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The Deep Ecology of the Human Body

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Abstract

Systems thinking has been used to define a deep ecology, in which humans are considered to be just one of many equal parts of the global ecosystem. This concept is being expanded in modern medicine. That is, the human body is an ecosystem that is part of the global ecosystem. The human body contains not just human cells, but also viruses, Bacteria, Archaea and Eukarya (protozoa, yeasts, fungi and worms). The skin, mouth, mucosal surfaces, anus, genitals, lungs and even human milk contain their own microbiota. Moreover, maternal transmission of some microbes occurs *in utero*, which contradicts the former sterile-womb paradigm. Even though viruses are usually thought of as being bad for human health, those that infect Bacteria (bacteriophages) help control the populations of various species of potentially harmful Bacteria. Moreover, viral infections can alter human immunity in subtle ways, leaving an indelible footprint on the immune network. So, the holistic view of health that comes from systems thinking must include the microbiome. Human eukaryotic cells provide only a small portion of the DNA in the human body. Viruses and Bacteria provide much more DNA and have essential roles in the human body. Like all plants and animals, we are just a small part of Gaia, which is mostly a viral and bacterial world. When we think of ourselves as ecosystems, new insights and terminology emerge. We can be thought of as "super organisms" or holobionts with a hologenome. Nested within the human body is the ecosystem that comprises the gut microbiome. It is like an organ in the neuroendocrine system. The roles it plays in various diseases are being considered in the pillars of P4 medicine – prediction, prevention, personalized and participatory activities. The goal is for researchers to be able to predict which group of people (cohort) is most likely to benefit from treatment with new drugs in clinical trials – based in part on the composition of their microbiomes. It is hoped that physicians will communicate with patients to let them know how to modify their diets to correct dysbiosis (an imbalance) in their microbiomes and discuss the possible risks and benefits of antibiotic therapy. The advice will be personalized to fit the overall needs of the patient. It will be participatory in that patients and their caregivers will participate in the changes to diet, therapies and/or behavior that will be needed to either maintain good health, or correct any health problems that emerge.

Keywords: *Deep Ecology; Holobiont; P4 Medicine; Ecosystem; Human Microbiome Project (HMP); Enteric Nervous System (ENS)*

Abbreviations

ANS: Autonomic Nervous System; BMI: Body Mass Index; CNS: Central Nervous System; DNA: Deoxyribonucleic Acid; DRG: Dorsal Root Ganglia; ECs: Enterochromaffin Cells; ENS: Enteric Nervous System; GBA: Gut-Brain Axis; GIT: Gastrointestinal Tract; HGC: High Gene Count; HMP: Human Microbiome Project; HPA axis: Hypothalamic-Pituitary-Adrenal Axis; LGC: Low Gene Count; LPS: Lipopolysaccharides; P4 medicine: Predictive, Preventive, Personalized and Participatory Medicine; PAMPS: Pathogen-Associated Molecular Patterns; RNA: Ribonucleic Acid; SCFAs: Short Chain Fatty Acids; TLRs: Toll-Like Receptors

Introduction

Systems thinking has become an important paradigm in many areas of science. Fritjof Capra described how it is important in modern physics and biology [1,2]. He and Pier Luigi Luisi further showed how it is important in mathematics, biology and medicine [3]. This in-

cludes a deep ecology, in which humans are viewed as just one of many equal parts of the global ecosystem [2]. This concept should be extended to include a deep ecology in the human body. That is, the human body is an ecosystem that is part of the global ecosystem. The human body contains not just human cells, but also viruses, Bacteria, Archaea and Eukarya (protozoa, yeasts, fungi and worms). The skin, mouth, mucosal surfaces, anus, genitals, lungs and even human milk contain their own microbiota [4-9]. Moreover, maternal transmission of some microbes occurs *in utero*, which contradicts the former sterile-womb paradigm [8]. Even though viruses are usually thought of as being bad for human health, those that infect Bacteria (bacteriophages) help control the populations of various species of potentially harmful Bacteria. Moreover, viral infections can alter human immunity in subtle ways, leaving an indelible footprint on the immune network [9]. So, the holistic view of health that comes from systems thinking must include the microbiome. The goal of this paper is to give examples of this and help explain why the concept of a deep ecology should be extended to the human body and the microorganisms that are an essential part of it.

Human eukaryotic cells provide only a small portion of the DNA in the human body. Viruses and Bacteria provide much more DNA and have essential roles in the human body.

