategy for the Human Genome Project’s first round of genome mapping efforts.

If it was rhetorically possible to hang onto old models of genetic causation during the purely descriptive mapping and sequencing of the human genome, it has become no longer possible in genomics ‘translational’ phase and the functional analysis of genes to which so much of genomics has turned. Even before the emergence of metagenomics, the Human Genome Project itself undermined the status of DNA as the ‘master molecule’ in human biology. For example, one of the interesting findings of genome research is that human beings only have about 25,000 genes, like mice, not the 100,000 that scientists previously predicted. What distinguishes humans is that genes we do have are often capable of ‘multi-tasking’ to help human cells produce a much greater variety of proteins than other organisms. In part, this ability is a function of the fact that our genome contains regions of non-coding DNA that break up our genes and allow their specific coding regions to be rearranged to describe different proteins. This dynamic is controlled by regulatory DNA elements, but only when activated by cues from the proteomic flux of the cellular environment. If there is anything that really distinguishes us from other species – or from one another – at the cellular level, it must lie in the forces that animate the cytoplasm, or even the extra-cellular influences that produce those forces. This means that, far from being a constant and consistent signature, across different tissues even our bodies’ human cells will be operating different functional nuclear genomes simultaneously.

The reconceptualization of the human genome as one component of a dynamic human metagenome obviously deals a blow to the old genetic determinism that is even more vivid than revelations about the internal plasticity of its ‘primate-lineage component.’ Far from being the ‘master molecule’ in our physiology, our nuclear DNA is demoted to simply another set of cellular genomes jostling for influence within us, reacting to and being regulated by, a set of microbial genomes that outnumber them 10 to 1. As Dupré and O’ Malley point out, ‘The original human genome sequencing projects were, from this perspective, about only a tiny and unrepresentative complement of our genes’ (Dupré & O’ Malley, 2007, p. 840).

This new level of indeterminacy has two important implications. First, it has the potential to undermine the social risks that a deterministic view exacerbates. If our insurers and employers appreciate the causal complexity and power of the metagenome, they may less likely to penalize us for the potential health risks lying dormant in any of its parts. More importantly to metagenomics status as a ‘translational’ science, however, the new causal complexity opens up possibilities for preventing and manipulating those health risks. In one interesting picture of the utopia waiting beyond the HMP, the project’s proponents manage to capture both these virtues

Our medical insurance cards will contain one chip for our primate genome, and one for our microbiome. As part of the annual physical exam, physicians will take a stool sample to update the microbiome profile. Just as today a rise in blood pressure from one visit to the next signals a risk of developing heart disease, tomorrow changes in the microbiome

profile will herald a predisposition to diseases such as obesity. Therapeutic intervention will follow, likely a combination of individualized nutrition, deliberate 'reprogramming'. Of the micro biota with addition/removal or stimulation of particular lineages or genetic complements within the microbiome, or use of microbial gene products themselves (or their revealed human gene product targets) as part of our 21st century pharmacopoeia. (Ley et al., 2007, p. 4)

It has been popular amongst genome scientists to cast the ethical, legal, and social issues in genome research as time-limited problems caused by the 'therapeutic gap' between our ability to read people's genomes and our abilities to offer effective remedies to any deficits we find there. As genomic medicine catches up with genome science, the argument goes, the issues caused by this awkward interim should evaporate, because it will no longer be in anyone's interests to discriminate on the basis of genotype (cf. Hood & Rowen, 1997). The relatively slow growth of human gene therapy, pharmacogenomic interventions, and other forms of 'personalized genomic medicine' over the last decade has been discouraging for this line of argument – until now. If interventions as easy and efficient as 'probiotic' inoculations of genetically modified bacteria can be counted amongst the armamentarium of personalized genomic medicine, then the closing of the therapeutic gap may well be at hand. This would achieve genomics' translational ambitions and perhaps relieve the 'ethical, legal and social' constrictions of its pipeline in the process.⁵

