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One Health—One Medicine: unifying human and animal medicine within an evolutionary paradigm

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One health is a concept since early civilization, which promoted the view that there was no major distinction between animal and human medicine. Although persisting through the 19th century, this common vision was then all but forgotten in the early 20th century. It is now experiencing a renaissance, coincident with an awakening of the role that evolutionary biology plays in human and animal health, including sexually transmitted infections (STIs). A number of STIs in humans have comparable infections in animals; likewise, both humans and animals have STIs unique to each mammalian camp. These similarities and differences offer opportunities for basic medical and public health studies, including evolutionary insights that can be gleaned from ongoing interdisciplinary investigation—especially with the molecular analytical tools available—in what can become a golden age of mutually helpful discovery.

Keywords: animals; STI agents; infections; vaccines; cancer; evolution; development

One Health–One Medicine: from history to evolution

Historical view

The close relation between animals and humans has been emphasized in different periods of history from a variety of perspectives. Already in prehistory, the art found in European caves reflects the early hunter-gatherers appreciation of animals—their speed, proportions, activities, and perhaps, most importantly, their food value.[1] About 5,000–10,000 years ago, the more agriculturally complex societies led humans to experience many closer contacts with animals through domestication—primarily for nourishment, labor, and travel. Many humans with such contacts in these early periods must have experienced novel severe diseases, now termed zoonoses,[a] whose causality evolved from animal infectious agents that spread through vectors or had become contagious in humans (e.g., the plague or measles). In relation to the older zoonoses, descendants of surviving men and women over many generations would have developed at least partial immunity to the infectious agents. Through exploration, conquests, and war, world history was markedly affected when "virginal" or naive populations, particularly in America and on the Australian continent, experienced the disastrous consequences from such older zoonotic infections.[2,3] We have experienced many emerging zoonotic diseases in the past century, but the most rapidly spreading global one has been human immunodeficiency virus (HIV)-1, which is primarily spread sexually.

Historically, the bridging of early knowledge obtained on human and animal health in the Greek and Roman eras, was first recorded by Hippocrates and Galen—his disciple—an early "physician."[4] Over the next millennium, practitioners of human diseases also dealt with animal diseases, with much being learned from anatomical, physiological, and other studies that could not be performed on human bodies. A particularly important historical example is Giovanni Lancisi, an Italian physician, who, in

[a]Animal-to-human transmission; and human-to-animal transmission as anthropozoonoses.

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1713, was dispatched by Pope Clement to investigate and provide descriptions of an outbreak in Rome of the "cattle plague," or *rinderpest*. Lancisi was probably the first to suggest its "contagious" nature, as being due to "some exceedingly fine and pernicious particles, which pass from one body to another, by contact." He also pioneered public health preventive measures by restricting the movement of cattle from areas in which there were many diseased animals.[5] Such a policy was among those used later to eradicate rinderpest, the progenitor of the measles virus, from the world in 2010; a similar concept led William Foege and others to vaccinate the people in the areas around infected communities, as part of the eradication of global smallpox in 1980.[6] This was accomplished by using the vaccine resulting from the one health–one medicine consciousness extant in the 18th century, when the English physician, Edward Jenner—with encouragement by John Hunter—adapted the cowpox virus as a live vaccine for humans.[7] Coincidently, widespread use of cowpox vaccines in humans may have initially promoted transmission back to cattle from recent vaccines; eventually, this practice reduced transmission of cowpox between cattle, thus indirectly controlling and later eliminating the disease in dairy herds.

The formal specific training of animal-related knowledge began in 1761,[b] with the founding of the first school of veterinary medicine in Lyon, France.[8] By the 19th century, several other scientific disciplines, for example, parasitology and entomology, played an important role for animal–human health. In addition, major contributions to both fields were made by Louis Pasteur, a chemist, assisted by several physicians in his laboratory.[9] The French and the German schools led by Robert Koch, joining in the new fields of bacteriology and immunology, identified many new bacteria in animals and humans. Their findings were instrumental in the diagnosis of many diseases and in the burgeoning immunological application to prevention and treatment.[10,11] Clinical pathology also became particularly prominent in its applicability to a better understanding of animal and human diseases, by such physicians as Robert Koch, Paul Ehrlich, William Osler, and Rudolph Virchow. The latter put it best: "Between animal and human medicine there is no dividing line—nor should there be one. The object is different, but the experience obtained constitutes the basis of all medicine."[12]