This was revealed in detail by the Human Microbiome Project, or HMP, as well as the European MetaHIT and the Eldermet Project [10-13]. The goals of the HMP were to sample, determine and quantify all human-associated microbial life. The European MetaHIT is determining the metagenomics of the human intestinal tract. The Eldermet Project is defining the microbial composition that is associated with aging. These three projects found that human-associated microbiota contains at least 40 000 bacterial strains in 1800 genera [12]. They contain at least 9.9 million non-human genes and about 500 times the number of protein-coding genes than human eukaryotic cells. Moreover, the approximately 100 trillion bacterial cells in the gastrointestinal tract (GIT) have a mass of 1 - 2 kg in an adult body. This is comparable to the weight of the adult human brain [12]. Even though the lungs and human milk were not part of the original HMP because they were thought to be germ-free, we now know that they do contain many Bacteria (or germs) [6,15]. Also, about half of the nucleotides in the human genome are retrotransposons that share a homology with retroviruses [15]. They can disrupt the expression of specific genes and are biased towards regions of where DNA is hypomethylated. L1 retrotransposons are active in the hippocampus and caudate nucleus in the human brain [15] and may account for much of the differences that are seen in so-called identical twins (actually, monozygotic twins). Retrotransposons are also important in generating new neurons throughout life in the hippocampus. L1 retrotransposons are also used in the developing human brain, in which new neurons are constantly being made. Like all plants and animals, we are just a small part of Gaia, which is mostly a viral and bacterial world [16]. When we think of ourselves as ecosystems, new insights and terminology emerge. We can be thought of as "super organisms" or holobionts with a hologenome [17]. The hologenome is the sum of all the genetic information of the host, its viruses and all its microorganisms [17].

Nested within the human body is the ecosystem that comprises the gut microbiome. It is like an organ in the neuroendocrine system. The roles it plays in various diseases are essential parts of the pillars of P4 medicine – prediction, prevention, personalized and participatory activities [18]. The goal is for researchers to be able to predict which group of people (cohort) is most likely to benefit from treatment with new drugs in clinical trials – based in part on the composition of their microbiomes. Researchers can communicate with patients to let them know how to modify their diets to correct dysbiosis (an imbalance) in their microbiomes and discuss the possible risks and benefits of antibiotic therapy. The advice will be personalized to fit the overall needs of the patient. It will be participatory in that patients and their caregivers will participate in the changes to diet, therapies and/or behavior that will be needed to either maintain a good healthy microbiome, or correct any problems that emerge.

This new concept of the deep ecology of the human biology expands our understanding of microbiology. The germ theory of disease stated that many diseases were caused by germs, that became known as microorganisms or Bacteria [19]. Reductionist thinking led scientists in the 20th century to believe that every organism contained its own genome (one genome-one organism hypothesis). However, we now understand that microbial symbiosis is an essential part of evolution, development and physiology [19]. Symbiosis is the close association of organisms. It can be either beneficial to just one organism (commensalism), both organisms (mutualism) or harmful to one

(parasitism). Note that symbiosis should not be confused with synbiotics, which is a mixture of prebiotic and probiotic Bacteria. In any case, the many diverse interactions between trillions of microbes and the human host that exists today are the result of a long evolutionary history. This is supported by DNA sequencing [16]. In the early 1970s, phylogenic relationships were discovered based on similarities in the DNA base sequence [20]. Biologists soon realized that all organisms share a deep evolutionary history that was described by the metaphor called the tree of life [16,20].

However, the rhizome of life is probably a better metaphor than the tree of life [21]. That is, DNA in all species is actually a mosaic of gene sequences with a variety of origins. Genomes are collections of genes with different evolutionary histories that are not well-represented by a single tree of life. At the same time, many genes have several different origins due to recombination. Bacteria and Archaea routinely transfer genes laterally from one species to another. Pieces of viral DNA and RNA may be the sources of retrotransposons that make our human brains so much different than that of other primates [22,23]. So, we are changing the way we think about the origins of life and its diversity.

We now know that there is a strong interdependence between complex multicellular organisms and their associated microbes [16,24]. Most life forms share about one-third of their genes, many of which encode enzymes that are part of central metabolic pathways [2]. In addition, many animal genes are homologs of bacterial genes. Most were derived by descent, but there was also gene transfer from Bacteria, Archaea and even other Eukarya [2,25]. That is, about 37% of the 23,000 genes in human eukaryotic cells have homologs in the Bacteria and Archaea, while another 28% originated in unicellular eukaryotes. Some of these homologous genes code for proteins that enable signaling between extant animals and Bacteria. At the same time, Bacteria communicate with each other to form biofilms and plaques while balancing their abundance by quorum sensing.