10.6 The Human Body as an Ecosystem

At the same time that the microbiomists are conceptualizing the human metagenome from a human point of view as simply another (vital) organ system within the body, they are also interpreting the body, from the microbial point of view, as an ecosystem hosting multiple interacting species. As they point out 'The GI tract can be regarded as a very complex ecosystem, because it does not involve solely eukaryotic tissues like in other organs, but involves interplay between food, host cells and microbes' (Zoetendal, Vaughan, & de Vos, 2006, p. 1639). On this construction, the body's bacteria are not simply absorbed into its boundaries as another human organ, but are allowed their own identity as participating species in an ecosystem that can benefit both them and their human 'host'. Thus, 'the microbial ecosystem of the mammalian gastrointestinal tract is in a homeostatic relationship with the host's immune system. As expected for co-evolving systems, both microbe and mammal benefit from this symbiotic partnership' (Saier & Mansour, 2005, p. 23).

To some extent, describing the human body as an ecosystem is meant literally: it is possible to discern and study 'microbial ecology' in ways that use the term ecosystem much as it is used in environmental sciences. It is evident that there also

⁵Although there remain good reasons to believe this hope would be vain: I've argued that the 'therapeutic gap' is not genomics' most important source of ethical and social challenges, compared to what it can imply about psychosocially potent dimensions of our identities (Juengst, 2004).

metaphorical ecosystems in play, however, when the literature begins describing the body in geographical terms, as a landscape. For example, As one scientist writes:

When a new human being emerges from its mother, a new island pops up in microbial space. Although a human lifespan is a blink in evolutionary time, the human island chain has existed for several million years, and our ancestors stretch back over the millennia in a continuous archipelago. (Ley et al., 2007, p. 3)

Like geographical island ecosystems, the human body contains many microclimates and ecological niches across three major zones: its inner lining (the gut), its exterior covering (the skin) and its multiple and very different orifices. Microbiologists speak of the microbial 'tide pools' of the teeth, and the 'rain forest' of the gut, using the strikingly 19th century language of mapping 'largely unexplored' terrain, populated by 'indigenous' species of bacteria (Blaser, 2006). As the proponents of the HMP say, 'Microbes thrive on us: we provide wonderfully rich and varied habitats, from our UV-exposed, oxic and desiccating skin to our dark, wet, anoxic and energy rich gut that serves as a home to the vast majority of our 100 trillion microbial (bacterial and archaeal) partners' (Ley et al., 2007, p. 3).

One useful consequence of reframing the human body and its places as ecosystems is that it provokes a line of thought about how to achieve the therapeutic manipulations of the metagenomic 'organ system' that seem so attractive under that metaphor.

Any ecosystem needs to be in a state of balance in order to function effectively. Disturb one component, and dire consequences to the entire system can follow. In nature, ecosystem disruption often results in massive death of the constituent species. The ecosystem we will focus on in this mini-review is the human gut with its extensive and complex flora of microorganisms. The human intestine is part of a truly amazing ecosystem that is essential for the successful and efficient absorption of nutrients. (Saier & Mansour, 2005, p. 22)

10.7 Discussion: Implications for Concepts of Health and Disease

One of the major conceptual effects of the doctrine of specific causation in 19th century medicine was the ontological reification of diseases in terms of their causal pathogenic agents. Both in Pasteur's germ theory and in Virchow's cellular pathology diseases were understood to be reducible to real things in the world: the pathogens or lesions which could provide necessary and sufficient targets for intervention. Under this view, diseases are separable from the patients that suffer them; they are understood best as predators attacking the patient, either as invading germs or as devouring wounds. Diseases like schistosomiasis and herpes fit clearly into this scheme: they are diseases identified with the invading entities that cause their clinical signs and symptoms. Explaining a set of clinical problems as a 'cancer' – an abnormal body part, consuming other normal body parts – is also to use this model, as is a diagnosis of 'spina bifida' – a localizable lesion in the body. On this model, the proper target for therapeutics is not the epiphenomenal clinical symptoms of the disease, but whatever the disease 'agent' does to cause those symptoms: the infection, the metastasis, or the break. The great successes of the public health movement

in combating infectious disease in the early 20th century, and the reorientation of psychiatry to look for the 'organic' bases of mental illness during the same period owe much to this interpretation of disease, as does the common correlative view that health is largely a matter of being 'clean' and 'whole'.