With the marked accumulation of basic and practical knowledge during the first half of the 20th century, veterinary, medical, and public health schools have experienced more divisions within, and among, themselves. A professor of veterinary epidemiology with broad medical experience, Calvin Schwabe, was instrumental in the 1960s to reintegrate the two in his textbook *Veterinary Medicine and Human Health*.[13] One of us (JHS), who also reviewed the book,[14] helped to extend this theme to include veterinary and human public health, through different contributions to national and global public health.[15,16] At Steele's 90th birthday celebration in 2003, William Foege noted the success of this integrative concept, "We made the point at the Center for Disease Control (CDC), the Pan American Health Organization (PAHO), the World Health Organization (WHO), and everywhere, that you cannot deal with the health of people without dealing with the health of animals—the two are inseparable."[17] We propose now to further integrate such unifying concepts, with the inclusion of many more relevant disciplines, to emphasize the evolutionary paradigm. The large diversity of causal viruses, bacteria, and parasites that can assume a sexual route of transmission represents a very large number of important diseases, including (re)emerging ones, in humans and many animal species. While the historical view is more limited with its shorter observation time on sexually transmitted diseases, the evolutionary and related perspectives can extend over "deep time" our comprehension of the causal infectious agents and interactions with their diverse hosts.

History meets evolution

Whether it was the great variety of local beetles, other insects, or small and large animals that Darwin observed and studied in his backyard or on his global voyage, there is little question that—together with the geopaleological and world demographic information of his time—his experiences with animals (and those of Wallace[18]) have provided the mainstay and development of their natural selection evolutionary theories.[19] The need for Darwin to include mating and hereditability selection aspects to his initial theory on the origin of species led

[b] A 250 year worldwide celebration is scheduled in 2011.

Table 1. Comparison of different sexual behaviors in humans and in primates[22]

Mating patterns	Apes	Humans	Relative likelihood of acquiring STIs
Monogamy	Gibbon/Siamang	Common (Serial monogamy with possible ↑ STI risk)	±
Polygamy	Gorilla	Infrequent ("harem")	±
Dispersed (nongregarious)	Orangutan (male > female)	Frequent ("one-night stand;" "hooking up")	++
Multimale/multifemale	Chimpanzee—*Pan troglodytes* *Pan paniscus* (bonobo)	Frequent (concurrency)	+++ ++++

him to write his second opus, *Descent of Man, and Selection in Relation to Sex*.[20] A variety of explanations for why sex evolved (probably around halfway through the four billion years of the evolution of life) have been debated ever since Darwin's time. Of particular relevance is the 1980 Nobel Symposium on "The Evolution of Sex,"[21] and the more recent 1998 book on *Primate Sexuality* by Alan Dixson,[22] the latter comparing mating patterns of monkeys, apes, and humans. Some of these differences relate to the very short period of penile–vaginal intromission of nonhuman primates, as well as the more limited seasonal period of mating based on hormonal effects. One can also gather, from these different aspects, that the likelihood of infectious agents being transmitted sexually will vary accordingly (Table 1).

Information about sexually transmitted diseases and their viral, bacterial, or parasitic infectious causes have increased markedly by the 1970s, with evolutionary perspectives already being considered, for example, "The Evolution of Viruses."[23] In 1974, two English workers, J.D. Oriel and A.H. Hayward, admonished their physician "venereologists" to pay more attention to sexually transmitted diseases and their causal infectious agents in animals, providing some interesting comparisons to humans and their agents.[24] About two decades later, Janis Antonovics and his evolutionary biology team in the United States, provided an extensive comparative evolutionary review of sexually transmitted infectious agents, not only in mammals, but also in insects and plants. The year of publication was 1996,[25] around the same time as the first genome sequencing of any microbial agent—*Hemophilus influenzae*.[26] Since that time, molecular biology has advanced almost logarithmically, being applied to various (proto)human, animal, and plant organisms and an increasing number of viruses, bacteria, fungi, and parasites that acquired the potential of sexual transmission over very long or sometimes short periods of time. Such information has helped to place evolution in its newer paradigm for basic and practical workers in the field, particularly for the kind of questions and possible answers that might be gleaned. It is important to note that focus is placed on a variety of infectious agents that can assume sexual transmission primarily in nature. Experimental studies on the evolution of drug resistance in the agents themselves, for example, bacterial, viral, or parasitic resistance to drugs, are of course most relevant (see later).

