• SPECIAL ARTICLE •

Homo Sapiens as Physician and Patient: a View from Darwinian Medicine

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Medicine's cardinal diagnostic and therapeutic resource is the clinical encounter. Over the last two centuries and particularly over the last five decades the function of the clinical encounter has been eroded to the point of near irrelevance because of the atomized and atomizing influence of technology and microspecialization. Meanwhile, over the past five decades the exceptionalist view of Homo sapiens inherent in the social and religious traditions of the West has similarly undergone radical changes. H. sapiens is now best understood as a microecosystem integrated into a much broader ecosystem: the biosphere. That human microecosystem is composed of constituents derived from the archaeal, bacterial, and eukaryan domains via endosymbiotic, commensalistic and mutualistic interactions. This amalgamation of 100 trillion cells and viral elements is regulated by a composite genome aggregated over the 3.8 billion years of evolutionary history of organic life. No component of H. sapiens or its genome can be identified as irreducibly and exclusively human. H. sapiens' humanity is an emergent property of the microecosystem. Ironically as H. sapiens is viewed by evolutionary science in a highly integrated manner medicine approaches it as a balkanized, deaggregated entity through the eye of 150 different specialties. To effectively address the needs of H sapiens in its role as patient by the same species in its role as physician the disparate views must be harmonized. Here I review some conceptual elements that would assist a physician in addressing the needs of the patient in integrum, as a microecosystem, by the former address the latter as a historical gestalt being. The optimal way to recover the harmony between patient and physician is through a revitalization of the clinical encounter via an ecological and Darwinian epistemology. [*P R Health Sci J 2013;3:113-123*]

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One of the more lasting attempts at establishing the essence of being human is the one provided by Aristotle: a rational (1), communal (2) (i.e., political) and imaginative animal (3). This is unarguably the most enduring definition to date and was employed by Carolus Linnaeus when he opted for the binomial designation *Homo sapiens* for our species (4). Medicine's characterization of a human being antedates this and all such definitions. From the outset its object defined medicine: the human being, but medicine has never attempted to define its subject's humanness. This is so because by its very nature medicine deals with particulars, not universals (5). Despite the conceptual dimness the object and center of gravity of medicine from the earliest Shamanist to Renaissance medicine was the patient *qua* human, not any particular altered aspect or component of the patient (6).

The healing philosophy of ancient Greek medicine stated that Man (*H. sapiens*) is a product and a part of nature. Health is living in harmony with nature, and disease results when harmony is perturbed. The core of the physician-patient relationship consisted in the collaborative restoration of the lost harmony (7). The cause of disease could be natural, as it was for Hippocrates, Galen, Dioscorides, and Avicenna, or the result of fate or divine displeasure. The latter view is historically exemplified by the approach to healing of the followers of the cult of Asklepios (8), or medieval monastic physicians with their *Christus Medicus* (9). Whether naturalistic or divine in origin for these schools of thought the ultimate locus of disease was the human being *in integrum*. This view began to wane during the 16th century. The anatomical works of Andreas Vesalius revealed *H. sapiens* not as a seamless totality but as an assembly –a *Fabrica*- of parts (10). The year 1543 is when the human began to be understood as an ensemble of organs and tissues thereby losing its wholeness, at least to medicine. A century later the disassembly project was advanced by Robert Hooke's

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discovery of cells as the ultimate constituents of all organisms (11). In 1761 Giovanni Battista Morgagni moved the project along when he sought and found the seat of disease in those very tissues and organs, as presented in his *De Sedibus et Causis Morborum* (12). The "seats and causes" of disease drifted further away from the human into the organs and from there into cells as Rudolf Virchow posited the latter as the locus of disease (13). Louis Pasteur ushered in exogenous natural disease causation. This concept matured by the end of the 19th century into the germ theory of disease. The locus of disease: the cell; the cause: microbes. The physician distanced itself even further from the patient with the latter becoming a battleground and the former a warrior against microbes. The 19th century, steeped in its conquering impetus, lent the metaphors for the new medicine: invaders to be repulsed with magic bullets (Zauberkugel) (14). And the 20th century with its metaphors of killer lymphocytes, attack sequences and wars against cancer ushered in the culmination of the patient as backdrop. Physicians had also begun to distance themselves from patients physically when an instrument was developed that greatly expanded the means with which to better discern signs: the invention by Rene Laënnec of the stethoscope and his publication of the presciently titled *De L'auscultation Mediate* (On Mediate Auscultation). For the first time there was an instrument mediating between the patient and the physician physically distancing one from the other (15). Today, the locus of disease lies amidst atoms and molecules. This coupled to the prevailing fragmentation of medicine into myriad specialties and subspecialties has led to an even greater balkanization of the patient further undermining the therapeutic value of the medical encounter (16). This has occurred at the same time that today's developments in science have ushered in a renewed *in integrum* view of *H. sapiens*.