Moreover, a host can expand its metabolism by using part of the vast collection of bacterial genes within it. Bacteria in the gut can metabolize complex carbohydrates to produce short chain fatty acids (SCFAs), such as acetic and butyric acids. SCFAs affect the amount of abdominal fat that is in the host, as well as the concentrations of hormones that help control the appetite. So, the gut microbiome responds to the diet of the host over both daily and evolutionary time scales. This gives the host enough flexibility to digest many more biomolecules and cope with changes in their diet. For example, the gut microbiome of people who consume the typical American fast food diet is quite different than that of people who don't consume so much saturated and trans fats or simple sugars [16].

Gut microbiome and the enteric nervous system (ENS)

The viruses, Bacteria and other microorganisms that extend from the esophagus to the lower intestines are part of a microbiota-gut-brain axis. The gut microbiome has been described as a second brain, our personal oncologist, and an essential part of our endocrine, immune and nervous systems (or networks) [26-28]. The average adult human intestine contains 10^{13} to 10^{14} Bacteria, the vast majority of which belong to the phyla Firmicutes and Bacteroidetes, even though *E. coli* in the Proteobacteria phylum are the best studied and most easily cultured outside the body [29,30].

The microbiota of most adults has been assigned to three predominant variants, or enterotypes [29,31]. They have different amounts of three different dominant genera: *Bacteroides*, *Prevotella* and *Ruminococcus*. The majority of the prokaryotes in human intestines are in the phyla Firmicutes (including the genera *Clostridium*, *Enterococcus*, *Lactobacillus* and *Ruminococcus*) and Bacteroidetes (including the genera *Bacteroides* and *Prevotella* in proportions partly determined by diet). The relative abundance of these phyla and genera are the basis for classifying the human gut microbiome into three enterotypes: (1) abundant *Bacteroides*; (2) few *Bacteroides* but abundant *Prevotella*; and (3) an abundance of *Ruminococcus*. Each of these genera has a different function in nutrition and metabolism. Their relative abundance can be affected by diet. The enterotype dominated by *Bacteroides* occurs mostly when people consume relatively large amounts of protein and animal fats. The *Prevotella* enterotype is linked to carbohydrate metabolism and a vegetarian diet [29,31]. The enterotypes do not correlate with age, sex, nationality or body mass index (BMI) [29]. However, many researchers feel that the concept of enterotypes is an over-simplification. That is, there is a gradient of species' functionality with a core microbiome at the gene rather than at

the organismal lineage level. Instead of a core group of species, we all share a core group of microbiome functions. However, obese people may display different patterns of gut microbes than the non-obese, but share a core group of functions. Changes in this core set of genes may affect one's health. On the other hand, it can be difficult to tell whether changes in one's microbiome when certain diseases emerge are causes or symptoms of the disease [29].

Some species of Firmicutes and Bacteriodetes can ferment dietary fiber to produce butyrate [30]. At the same time, some species of Bacteriodetes can degrade polysaccharides. There are also some Actinobacteria (*Bifidobacterium colinsella*) and Melainabacteria that can produce essential vitamins. Deferrobacteres degrade iron. Verrucomicrobia can degrade mucin and decrease inflammation, while increasing the production of butyrate and making the mucus layer thicker. There are also methanogenic Archaea that convert hydrogen gas to methane [30].

The bacterial content of the gastrointestinal tract (GIT) varies along its length [29]. It ranges from a low diversity and number in the stomach to a wide diversity and high number in the large intestine. In the adult distal colon, there are about 1100 prevalent species, with at least 160 such species per individual. There is much inter-individual variability in the composition of the gut microbiota. There is a core group of > 50 taxa in nearly half of the human population [29]. There is a bimodal distribution of Bacteria in the gut microbiome [32]. Some people have less biodiversity in their gut microbiomes (known as low gene count (LGC)) than others (known as high gene count (HGC)). The LGC microbiota tends to be dominated by *Bacteroides* species and have fewer butyrate-producing Firmicutes. LGC people tend to have a higher incidence of obesity and metabolic syndrome. Furthermore, obese people with an LGC microbiota who switched to a controlled weight-loss diet showed an increase in the diversity of their gut microbiota. It approached that of a HGC community. Thus, diet can have a major impact on the composition of the gut microbiota. For example, changes in carbohydrate intake mostly affect Firmicutes and Actinobacteria. Weight loss diets that involve low carbohydrate consumption can cause a decrease in Firmicutes and Actinobacteria phyla that make butyrate. There are also important changes in the composition of the gut microbiota when one switches between extreme plant-based diets (that contained high levels of fiber and low levels of fat and protein) and animal-based diets (that contained no fiber and had high levels of fat and protein). The abundance of Bacteroidetes (such as *Bacteroides* and *Alistipes* species) and *Bilophila wadsworthia* increased, and several members of the Firmicutes decreased in the animal-based diet. One's long-term dietary habits also affect the composition of the gut microbiota. For example, people with a high proportion of *Prevotella* species tend to consume more fiber, while *Bacteroides* species are more abundant in people who consume high amounts of protein and fat. So, within the Bacteroidetes phylum, *Prevotella* species are better able to digest dietary fiber than *Bacteroides* species [32].