Sexually transmitted infection (STI) and STxI agents in selected animals and humans

Infectious agents in animals and humans can be classified by whether sex is their primary mode of transmission (STI agents) or whether they have other primary transmission modes (STxI agents).[c] For practical considerations, only mammals were selected for review as better information is available, since more have been identified because of their veterinary import, their clinicopathologic manifestations, and/or as occurring as epizootics, including in the wild. (The likelihood is that there are many more unidentified STI and STxI agents in mammals, if not earlier animals.) We are also aware that there are other agents, as well as some of those listed, that are

[c]For example, see Tables 1 and 2 in the appendix to: Nahmias, A. and D. Danielsson. 2011. Introduction to The Evolution of Infectious Agents in Relations to Sex. *Ann. N.Y. Acad. Sci.* **1230:** xiii–xix.

acquired through artificial insemination, particularly in cows, mares, and sows. The reader is directed to reviews of these agents[27,28] for additional detail. These relate to several problems: differentiating contamination from true infectious causes, whether acquisition in the male had been via earlier sexual contact or from blood to the genital econiche, and the variety of control methods.[29] *In vitro* and *in vivo* insemination has also been performed in humans, with methods being developed to "clear" semen of the virus, when HIV-infected men wish to have their own babies with an HIV-negative partner.[30]

Some of the questions with evolutionary connotations that were addressed at this symposium had general and practical implications in the discussion of several lesson-providing individual animal and human STIs and STxIs. A possible framework "From Origin to Disease" was provided during the introduction at the symposium (Fig. 1 in the general introduction to these proceedings.)

Some evolutionary questions

- Why are there some sexually transmitted agents that have been identified (so far) only in humans (e.g., gonococci) and some animal agents only in animals (e.g., Brucella)? Are these primarily absent because of lack of investigation, or was it because of extinction of the agent and/or its host? Are there animal diseases related to the gut/genital microbiota similar to bacterial vaginosis in women? Because there are venereal tumors in dogs, which are transmitted sexually but have no infectious agent identified, are there any that occur in humans?[31]
- Did the infectious agent over large periods of time mostly coevolve with its speciating host, and/or was the agent acquired as a zoonosis, and, if so, did this occur centuries or millions of years ago? Will we be able to recognize early those zoonoses that can assume human-to-human transmission, as was done for severe acute respiratory syndrome (SARS)? What if they were sexually transmitted ones, like HIV?
- Why are some agents predominantly sexually transmitted and others only occasionally, if at all? To what extent will STxIs become STIs from natural or human interactions? Do the ways in which similar infectious agents in different hosts use sex to be transmitted, for example, treponemes in rabbits and humans, give any indication of the evolution of how the host itself evolved? Can one identify whether agents reached the genital econiche by blood, from the gut or other routes of entry to eventually become sexually transmissible?
- What is the role of epigenetics and sexually transmitted endogenous retroviral (ERV) genes—do they have evolutionary beneficial or possibly harmful effects?
- How does human intervention impact animal and agent evolution?

In addressing these concerns, we hold the expectation that more information will be pursued beyond the knowledge shared at the symposium and its proceedings.

Current and future aspects of the evolutionary paradigm

Drug resistance

In treatment of all infections in humans and animals, including STIs, the specter of increasing resistance looms for both clinicians and public health workers. The historic overuse of antimicrobial agents in human medicine has been acknowledged for some time, with some measurable progress made in continuing efforts to reduce the excess usage. A different approach extends through most of the animal health and veterinary communities particularly in managing antibiotic administration to livestock and, less so, to companion animals. Specifically in the case of livestock, continuing use of antibiotics at subtherapeutic dosages is employed for assuring optimal feed conversion ratios and to some extent as a prophylactic measure to control disease, especially in intensive concentrated animal feeding operations. The actual means by which feed conversion is enhanced remains not fully explained, and was serendipitously discovered from feeding leftover mash from chlortetracycline antibiotic production to chickens.[32] DuPont and Steele have offered a balanced summary of this issue noting, "While the extensive body of knowledge that exists on the subject provides convincing evidence that the widespread use of antimicrobial drugs as feed additives in animal populations has economic benefits, minimal convincing evidence exists that the practice poses substantial hazards to human health."[33]

A number of considerations contribute to these disparate views and include the fact that almost all

antibiotics used in human medicine and veterinary medicine overlap by >90%. Resistant microorganisms are selected by various mechanisms that can then horizontally transmit resistance to the same, or other, species. Most importantly, the agents can spread between humans and animals through direct and indirect contact, as well as by associated food products. Heretofore, pharmaceutical companies have been able to address increasing resistance through development of second and third generation agents, but that pipeline is becoming exhausted. Development of new agents is greatly reduced and we are now approaching the era of super "super bugs."[34]