The coalescence of late 20th and ongoing 21st century developments in the life sciences, have led to a return to a more comprehensive approach to understanding the natural world and *H. sapiens* as an integral part of it (17). Several hitherto dominant concepts have been gradually rendered insufficient to explain the natural world *H. sapiens'* locus in nature. Sigmund Freud declared that the relocation of the Earth among the planets, led by Copernicus in 1543, displaced man from universal centrality. Darwin, in 1859, displaced *H sapiens* from special creation to being one among the multifarious forms of life. Freud himself delivered the third blow in the naturalization of man (18). The reconceptualization of the universe, Earth, and life on Earth as dynamic entities providing the building blocks for life began to erode the reductionist approach to our understanding of the natural world (19). Such an approach had been initiated by Aristotle (20). Reductionism has been an extremely fruitful heuristic but limitations emerged as it became evident that nature operates at multiple levels of interacting complexity impervious to reductionist analysis, as Aristotle had also already noted (21). Life, a still inadequately defined concept, appears to be an emergent property of interacting inanimate entities (22) much as mind is an emergent property sprouting from the electrochemistry of interacting cerebral and extra cerebral somatic components (23). Emergent structures or properties are not reducible to individual components. They are the products of interactions exquisitely susceptible to fluctuations in initial conditions. As an emergent structure *H. sapiens* is now understood as a far-from-equilibrium self-organizing dissipative composite structure (24).

The evolution of organisms seems to show a temporal proclivity for increasing complexity (25), although the simplest organisms, -prokaryotes and viruses- have always been dominant. They comprise up to one-third or more of the Earth's biomass and occupy every available niche, from the simplest –other viruses (26)- to the most complex. *H sapiens* is comprised of 10 x 10^{13} cells of which 10% are eukaryotes and 90% archaea and eubacteria (27). In addition the virome accounts for *ca.* 10% of *H sapiens'* genome (28). The several populations exchange information via multiple communication channels (29). Information is essential to life as the intergenerational continuum though it is clear that since the first form of persistent life emerged (the Last Universal Common Ancestor or LUCA) both information and structure participate in the generational progression (30).

Albert Bernhard Frank in 1877 introduced a new biological concept: "We must bring all the cases where two different species live on or in one another under a comprehensive concept … for which the term *Symbiotismus* is to be recommended" (31) initially employing the term with lichens and mycorrhizae (32). Heinrich Anton de Bary introduced the modern term in *"Die Erscheinung der Symbiose"* [*"The Phenomenon of Symbiosis"*] in 1879 (33). The concept was expanded with added speciating agency, in 1909, as *symbiogenesis* by Konstantin Mereschkowsky, who posited "the origin of [new] organisms through the association or combination of two or more beings that enter in symbiosis" as a substitute for speciation via Darwin's evolutionary theory (34). In 1926 he proposed that chloroplasts originated from cyanobacteria captured by a protozoan (35). In the 1920s Ivan Wallin in his book *"Symbionticism and the Origins of Species"* (36) extended the concept of symbiogenesis to mitochondria, a concept reformulated in 1966 in the context of Darwinian evolution by Lynn Margulis as her modern *Endosymbiotic Theory* in: "Life did not take over the globe by combat, but by networking" (37).

The concept of living organisms as cooperative entities devalued the idea prevailing up to the 19th century that all species, particularly *H. sapiens*, are products of a special creation. By the late 19th century it was becoming apparent that all organisms were the product of descent with modifications upon which natural selection operated. However, even though in the 20th century this idea became dominant there persisted from the previous century an inclination to think of evolution as linear: a progression of an ever better-adapted, "superior" species replacing or surpassing "inferior" ones, a Victorian view splendidly portrayed in Ernst von Haeckel's "Tree of Life" with Man perched at its uppermost branch (38). With the advent of genetic technologies it has become evident that organisms like *H. sapiens* are products of evolution coupled to a reticulate genetic collaboration between and amongst antecessors (archaea, prokaryotes, eukaryotes, and viruses). *H. sapiens* is not a monogenomic organism. It is inhabited by a multitude of essential endo- and exosymbionts without which its natural existence would be unsustainable. Furthermore, *H sapiens* continues to evolve (39).