One of the important corollaries of this ontologically robust view of disease is that it becomes possible for diseases to be 'carried' by organisms who, while unaffected themselves, serve to transmit disease to potential hosts. As historians note:

The simplistic interpretation of the germ theory, one which many physicians embraced at first, was that pathogenic bacteria in a human host equaled a disease. Before long it became clear that some individuals could harbor large numbers of dangerous bacteria and suffer no effects. The most famous of these was Mary Mallon, whose gallbladder teemed with typhoid bacilli, while she enjoyed perfect health. . . . The carrier state is now recognized as extremely common in many diseases. (Hudson, 1987, p. 164)

Moreover, the lesson of Typhoid Mary was that the 'carrier state' is also a crucial target for intervention in any attempt to forestall the spread of a disease of this sort. From the point of view of preventive medicine, carriers do not enjoy perfect health at all: they are infected with disease which could either eventually blossom to harm them or spread to those around them. This made possible the concept of screening otherwise healthy people to detect their hidden diseases, both for the purposes of providing them with 'pre-emptive therapy' and providing others with protection from the danger they represented (Brandt, 1987).

Viewing the human body as an ecosystem of co-existing cellular species poses a major challenge to the doctrine of specific causation and the models of health and disease it supports. If the human body is essentially an ecosystem, the notions of 'purity,' 'integrity,' and 'wholeness,' on one hand, and 'infection,' 'contagion' and 'corruption' on the other make little sense, since ecosystems are understood to have fluid boundaries and to support multiple species in cycle of growth, predation and decay. Moreover, there are no 'bad guys' in ecosystems, so, as the microbiomists point out, the metaphors of war no longer apply so well to our understanding of health and disease

In the face of these challenges, the metaphor of 'war' on infectious diseases – characterized by the systematic search for the microbial 'cause' of each disease, followed by the development of antimicrobial therapies – can no longer guide biomedical science or clinical medicine. A new paradigm is needed that incorporates a more realistic and detailed picture of the dynamic interactions among and between host organisms and their diverse populations of microbes, only a fraction of which act as pathogens. (Forum on Microbial Threats, 2006)

Of course, ecosystems can have problems, if they are forced into crises by changing contextual conditions. Species can overpopulate, resources evaporate, and interdependent processes collapse. This kind of problem provides another ready model for human health and disease. In fact, it leads immediately to the metaphors of 'balance' and 'harmony' that frame the traditional philosophical competition for the doctrine of specific causation: the old ideas of Galenic humoral pathology and the 'constitutional pathology' that followed it at the end of the 19th century. On this model, which the microbiomists adopt in ecological form, human health is a matter

of having ones physiological processes and predispositions (or dyscrasias) aligned correctly to promote homeostasis, so that the body runs as much like a self-regulated and self-sustaining system as possible. As Dupré and O' Malley suggest, 'Indeed, it may turn out that diseases caused by microbial pathogens are best seen not so much as an invasion by a hostile organism, but rather as a kind of holistic dysfunction of the microbiome' (Dupré & O' Malley, 2007, p. 840).

On this model, there are no diseases in an ontological sense; only sick patients whose bodily processes have gone awry in one direction or another. Thus, while infecting patients with new germs seems a counter-intuitive form of treatment against the doctrine of Specific Causation which gave us antibiotics, repopulating a depleted stock of commensal organisms through 'pro-biotic' infusions is entirely plausible under this reframing, in just the same way that restocking a habitat with keystone species makes sense for environmental preservation. Thus:

Individualized medicine will only become truly individualized when all aspects of an individual, human and bacterial alike, can be considered. A potential model is emerging, in which a disruption in the microbiome results in a functional imbalance, contributing to a pathological state (Fig. 1b). Treatments such as drugs, changes in diet or re-seeding efforts could facilitate a return to the steady state between the human body and resident micro biota, thereby restoring the functions of supermetabolism. (Sekirov & Finley, 2006, p. 737)