Within the animal health sphere, many of our European colleagues have taken measures to eliminate the practice of subtherapeutic administration of antibiotics, and they urge the United States to do likewise.[35] The movement of people, animals, and food products globally between continents is very much a part of our contemporary world. Antonovics and colleagues have reminded us that the correct word is not "emergence" of antimicrobial resistance, but "evolution" that follows use of antimicrobial agents—in effect putting evolution on a fast track by drastically changing the environment with antimicrobials.[36] Recognizing that microorganisms' generation time can be as short as 20 min, coupled with the development time for new antimicrobials being approximately 10 years, indicates we are dealing with an emergency. Interspecies transmission of resistant factors is also distressing, especially in light of the fact that gut flora and urogenital floras overlap by 80%.[37]

Vaccines

Immunizing products are the holy grail of infectious disease and public health prevention. Within the human STI sphere, we have papilloma virus vaccine for young women that promise to greatly reduce this annoying problem, including subsequent cervical cancers resulting from long-term infections. Of comparative interest, Scase *et al*. in the UK studied the etiology of genital squamous cell carcinoma in horses and identified a papilloma virus in the affected tissue.[38] This novel virus has been identified as *Equus caballus* papillomavirus-2 and was present in the genital tumor samples but not in the adjacent histologically normal tissue. The author's summary is quoted, "Potential relevance: Identification of a papillomavirus causal for genital carcinomas in horses may lead to development of a vaccine that could be used to prevent this serious disease in horses. This would be analogous to man, where vaccination against oncogenic papillomavirus species is currently being used to help prevent cervical cancer."

From an animal standpoint, herpesvirus infections of poultry, also known as Marek's disease (MD), results in neoplastic disease. It can be controlled by improved sanitation and administration of a bivalent vaccine that, in this case, was the first vaccine for "cancer" in veterinary medicine.[38] But with evolutionary pressures, increasing evidence is reported that Marek's disease vaccine may be selecting for MD viruses of increasing virulence that in turn call for use of more potent vaccines and possibly vaccination at the embryonic stage to provide earlier protection.[40]

The success noted with smallpox eradication and with rabies vaccination in humans and domestic or wild animals should emphasize the one health–one medicine approach to vaccines. Many of the problems, for example, with influenza vaccines,[d] whether technical or practical are similar. We wish primarily to emphasize here the many possible contributions that evolutionary perspectives on the agents and their hosts can provide to vaccine strategies.

Molecular genetics and metagenomics

Technological progress continues at a dizzying rate with new research and diagnostic tools being developed and applied to define better disease causation through particular molecular techniques. Newer methods involve assessing the molecular biology and genetics of infectious agents in various living organisms or in environmental samples—also, coincidentally, often helpful for improving evolutionary knowledge of the agent. Some of the latest molecular

[d]Of personal interest to one of the authors (JHS) is a bivalent poultry vaccine, containing H5 and H7 influenza strains, developed for injection into embryonating eggs. Just over 100 years ago, H7 strains were demonstrated to be the cause of "fowl plague," a serious poultry disease. Rare infections of humans can also occur, as in the unfortunate death in 2003 of a veterinarian assisting with a poultry episode in the Netherlands. JHS happens to have been the first to conclusively prove a case of human infection with fowl plague virus in the United States.

advances enable recognition of viruses, bacteria, or other infectious agents that may not be identified by standard cell culture systems or microscopy. Several of the new methods are permitting identification of multiple agents in a single sample, for example, for respiratory syndrome investigation, to identify influenza A and B, adenovirus, and coronavirus.[41]

A particularly novel technology—metagenomics—is allowing identification of many more, previously unrecognized, microorganisms: Examples of metagenomics applications in veterinary medicine have been well characterized by Blomström in her recent doctoral thesis work.[42] In one series of applications, metagenomic techniques were used to study viruses involved with postweaning multisystemic wasting syndrome (PMWS) in swine. While caused by porcine circovirus type 2 (PCV-2) virus, a high percentage of pigs are coinfected with torque teno virus, genotypes 1 and 2 (TTV-1 and TTV-2), and two viruses, as well as a novel porcine bocavirus. Likewise, a metagenomics study of shaking mink syndrome, a disease of unknown etiology, using classical testing methods, identified a mink astrovirus in brain tissue, heretofore associated with preweaning diarrhea, as a possible cause. In yet another effort, soft ticks collected in Uganda were tested, using random amplification and large-scale sequencing. A novel RNA virus, most closely related to the hepatitis-E genogroup, was identified.[42] The promise of these techniques to better identify and characterize various infectious agents, including STIs, is almost limitless and could lead to novel prevention and control strategies. However, establishing causation with newer agents to particular diseases is a fundamental problem, as is determining the clinicopathologic and evolutionary importance of newly identified agents.