Endogenous and exogenous symbionts

Viral elements and microbial symbionts have co-evolved with their multicellular hosts since the latter's emergence during the early Ediacaran period (40, 41). Thus the narrative of the assembly of the human genome extends into deep evolutionary time to the origin of Animalia. Phyla Cnidaria (42) and Porifera (43), the oldest representatives of Animalia harbor species-specific microbes essential for their reciprocal survival. Viruses and their cognates are found dispersed through all cellular genomes (44). The idea is reemerging that RNA and DNA virus antedate cellular life as originally proposed by Felix D'Herelle (45). This includes viruses infecting viruses (46). Many viruses have become part of their host species' genetic endowment, including *H. sapiens*, via a process termed endogenization, thus becoming endogenous viral elements (EVE) (47). EVEs are predominantly derived from retroviruses (48). Such elements are the result of the chromosomal integration of copies of viral RNA into the host germ cells genome from where they spread vertically. Integration of the viral genome into the host is a required step in their replication strategy, and if they successfully integrate into the host germ line they are assured vertical transmission along with the host. As such they have participated and are probably ongoing participants in the evolution of *H. sapiens* (49).

Other exogenous genomic components include transposable elements (TE) found in the genomes of all organisms (50). They migrate within and between them transferring laterally between the three domains of life. The composite construction of genomes has come via genealogical transmission and lateral exchanges of genetic material making every genome chimeric. Eukaryotic genomes contain millions of copies of TEs and other such sequences. They are the major genomic component of most plant species. Humans harbor three million of them in their genome where they amount to at least 45% (51) and perhaps up to two-thirds of the total human genome (52). Some have ancestries dating back ca.100 million years (53). Their ubiquity across the three domains of life is due to their deep evolutionary lineage reason for which they are considered to play an important role in the origin and evolution of all organisms (54). Their transfer within and between genomes has lead evolution having a reticulate pattern. It is currently accepted that these multifarious mobile elements, once collectively considered "junk," exert a profound influence on genomic structure and function by augmenting the coding and non-coding genetic repertoire of their hosts (55). In *H. sapiens* they have played a role in its evolution (56) and are active participants in the genesis of certain diseases (57).

In addition to TEs there exist other migrating informational macromolecules such as the incorporation into an organism of free extracellular nucleic acids and interspecies hybridization. Extracellular nucleic acids are ubiquitous being found free in the environment (58). Such extracellular DNA and RNA play important biological roles in microbial communities and in higher organisms (59). They are found in *H. sapiens* under normal circumstances (60) and in some diseases (61). Cells have mechanisms for rejecting extraneous nucleic acids, nevertheless it has been demonstrated that human skin cells will incorporate and express naked mRNA (62). A particularly important subset of extracellular nucleic acids is the small non-coding microRNAs (miRNA). miRNAs are short molecules that average 22 nucleotides and function as post-transcriptional regulators that bind to complementary sequences on target mRNAs usually resulting in translational repression and gene silencing. They can be transferred between cells within the same organism (63). A salient aspect of the broader view of *H. sapiens* I posit lies with the fact that we are beginning to encounter new interindividual and interspecies exchanges that are as significant as they were unexpected. Circulating placental miRNA and feto-maternal horizontal transfer of miRNAs has been detected in pregnancy (64). Human breast milk contains and exports to the infant at least 602 unique miRNAs originating from 452 miRNA precursors enclosed in maternal exosomes (65). These miRNAs have a regulatory role in the development of the infant's defense system (66). Coupled to transfer of breast milk microbiota this lateral transfer of mobile genetic elements amounts to a phenotype transfer (67). It should be noted that organisms with genomes sequestered within germ cells are generally less amenable to lateral transfer (68) so ubiquitous in bacteria and archaea (69), except when dealing with the genomic contributions of endosymbionts (70).

Trans-kingdom or inter-kingdom signaling represents a new stratum of interaction between organisms. Inter-kingdom transfer of miRNAs has been described for *Oryza sativa L.* (Asian rice). Dietary genetic material can survive digestion, circulate, and modulates gene expression (71). Ingested *O. sativa L.* miRNA enters mammalian blood and interacts with the human/mouse low-density lipoprotein receptor adapter protein 1 (LDLRAP1) mRNA, thereby inhibiting LDLRAP1 expression thus causing reduced LDL removal from plasma (72). These informational molecules build up in the serum providing exogenous regulatory signals for gene expression in a sequence-specific manner (73). miRNAs laterally transferred function as active signaling molecules conveying information across species, genera, and even kingdoms.