Of course, constitutional pathology also has its constitutional weaknesses from a psychosocial point of view, as history has shown us (cf. Juengst, 1999). First, if sustaining and recovering my health is a matter of controlling the contextual forces that influence my inner homeostasis, this means that much more of my 'health care' becomes my own responsibility. My physicians (and insurers) cannot and should not be expected to police and redress my complete lifestyle. Instead, it is up to me to improve my diet, avoid toxic environments, and insure that my habits are conducive to sustaining a health microbiosphere. This reallocation of responsibility is both 'empowering' for the individual, and potentially exculpatory for the social actors who might ordinarily bear responsibility for health care (Foster & Sharp, 2008).

Moreover, an extension of this shift of responsibility is the form of stigmatization that typically accompanies 'balance' models of health and disease: the social perception of an individual as intrinsically inclined to go awry in specific ways. We already know the alcoholic, the 'presymptomatic' victim of Huntington's Disease, and those put in the 'at risk' role by probabilistic genetic testing (Novas & Rose, 2000): now it is possible to be vulnerable to disease by sustaining a maladaptive microbiome as well, like the habitual 'abusers' of antibacterial products who encourage the selection of drug resistance within their indigenous flora.

Finally, as this discussion of health suggests, the metagenomic model also raises questions about who is the beneficiary of health or the victim of disease. As the microbiomists point out, 'In addition to being numerous, our microbes also are enormously varied – more than 1,000 bacterial species abound in a variety of niches in our bodies. This immediately raises the question of who we are' (Blaser, 2006, p. 957).

10.8 The Human Being as a Super-Organism

There is a strikingly universal answer to Baird's question in the literature promoting human metagenomics: biologically, at least, we are not intrinsically individuals, but collective super-organisms, assimilating multiple species and millions of individual organisms. As almost every article in this literature argues, both understanding our metagenome as a sensory-motor organ and seeing our bodies as ecosystems encourages us to find a way to incorporate our microbiome into our sense of self. 'Thus, it seems appropriate to consider ourselves as a composite of many species – human, bacterial, and archaeal – and our genome as an amalgam of human genes and the genes of our microbial "selves"' (Gordon et al., 2007, p. 1).

In order to explain this amalgam, the microbiomists borrow from zoology the concept of the 'super-organism' and invite us to 'Step forward into the world of metagenomics and we start to see ourselves as supra-organisms whose genome evolved with associated microbial genomes (the microbiome)' (Ley et al., 2007). The microbiomists themselves cannot get enough of this vision:

A metagenomic analysis of the microbes in the human gut reveals their diversity and just how interdependent we are on them. Together with our microbes we are a human-bacterial superorganism with immense metabolic diversity and capacity. [...] This study supports the theory that we are in fact 'superorganisms' whose metabolism integrates microbial and human features. (Sekirov & Finlay, 2006, pp. 736–737)

Of course, on this line of reasoning humans are far from unique in having this status:

All plants and animals, including humans, can be considered superorganisms composed of many species, animal, bacterial, archaeal, and viral. Historically, the study of physiology as not focused on these host-associated microbial communities: metagenomics offers an opportunity to understand their physiological role. [...] The metagenome of these communities encodes physiological traits that humans have not had to evolve, including the ability to harvest nutrients and energy from food that would otherwise be lost because we lack the necessary digestive enzymes. (National Research Council, 2007)

This is an important point to establish for the proponents of the Human Microbiome Project, because it allows them to point out that 'although the primate lineage component of the human genome is decoded, sequencing of the microbiome is just beginning (Ley et al., 2007, p. 3) and argue in favor of a concerted effort to complete it, since: 'without understanding the inhabitants of the human microbiome and the mutualistic human-microbial interactions that it supports, our portrait of human biology will remain incomplete' (Gordon et al., 2007, p. 2).