There is an extensive communication network among different microbes and between microbes and human (eukaryotic) cells. Commensal and pathogenic Bacteria interact with the central, autonomic and enteric nervous systems (CNS, ANS and ENS, respectively), as well as the hypothalamic-pituitary-adrenal (HPA) axis [33]. These interactions form the gut-brain axis (GBA). The interactions go both ways in a bidirectional network of communication. This network connects the emotional and cognitive centers of the brain with peripheral intestinal functions through neural, endocrine, immune, and humoral links. These interactions contribute to both health and disease [34]. For example, neurotoxins produced by *Clostridium* species can stop neurotransmission to or from neurons, producing the characteristic paralyses of botulism and tetanus. Gut Bacteria produce biochemicals that act on enteric neurons to influence gastrointestinal motility, and metabolites that alter neural circuits, autonomic function, and higher-order brain function and behavior. The intrinsic neurons in the gut make up the ENS, which forms a complete sensorimotor reflex circuit. It contains intrinsic primary afferent neuron, interneurons and motor neurons that are within the wall of the gut. These enteric neurons play critical roles in regulating gut motility and peristalsis. There are also extrinsic neurons that relay sensory information from the gut to the CNS. Neurons in the nodose/jugular ganglia mediate the sensation of nutrients, nausea, appetite, and satiety. Neurons in the dorsal root ganglia (DRG) detect noxious stimuli and mediate pain. Biochemicals that are produced within the gut lumen influence the intrinsic enteric neurons in the ENS through directly and indirectly. For direct actions to occur, a biochemical must pass through the epithelial barrier to access the nerve endings of enteric sensory neurons, which are in the connective and muscular tissue immediately beneath the intestinal epithelium. In a healthy gut with an intact epithelial

barrier, bacterial products must pass through the barrier by active or inactive transport or through transcytosis. In an unhealthy gut in which the epithelial barrier is damaged by inflammation (leaky gut), both Bacteria and their products can undergo paracellular translocation between cells whose tight junctions are no longer intact [34].

There are also indirect interactions between the Bacteria in the lumen and the ENS [34]. This occurs through endocrine or immune cells in the gut. Enteroendocrine cells in the epithelium can release paracrine signals that are detected by sensory neurons that innervate the gut. One set of enteroendocrine cells called enterochromaffin cells (ECs) can transduce signals that convert bacterial stimuli into downstream neuronal responses. Enteric neurons also express toll-like receptors (TLRs) that detect bacterial pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharides (LPS) that are produced by gram-negative Bacteria. They are detected by TLR4. Enteric neurons activated by TLR-4 regulate neuronal survival and gut motility. In addition, TLR2 can detect peptidoglycans and lipoproteins from gram-positive Bacteria. TLR2 signaling affects the structure of the ENS, as well as intestinal contractility [34]. So, there is extensive communication among different microbes and between microbes and human (eukaryotic) cells in the ENS, CNS and microbiota-gut-brain axis.

Conclusion

In conclusion, it is proposed that the concept of a deep ecology [2] should be expanded to include a deep human ecology. That is, the human body contains not just human cells, but also viruses, Bacteria, Archaea and Eukarya (protozoa, yeasts, fungi and worms). The skin, mouth, mucosal surfaces, anus, genitals, lungs and even human milk contain their own microbiota. Moreover, maternal transmission of some microbes occurs *in utero*, which contradicts the former sterile-womb paradigm. Even though viruses are usually thought of as being bad for human health, those that infect Bacteria (bacteriophages) help control the populations of various species of Bacteria. Moreover, viral infections can alter human immunity in subtle ways, leaving an indelible footprint on the immune network. So, the holistic view of health that comes from systems thinking must include the microbiome.

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Conflict of Interest

The author declares that there is no conflict of interest.

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