Transfer of mobile genetic elements between cells of an individual or between members of the same species has been demonstrated. Such transfer from exogenous microorganisms to microbiota in *H. sapiens* can generate new phenotypes. The human microbiota's diversity stems from environmental and host factors. *H. sapiens'* genomes are >99% homologous, but not so the microbial species and genes that comprise individual microbiota even in the case of twins (74). Microbiota must adapt to changes in food staples, preparation methods, and host migration into areas with novel foods (75). More recently the generalized use of antibiotics in animal husbandry and the exchanges of populations due to modern transportation, famines, wars, and migration have increased the adaptive pressures upon the resident microbiota. An example of such has emerged among the Japanese that couples lateral gene transfer (LGT), microbial diversity, and culinary culture due to their use of algae as a staple. Algae provide some key nutrients but their complex polysaccharides are indigestible to *H. sapiens*. It has been demonstrated that the resident oceanic algal bacterium *Zobellia galactanivoran* has transferred genes for carbohydrate-active enzymes to the symbiotic intestinal bacterium *Bacteroides plebeius* resident in Japanese making possible the digestion of algal polysaccharides through the enzymatic activity of the genetically transformed *B. plebeius* (76). The host and its microbiome derive nutritive value from otherwise indigestible algae. Other bacteria were integrated into the prokaryotic ancestors of eukaryotic cells as endosymbiont-derived organelles followed by extensive LGT. This event led to the emergence of eukarya following genomic integration between the host cell and the newly incorporated symbionts. During the last 2 billion years of shared evolution between alpha-proteobacteria and eukaryota 90% of the original alpha-proteobacterial genes have been transposed into the nucleus. LGT within archaea and bacteria as well as between them was and continues to be prevalent (77). Other than the endosymbiotical LGT there are no credible cases of bacterial LGT into the genome of *H. sapiens* (78).

The oldest representatives of Animalia, phyla Cnidaria (79) and Porifera (80), and all metazoans thereafter harbor species-specific microbes essential for their reciprocal survival. Furthermore microbial symbionts co-evolved with their multicellular hosts since the latter's emergence during the early Ediacaran period (ca. 635-600 million years ago – mya-), a process preceded by endosymbiosis. The level of complexity this relationship has achieved is made evident by the recent discovery of nested symbioses coupled to lateral gene transfer (81). *H. sapiens* hosts multiple niches that harbor about 90 trillion non-germ line derived cells belonging to archaea and bacteria. These do not normally occupy intracellular spaces (as mitochondria do), but their genetic presence is let felt through their collective metabolism. The genus Homo and its commensal organisms have coevolved over two million years thus becoming reciprocally dependent (82, 83). The microbiota adjusts to varying environmental conditions like those brought about through human migration and food preferences by modifying species composition and population size. The effects of microbial metabolism in different somatic niches are coupled to the physiological imperatives of the niche (84). Symbiont contributions include structuring vascularity of the gut (85), digestion, and immune regulation (86), partaking of the pharmacokinetics of therapeutic agents (87) and anatomical and functional sculpting of brain structure and function (88). No metazoan entity, including *H. sapiens*, can survive in a natural state bereft of its symbionts: it either inherits or acquires them, or perishes (89).

Endo- and exosymbionts and behavior in *H. sapiens*

The definitory attribute of *H. sapiens* resides in its capacity for reasoning via symbolic representations of its surroundings and mental states of congeners. It is of importance to determine whether this attribute is the exclusive province of the germ line genome, or if is it distributed across the various groups of resident and transient genomes that have coalesced into *H. sapiens*. No known Animalia germ line genome is free of exogenous viral constituents. Endogenous retroviruses (ERVs) are derived from ancient germ line infections by endosymbiotic exogenous retroviruses (90), are an integral component of the germ cell line genome of every vertebrates and contribute to genome evolution (91). They replicate in Mendelian manner passing vertically into the genome of future generations. About 9% of the human genome consists of human endogenous retroviruses (HERV) residing as an integral part of *H sapiens'* germ line genome and this relationship extends into deep biological antiquity (92). HERVs are the viral equivalent of the microbial symbioses that gave rise to mitochondria (93). The exogenous retrovirus that gave rise to the HERV-W group entered the ancestral genome around 40 million years ago, i.e., prior to the emergence of the catarrhini clade (94). This endosymbiotic relationship has been conserved by natural selection throughout primate speciation (95). The Env protein of that HERV-W locus, named Syncytin-1, has been selected during evolution for contributing to fusion of cell membranes of trophoblasts to form syncytiotrophoblasts, which is an essential process during human placenta formation (96). The HERV-K group entered the human genome since the divergence of human and chimpanzee 6 mya, causing human genomic changes (97). They have coding capacity and potential clinical involvement. It encodes retroviral proteins that interact with cellular proteins such as promyelocytic leukemia zinc finger protein and might thus be involved in tumorgenesis (98). Not only *H. sapiens*, but the germ cell lineage of the sister species *H. neanderthalensis* and the Denisova hominins were reinfected multiple times by HERV- K (99).