10.9 Discussion: Implications for Human Identity

As the microbiomists acknowledge, 'We are just beginning to realize the implications of being a superorganism, and the benefits of better knowing our intestinal inhabitants' (Sekirov & Finlay, 2006, p. 737). Indeed, one of the most tantalizing

features of the promotional literature on human metagenomics is the suggestion by the heralds of the HMP that this research has revolutionary implications for our ordinary understanding of human nature and what it means to be a human being. In particular, two issues with significant ethical and social implications seem to be made more challenging by the superorganism conception.

First, a superorganismic anthropology recalls the debates inspired by the philosopher Derek Parfit over the stability of the human individual over time, and the ethical implications of a transient conception of the self (Parfit, 1984). Our conventional moral commitments to respect for personal autonomy, promise-keeping, truth-telling, and the rights and responsibilities that come with moral agency all assume that human individuals display a continuity of identity over time. Parfit's critique of that continuity has created a philosophical industry in efforts to either rebut his views on behalf of ethics or show how ethics can still apply across serial selves. If metagenomics suggests that our symbiotic microbial populations are integral to our identities as individual organisms and that they change over environments and time, this will bring Parfit's view to the public in tangible ways, by suggesting that even the most 'personalized medicine' possible will face continuously shifting patients. As Dupré and O' Malley point out,

A final crucial point about metaorganisms is that they are paradigmatically dynamic entities and therefore very clear illustrations of the ultimate necessity of a process-oriented approach to biological investigation. None of the entities that constitute organisms, or which organisms constitute, are static. Genomes, cells, and ecosystems are in constant interactive flux: subtly different in every iteration, but similar enough to constitute a distinctive process. (Dupré & O' Malley, 2007, p. 841)

Mining the literature on the ethical implications of the loss of the 'enduring self' may be an important first step in preparing for the public reception of this paradigm shift.

Second, the super-organism concept has dramatic implications for our notions of the integrity of the human species. The normative importance of 'species integrity' has been posited before within bioethics, to critique biomedical practices as varied as the fertilization of hamster ova with human spermatozoa, the transplantation of porcine organs into humans, and the propagation of human stem cell lines in mice and the transfer of human genes into bacteria. 'Crossing species barriers' sounds like trespassing, and the qualms it provokes have been explained in a variety of ways, from invocations of essentialistic or theological visions of human (and animal!) nature to fears about risks of creating new forms of disease or ecological disruptions. Common across these claims, however, is the worry that biomedicine will undermine a given stability in the world by violating the categories that order it. Drawing in equal measure from Aristotelean essentialism and 19th Romantic sensibilities, this concern gives high normative weight to the biological kinds produced by the 'Wisdom of Evolution,' and their relative ranking in a hierarchical 'great chain of being'. On this view, 'splicing life' in the creation of transgenic organisms, or interspecies tissue chimeras, or hybridized embryos – like importing alien species into an established ecosystem – is always dangerous enough to justify the use of the

'precautionary principle'. For some, as Jeffrey Stout has pointed out, the creation of such 'abominations' is also morally suspect, simply in its willful disregard for the natural order it crosses.

Anthropologists suggest that these concerns are often animated by the tacit roles that concepts of 'purity' and 'pollution' play in our cultural definitions of human bodily boundaries, health and disease (Douglas, 1966). In situations that involve the integrity of the human species, like xenotransplantation, or the creation of man-machine 'cyborgs,' this moral hazard can be explained as the danger of dehumanization: that polluting the constellation of traits that humans' have inherited from our ancestors – our given 'human nature' – with nonhuman attributes we will inevitably degrade the elements of human identity we find morally important, like human dignity, autonomy, and vulnerability. As Jurgen Habermas puts it,

What is at stake is a dedifferentiation, through biotechnology, of deep rooted categorical distinctions which we have as yet, the description we give of ourselves, assumed to be invariant. This dedifferentiation might change our ethical self-understanding as a species in a way that could also affect our moral consciousness. (Habermas, 2003)