Similarities and differences in impact of human and environmental influences

Population concentrations and migrations remain important factors in disease transmission for both animals and humans. A case in point is human settlement in the great plains of the United States that restricted bison movements. Decades later, these animals, confined in large numbers to U.S. parks such as Yellowstone and Glacier, have now sustained brucella infections (occasionally sexually transmitted) that are difficult to manage. The bison problem then becomes a reservoir for domestic livestock that potentially can infect ranch workers and packing house employees.[43]

A related recent perverse example is the practice of deliberate feeding of waste foods to area deer populations in Michigan as a means to improve hunting. The concentration of these animals during feeding or "baiting" has resulted in tuberculosis transmission (*Mycobacterium bovis*) and risk of prion disease ("chronic wasting disease") amplification, thus establishing reservoirs where no previous problem existed.[44,45] Prion diseases are particularly worrisome (although not determined to be sexually transmitted at this time). These newly recognized infectious proteins were identified initially in sheep with "scrapie"—a chronic neurological disease. Prions have "evolved" to cause bovine spongiform encephalopathy in cattle, new variant Creutzfeld–Jakob disease in humans, and most recently chronic wasting disease of various cervid species. Culling or depopulation of affected animals has been used to reduce risk of propagation, but this strategy remains most challenging for wild cervids.

Another example of human environmental effects relates to the more recent increase in day care centers (DCCs), and the placement of elderly relatives into long-term care (LTC) facilities. Both of these environments have experienced greater scabies problems than those ensuing from sexual transmission alone. The DCCs, and even more so the LTCs, represent a new niche wherein hands-on care transmission maintains reservoirs and helps to expand the distribution of scabies.[46]

Concluding remarks

We have provided here a brief review of the long-term interactions over the past two millennia between human and veterinary medicine/public health. The evolutionary perspectives have helped to stimulate several questions related to their commonality and differences, as well as some of the major examples of one health–one medicine, for example, antibiotic resistance and the role of the environment. As noted earlier in the introduction based on this symposium, the evolutionary paradigm could even be expanded, if combined also with development, in what is now termed evolution–development, or "EVO–DEVO."

The organizers' focus on the evolutionary aspects of sexually transmitted infectious agents in animals and humans provided particular one health–one

medicine lessons (further detailed in these proceedings): (1) The role of lice in helping to improve understanding of the evolutionary relations to their animal or human hosts, and the likelihood that the ectoparasites of scabies of dogs were acquired after their domestication from humans. (2) The lack of a phylogenetic homology between the *Trichomonas fetus* of cows and *T.vaginalis* of humans raises some important general points. Although two infectious agents of the same genus can assume a similar mode of sexual transmission, this does not imply necessarily a close phylogenetic relation of the agents themselves; nor does a close phylogenetic relation between, for instance, a sexually transmitted bovine herpesvirus and a human herpesvirus indicate that humans originated from cows. (3) The short- or long-term temporal perspective is well illustrated by the koalas. In these marsupial animals, the severe reproductive diseases caused by *Chlamydia pecorum* (also identified in sheep and cows) likely emerged in recent decades; on the other hand, ERV genes, associated with cancer in the koala, originated several thousand years ago. (4) The transmission of HIV-1 to humans from chimpanzees less than a century ago has already caused a global pandemic of over 30 million infections in men, women, and children, whereas the less virulent and more geographically limited HIV-2 was acquired most likely from sooty mangabees (SM). Together with the studies of ill-effects of the SM virus on macaques, old and new world monkeys are providing important information helpful for research on the virology and immunology, as well as preventive and therapeutic interventions, of the two human retroviruses.

Some of the evolutionary questions we raised in the text have had only partial answers in the symposium proceedings, and subsequent papers note what further studies are needed that would improve our basic information and suggest possible approaches to practical interventions. We look forward to further applications of the evolutionary–developmental perspectives on the many issues that link human and veterinary medicine and public health.[e]

[e]It is with pride we recognize that a veterinarian, Peter C. Doherty, who won the Nobel Prize for immunological discoveries applicable to both humans and animals. His book *The Beginner's Guide to Winning the Nobel Prize* should provide a model for our veterinary students.[47]

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Conflicts of interest

The authors declare no conflicts of interest.

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