HERVs affect the neurobiology of *H. sapiens* having been associated with neurological and neuropsychiatric disorders particularly schizophrenia (100), schizophrenia spectrum disorders, and bipolar disorder (101). HERV-W proteins are physiologically expressed in human cingulate gyrus and hippocampal neurons and this expression is altered in schizophrenia, major depression, and bipolar disorder (102). The hippocampus is a region that expresses abnormalities in these conditions, a region vulnerable to structural alterations due to changes in the intestinal microbiota, as highlighted below (103). This interaction is distinct from the host-pathogen interaction leading to neurobehavioral conditions as those provoked by agents such as *T. gondii*, cytomegalovirus, influenza, rubella, herpes viruses, *C. pneumoniae*, *H. pylori*, *C. neoformans*, and *Epstein-Barr virus* (104).

Just like the endogenous viral elements, components of the *H. sapiens'* microbiota have been found to participate in the assembly of its behavioral apparatus. Low proportions of Bifidobacterium, key biological markers of healthy breast-fed infants, as well as a low prevalence of gut Lactobacillus are associated to infant restlessness (105). It has been shown that commensal gut organisms participate in programming the sensitivity of the stress system, with stress being an acute threat to homeostasis (106). Germ-free (GF) animals show exaggerated hypothalamic-pituitary-adrenal axis (HPA) responses to psychological stress, which normalizes upon colonization by *Bifidobacterium infantis*. Normal anxiety responsiveness is restored to GF mice upon restitution of their intestinal microbiota (107). Stress provokes heightened gut permeability, allowing bacteria and their antigens to cross into the gut mucosa triggering an immune response which leads to enhanced HPA activity (108). Therefore host responses to stressful stimuli are modulated by the indigenous microbiota via alterations in gut function, innate and acquired immunity causing modification in host responses to environmental threats. In this manner the indigenous microbiota modulates how a host perceives and responds to environmental stresses (109).

Added to the viral effects gut microbiota also influences host structural neural development. Peripheral and central neural functions are influenced by microbial composition with some species having signal importance (110). Compared to normal mice GF mice show anatomical hippocampal alterations (111). This has long-term consequences on maturation and functioning of the brain which may emerge late in the host's life (112). Alterations are evidenced via modifications in the expression profiles of signaling pathways, neurotransmitter metabolism, and synaptic architecture contrasting mice having a native microbiota with GF mice (113). Restoration of microbiota equilibrium via administration to GF mice of *Lactobacillus* strains regulates emotional behavior and central neurotransmitter receptor expression (114). Similarly there is a reciprocal relation between the overall microbiota composition of *H. sapiens* and the function, gene expression, developmental programming, structure, and cognitive expression of its brain (115).

Hominin inheritance in *H. sapiens*

Just as through evolution numerous genomes and life forms coalesced to assemble even the simplest organisms, *H. sapiens* is the product of such a coalition of endogenous and exogenous genes, genomes, and organisms. The evolutionary line tracked back from the present to the cleavage of the *Pan* line runs for approximately six million years (116). As the genus *Pan* drifted away the occupants of the niche that led to the genus *Homo* underwent introgressive hybridization. The human and chimpanzee lineages initially diverged and then later exchanged genes before separating permanently (117). The most likely participant from the *Homo* lineage seems to have been *Sahelanthropus tchadensis* (118). Other archaic admixture scenarios have been posited (119) the next most distant being that between *H. erectus* and anatomically modern *H. sapiens* via an introgression event sited in Africa (120). It has been estimated that these introgressions occurred relatively recently during the Lower-Middle Pleistocene (ca. 0.126-0.781 Kya) (121). Further data stemming from the recovery of archaic *Homo* DNA strongly supports other hybridization events that contributed to the composite genome of modern humans. Paleogenomic data imply that during the Late Pleistocene (0.0117–0.126 Kya) in Eurasia there was interbreeding between *H. neanderthalensis* and anatomically modern *H. sapiens* (122), as well as between Denisovan hominins and *H. sapiens* (123). It has been posited that a resident human population in the Levantine region provided a fluid population that participated in these interbreeding events (124). These hybridization events are of signal importance for they endowed the initial migratory *H. sapiens* with human leukocyte antigens genes already primed for detection of hitherto unencountered antigens (125). The genotyping of *H. neanderthalensis* and Denisova hominins reveals functional archaic HLA alleles that have introgressed into modern Eurasian and Oceanian populations. These alleles comprise close to 50% of the HLA alleles of modern Eurasians (126). Between 4% and 6% of the genome and 90% of the HLA genes of Papua New Guinean and Bougainville Islander derives from a Denisovan population (127). Evidence of admixture between Denisova hominins and Australian Aborigines as well as with Negrito Mamanwa has also been identified (128). These genetic contributions towards the final assembly of *H. sapiens* are extant in the species. This species configured as a consortium genome and composite ecosystem with deep historical and biological roots now becomes both patient and physician.