But meanwhile, we know that on and in the healthy human body microbial cells outnumber human cells ten to one, and play an active role in maintaining our normal physiology (Clarke & Bauchop, 1977). Now the HMP is underlining the significance of that role by suggesting that it may involve interactions at the genetic level as well, between human and bacterial cells. Our commensal bacteria, in essence, serve as crucial genomic extenders, much as they do in termites (whom they allow to digest wood). If so, the microbiologists argue, our basic concept of the human organism should be expanded to include our normal symbionts. Moreover, since our metagenomic profiles will vary between individuals and wax and wane over time, this science suggests that a canonical set of 'human genes' will never be available as a ground for human rights, or for determining when humans' 'species integrity' has been breached.

No one seems much concerned that we are all mixtures of many indigenous bacterial species and human cell lines. It neither undermines our fundamental rights, nor confers special moral status on bacteria. But it does seem as if concerns about the moral implications of blurring boundaries between the human species and non-human organisms are animating those who are striving to protect our species' 'dignity and integrity.' If we are already super-organisms, proponents of that concern are going to have to look further for an explanation for their anxieties.

10.10 Conclusion

In the glare of medicine's 19th century paradigms, it is hard to see what the metagenomic revolution might produce. It is clear, however, that better approaches to the understanding of complex systems will be required to translate both its science into practical benefits and its message into public discourse. As the microbiomists say,

The level of complexity required to take a dynamic ecological view of human microbiota is daunting, and will require collaborations among many disciplines including molecular biology, ecology, medicine, epidemiology and mathematics. To fully understand the mechanisms that drive community structure and function, microbiota must be examined over time to determine the dynamics of its processes, and over space to determine the interconnectedness of microbiota within an individual host and the range of microbiota among individuals. (National Research Council, 2007)

Attempting to translate that complexity to the public will be equally daunting, and not merely because of the multiple causal factors involved in the story. To the extent that the metaphors of metagenomics accurately capture the philosophical implications of the science, translating the message of microbiomics will require tools for talking about issues of human identity, health and disease, and genetic causation in ways that run counter to the messages that genomics has taught us in the past. For this form of 'translational genomic research,' it may be more important than ever for the many collaborators involved to include not just the list above, but also those disciplines that specialize in catching what can be 'lost in translation' in public discourse: the social sciences, the humanities, and the arts.

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References

- Blaser, M. J. (2006). Who are we? Indigenous microbes and the ecology of human diseases. *EMBO Reports*, 7, 956–960.
- Brandt, A. (1987). *No magic bullet: A social history of venereal disease in the United States since 1880*. New York: Oxford University Press.
- Clarke, R., & Bauchop, T. (1977). *Microbial ecology of the gut*. New York: Academic Press.
- Coque, T. M., Oliver, A., Perez-Diaz, J. C., Baquero, F., & Canton, R. (2002). Genes encoding TEM-4, SHV-2, and CTX-M-10 extended-spectrum beta-lactamases are carried by multiple *Klebsiella pneumoniae* clones in a single hospital (Madrid, 1989 to 2000). *Antimicrob Agents Chemotherapy*, 46, 500–510.
- Douglas, M. (1966). *Purity and danger: An analysis of the concepts of pollution and taboo*. London: Routledge.
- Dupré, J., & O' Malley, M. (2007). Metagenomics and biological ontology. *Studies in the History and Philosophy of Biology*, 38, 834–846.
- Forum on Microbial Threats – Board on Global Health. (2006). *Ending the war metaphor: The changing agenda for unraveling the host-microbe relationship: workshop summary*. Washington, DC: National Academies Press.
- Foster, M., & Sharp, R. (2008). The contractual genome: how direct-to-consumer genomic services may help patients take ownership of their DNA. *Personalized Medicine*, 5, 399–404.
- Foxman, B., Goldberg, D., Murdock, C., Xi, C., & Gilsdorf, J. (2008). Conceptualizing human microbiota: From multi-celled organ to ecological community. Retrieved on October 1, 2008, from <http://www.hindawi.com/RecentlyAcceptedArticlePDF.aspx?journal=IPiD&number=613979>