Conclusion: The object of medicine redefined

And what does all this have to do with medicine and its future practitioners. Future physicians will have to probe deeper that ever into the structure and function of *H. sapiens* in search of greater diagnostic and therapeutic accuracy. Epistemically this has been accomplished to date employing unyielding clinical reductionism. Mechanistic thinking of the reductionist variety is not robust enough to deal with non-linear, chaos driven complex systems, let alone with a consortium organism (metaorganism (129), holobiont (130)) that is composed of sectors that evolve at markedly different time rates over time frames encompassing differences of multiple orders of magnitude. Neither the patient nor medicine is reducible to knobs, switches, and gauges. This emerging reality requires of a new medical pedagogy that educates physicians to view patients from a systems point of view. During recent history physicians have dissociated themselves from the messiness inherent to the clinical history, fraught with the perils of human subjectivity. This view has been advanced via the fragmentation of the patient, each fragment explored by one of over 165 different types of medical specialists and subspecialists. The emergence of modern genomics has added impetus to this process of fragmentation of the patient as well as the practitioners. This development alienates the participants in the clinical encounter while paradoxically cloaking over this distancing with the discourse of personalized medicine. In this new acceptation of medicine the patient communicates its distress in an atomized manner through algorithms and machines and consequently receiving fragmented care. This view of medicine must be removed to the realm of Foucault's *regard medical* (131) with its requirement for absolute, detached objectivity through decomposing the human into body, action, behavior, and discourse. The biology of *H. sapiens*, as that of any other organism, cannot continue being thought off as grounded on the old dogma of lineal correspondence between genes and phenotype; of pretending that the human embodied in *H. sapiens* is defined solely by its germ line genes which comprise but a miniscule portion of it as a consortium organism. The physical identity of the genes as well as that of the "individual" has lost its previously conceived clear boundaries and concrete structure. A single locus can harbor several messages at the same time and phenotypically express them separately as arrays of norm of reaction diversity and thus be subjected to multidimensional selective pressures. At the cellular level genes operate in the midst of a dense mesh of networks of interacting nucleic acids, proteins, other biomolecules and myriad symbionts emerging or acquired from internal as well as exogenous sources. These networks, characterized by modularity and robustness, operate as hierarchically tiered multi-scale systems. Linear relations are not possible under such circumstances. The flow of information is multidimensional, iterative, and recursive. The various components of the total genome such as viruses, transposable elements, non-coding RNAs, and cells (with their constituent endosymbionts and epigenetically guided differentiation) as well as symbionts (with their epigenetic sculpting and pruning along and across their genealogy) are interactively charged with responding in an organized, reciprocating manner to environmental changes including behavioral adjustments. *H. sapiens* is fine-tuned by the environment while in response it modifies its niche via reciprocal interactions: a Darwinian dialectic. It is evident that the information required for the assembly of H. sapiens is not exclusively inherent and internal to the organism; it is not mere body, action, behavior, and discourse. It comes from endogenous and exogenous sources; from ancient and extant participants such as endosymbionts up to the ever-changing resident microbiota. It is a network where vertical and horizontal heredity meshes. The resulting norm of reaction is then sieved by natural selection across biological space and time. Upcoming physicians need be educated in the macro- and microecologic maladjustments that are the raw material for disease.

I am here presenting the human not from the mere perspective of the human-in-an-ecosystem but from the perspective of the human-as-ecosystem. Future physicians would do well to view patients from the latter perspective: *H. sapiens* is a symbiotic consortium of atavistic and extant components. This consortium conditions and regulates its evolution, development, and behavior as well as its interactions with living and non-living forms: it unfolds the norm of reaction of *H. sapiens*-as-ecosystem. To define *H. sapiens* employing the popularly termed "human genome" is to leave out millions of essential as well as transient components that are fundamental to its functioning and evolving. *H. sapiens* is not a categorically genetically discernible organism, a view dispelled by Darwinian evolutionary gradualism. It is a metaorganism or holobiont that blends back into its ancestry as well as into the terrestrial ecosystem. This complex conformation has generated the unfolding species it is until its eventual extinction (132).