- Gilbert, W. (1992). A vision of the grail. In D. Kevles & L. Hood (Eds.), *The code of codes: Scientific and social issues in the Human Genome Project* (pp. 83–90). Boston: Harvard University Press.
- Gordon, J. I., Ley, R. E., Wilson, R., Mardis, E., Xu, J., Fraiser, C.M., et al. (2007). Extending our view of self: The Human Gut Microbiome Initiative (HGMI). <http://www.genome.gov/Pages/Research/Sequencing/SeqProposals/HGMIseq.pdf>, accessed June 24, 2007.
- Guyer, M., & Collins, F. C. (1993). The Human Genome Project and the future of medicine. *American Journal of Diseases of Children*, *147*, 1145–1152.
- Habermas, J. (2003). *The future of human nature*. Cambridge, UK: Polity Press.
- Hauskeller, C. (2004). Genes, genomics and identity: Projections on nature. *New Genetics and Society*, *23*, 285–301.
- Hood, L. (1988). Biotechnology and medicine of the future. *Journal of the American Medical Association*, *259*, 1837–1844.
- Hood, L., & Rowen, L. (1997). Genes, genomes and society. In M. Rothstein (Ed.), *Genetic secrets: Protecting privacy and confidentiality in the genetic era* (pp. 21–29). New Haven: Yale University Press.
- Hudson, R. (1987). *Disease and its control: The shaping of modern thought*. New York: Praeger Press.
- Juengst, E. (1999). Concepts of disease after the Human Genome Project. In S. Wear & J. Bono (Eds.), *Philosophy and medicine book series: Vol. 62. Ethics and values in health care on the frontiers of the twenty first century* (pp. 125–150). Dordrecht: Kluwer Publishers.
- Juengst, E. (2004). FACE facts: Why genetics will continue to provoke bioethics. *Journal of Law, Medicine and Ethics*, *42*, 252–267.
- Ley, R. E., Knight, R., & Gordon, J. (2007). The human microbiome: eliminating the biomedical/environmental dichotomy in microbial ecology. *Environmental Microbiology*, *9*, 3–4.
- Mayr, E. (1963). *Animal Species and Evolution*. Harvard University Press, Cambridge, Massachusetts.
- National Research Council (US). (2007). *The new science of metagenomic: Revealing the secrets of our microbial planet*. Washington, DC: National Academies Press.
- Nelkin, D. (2001). Molecular metaphors: The gene in popular discourse. *Nature Reviews: Genetics*, *2*, 555–559.
- Novas, C., & Rose, N. (2000). Genetic risk and the birth of the somatic individual. *Economy and Society*, *29*, 485–513.
- Parfit, D. (1984). *Reasons and persons*. Oxford: Clarendon Press.
- Riesenfeld, C. S., Schloss, P. D., & Handelsman, J. (2004). Metagenomics: Genomic analysis of microbial communities. *Annual Review of Genetics*, *38*, 525–552.
- Saier, M. H. Jr., & Mansour, N. M. (2005). Probiotics and prebiotics in human health. *Journal of Molecular Microbiology and Biotechnology*, *10*, 22–25.
- Sekirov, I., & Finlay, B. (2006). Human and microbe: United we stand. *Nature Medicine*, *12*, 736–737.
- Van der Weele, C. (2005). 'Images of the genome: From public debates to biology, and back, and forth.' In T. C. Reydon & L. Hemerik (Eds.), *Current themes in theoretical biology* (pp. 9–31). Dordrecht: Springer.
- Watson, J., & Cook-Deegan, R. (1990). The Human Genome Project and international health. *Journal of the American Medical Association*, *263*, 3322–3324.
- Wilson, J. (1999). *Biological individuality: The identity and persistence of living entities*. New York: Cambridge University Press.
- Zoetendal, E. G., Vaughan, E. E., & de Vos, M. (2006). A microbial world within us. *Molecular Microbiology*, *59*, 1639–1650.