Physicians of the future must be cognizant that the many perturbations that befall *H. sapiens* – e.g., infectious, metabolic, proliferative, degenerative, behavioral, complex - cannot be understood absent exploring the dynamic continuum that mediates antagonism and cooperation amongst its constituents. It is also evident that *H. sapiens* is composed of populations with disparate evolutionary time-scales down to the quantum level (133). *H. sapiens*, because of its capacity for cultural evolution (e.g., antibiotics) can have an almost immediate impact upon symbionts as well as the exogenous ecosystem. Thus humans evolve biologically at a slower rate than all its resident constituents while it evolves almost instantly culturally. This begins to define the new object of medicine and physicians: the patient as a metaorganism with all its components in synergistic interdependence. The availability for upcoming physicians of novel high-throughput sequencing methods will enable them to dissect the mechanisms that control the interdependent associations inherent to our consortium genome and its attendant microecosystem. A physician so empowered will be able to examine the co-evolved multi-species relationships that connect genomes, phenotypes, ecosystems, and the evolutionary forces that have shaped them. Disease will cease to be a "thing" that happens within cells of organs of an individual. Disease will be understood as a damaging perturbation of *H. sapiens*-as-ecosystem.

This influence of host/microbiome interactions playing out on a scenario of a complex genomic assemblage garnered over millennia extends into deep aspects of brain structure and its behavioral output. The endogenization of novel constituents through time, (e.g., beneficial microbes, endogenized viruses) has contributed to the evolution of individual, social, and group behavior, which facilitates the horizontal and vertical transmission of endogenous and exogenous symbionts, pathogens, and units of cultural transmission to new hosts. These host constituents anatomically and functionally mark the very locus of rationality which is the defining attribute of *H. sapiens* since the Pleistocene. Far from being the Cartesian automaton envisioned through classical genetics and quotidian medicine *H. sapiens* like all other organisms is the end-product of the germ-line information and environmentally acquired information dialectic; between the myriad organisms cohabiting within and outside the host; between resident information and the environment. Accurate diagnostic and therapeutic interventions require a deep knowledge of this reality in order to achieve effective individualized care.

For the physician the entry point to Man in a medical encounter is the clinical history. Through it the resultant patient-physician relation is established so as to attain the therapeutic effect accrued through the encounter. This diagnostic and therapeutic instrument has been foundering for decades. Medicine has been the only realm of biology to have eschewed evolution as a conceptual and operational tool. Because of this lack medicine is still operating under the obsolete ontology of the 19th and 20th centuries. There is an urgent need of establishing a new physician-patient relation that envelops what has been discussed. When this re-engagement finally occur the physician and the patient will again recover the lost proximity, and the patient the agency essential for a fruitful and enduring clinical outcome that has been eroded because of the balkanization of the medical encounter coupled to a misread human biology. Thus the objective of every physician: as a human to engage the human through a revitalized clinical encounter employing an ecological and Darwinian epistemology.

Resumen

El recurso diagnóstico y terapéutico cardinal de la medicina le es el encuentro clínico. Durante los pasados dos siglos y particularmente durante las pasadas cinco décadas este atributos del encuentro clínico han sido erosionados hasta acercarlo a la irrelevancia por la visión atomizada y atomizante de la tecnología y la microespecialización. Mientras tanto durante las pasadas cinco décadas la visión excepcionalista de *Homo sapiens* inherente a las tradiciones socioculturales de Occidente ha sufrido cambios igualmente radicales. Estos cambios han traído consigo una visión de *H. sapiens* como un microecosistema integrado a un amplio ecosistema. El microecosistema humano está compuesto por constituyentes de los dominios bacteria, arquea y eucariota organizado mediante interacciones endosimbióticas, comensalistas y mutualistas. Esta amalgama de 100 trillones de células, mas componentes virales, es regulada por un genoma compuesto y que ha ido agregándose durante los 3.8 billones de años de historia evolutiva de la vida orgánica. No existe componente alguno de *H. sapiens* o de su genoma que pueda identificarse como irreducible y exclusivamente humano. La humanidad de *H. sapiens* es una propiedad emergente del microecosistema. Es irónico que mientras las ciencias naturales entienden a *H. sapiens* como un ente altamente integrado la medicina le aborda en forma balcanizada y desagregada por vía de 150 especialidades medicas diferentes. Para abordar correctamente a *H. sapiens* am su rol de paciente por la misma especie en su rol de medico estas dos visiones antónimas requieren de ser armonizadas. Aquí reviso algunos elementos conceptuales que han de ser de utilidad al médico atender las necesidades de su paciente *in integrum*, como microecosistema, para que el primero aborde a este último como un ente histórico-gestáltico. La manera óptima de recobrar la armonía entre el paciente y su médico es mediante la revitalización del encuentro clínico por vía de una epistemología Darwiniana y ecológica.

Glossary

1. *Agency (Phil.)*: The capacity of a patient (agent) for autonomy over his own thought processes, motivation, and action being the latter the capacity of a patient (agent) to act in a world, i.e., to generate causal processes. Self-generated activities lie at the very heart of causal processes. They not only underwrite the import and valence of external influences, but they also operate as proximal elements of motivation and action. Agency is a uniquely human characteristic.
2. *Animalia*: Eukaryotic and mostly multicellular heterotrophic organisms generally digesting food in an internal chamber. All members of Animalia are motile, even if only at certain life stages. An embryonic blastula stage is a characteristic exclusive to animals.
3. *Archaeal/archaea*: Any of the unicellular prokaryotic microorganisms that is genetically distinct from bacteria and eukaryotes, and often inhabiting extreme environments (e.g., halophiles -salt resistant-, methanogens –produce methane-, and thermophiles –heat tolerant). Archaea is one in the three-domain system of biological classification introduced by Carl Woese in 1990. The other two are Eukarya and Eubacteria.

4. *Asklepios*: the ancient Greek god of medicine and healing, worshiped by the Romans as Aesculapius.
5. *Ediacaran Period*: The time elapsed between ca. 635-542 million years ago (Mya) named after the Ediacara Hills of South Australia, being the last geological period of the Neoproterozoic Era (1,000 to 541Mya) and of the Proterozoic Eon (2.5 Bya-542.0 Mya), immediately preceding the Cambrian Period (541- 485Mya); (International Union of Geological Sciences nomenclature).
6. *Eubacteria*: Organisms lacking a membrane-enclosed nucleus, predominantly unicellular, with DNA in single circular chromosome, and have peptidoglycan on cell wall whenever present.
7. *Eukarya*: The biological domain whose members are characterized by being composed of cells having internal membrane bound structures. The membrane-bound structure that sets eukaryotic cells apart from prokaryotic cells is the nucleus, or nuclear envelope, within which the genetic material is carried.
8. *Genome*: The sum of an organism's hereditary information whether encoded as DNA or (as in viruses) RNA and includes all non-protein coding sequences.
9. *HERV*: Human endogenous retrovirus are proviruses comprising ca. 8% of the human genome. Almost all HERV genomes contain obviously inactivating mutations, and most are thought to be incapable of replication.
10. *HERV-K*: Type-K member of the Human Endogenous Retroviruses family. Among the various human endogenous retroviral families, the K series was the latest acquired by the human species and is the most complete and biologically active family. HERV-K expression has been detected in different types of tumors like the majority of dysplastic and normal naevi, as well as other tumors like sarcoma, lymphoma, bladder, and breast cancer.
11. *HERV-W*: Type-W member of the Human Endogenous Retroviruses family. Expressed in patients with recent onset of schizophrenia, multiple sclerosis, and other types of autoimmune diseases.
12. *Holobiont*: an organism and all of its associated symbiotic microorganisms, including parasites, mutualists, synergists, and commensalists (microbiome) evolved as a result of symbiopoiesis, or codevelopment of the host and symbionts.
13. *Introgressive*: Said of a gene that has moved via gene flow from one species into the gene pool of another by the repeated backcrossing of an interspecific hybrid with one of its parent species. Strong evidence for introgression of Neanderthal and Denisovan genes into parts of the modern human gene pool has recently emerged.
14. *Lateral Gene Transfer*: Lateral (horizontal) gene transfer refers to the transfer of genes between organisms of the same or different species in a manner other than the traditional vertical transfer that consists of genes from the parental generation being passed to offspring via sexual or asexual reproduction.
15. *Lichens*: Composite organisms consisting of a fungus (the mycobiont) and a photosynthetic partner (the photobiont or phycobiont), usually an alga or cyanobacteria, growing together in a symbiotic relationship.
16. *Microbiota*: It is said of the aggregate of all microbes colonizing a multicellular organism. In the case of the human body these are collectively referred to as the human microbiota.
17. *Mycorrhizae*: The structure that results from arbuscular fungus' hyphae living in symbiosis with a living vascular plant root. Arbuscular mycorrhizal fungi form associations with roots of ~80% of land plant species to obtain carbon from their host plants in return for mineral nutrients.
18. *Symbiot*: it is said if an organism living in symbiosis; especially employed to refer to the smaller member of a symbiotic pair.
19. *Transposable Elements (TE, transposon or retrotransposon)*: It is said of a DNA sequence that can change its position within the genome, sometimes creating or reversing mutations and altering the cell's genome size.
20. *Virome*: It is said of the genomes of all the viruses that inhabit a particular organism or environment.

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