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Evolutionary perspectives on the origins of disease

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1. Why is human evolutionary biology not an integral part of medical education?

Humans are primates that shared a common ancestor with the so-called 'great apes' (chimpanzees, gorillas, orangutans and bonobos), later emerging out of Africa about 100,000 thousand years ago to populate the entire planet [1,2]. The practice of modern medicine originated as an art and a trade in the 18th and 19th centuries, and began to develop a scientific basis in the early part of the 20th century [3]. At the time this initial scientific revolution in medicine was taking place, the concept of evolution and Darwinian natural selection was not yet well accepted. The major reasons were that while Mendel's laws of heredity had yet to be fully appreciated, and Weissman's germ cell theory had become accepted, indicating that heredity did not involve somatic cells, but rather, only the germ line. For these and other reasons, many even questioned the Darwinian paradigm at that time. It was only later with the introduction of Mendelian genetics, population genetics, and other critical components, that the 'modern synthesis' in evolutionary biology took place in the mid-20th century [4]. By this time medicine had become an established 'science' and had already incorporated those basic sciences that were important for its practice, such as anatomy, physiology, biochemistry and cellular and molecular biology. Evolution, as a more recently developed science, was thus left out of this modern revolution in medicine. Consequently, evolutionary biology is not taught as a formal discipline in the medical curriculum, and very few medical schools even have basic science teachers with a primary interest in evolutionary biology [5].

2. Human evolution is highly relevant to medicine

In retrospect, this has been an unfortunate historical mistake. After all, of the numerous species on the planet, medical doctors are asked to care for a single one, i.e., humans. Is it not then self-evident that such practitioners should have at least a basic knowledge of the origins of the species that they so intensely study and treat? In recent times this point has been brought up by several scientists, including a few from the medical profession [5,6] and the basics about evolution are now being taught in a few medical schools.

My own epiphany in this area came about serendipitously, as a consequence of studying an immune reaction of humans against animal serum, which eventually resulted in the discovery of the first known genetic difference between humans and great apes, a defect in the synthesis of one specific kind of cell surface molecule [7] belonging to a family of sugars called sialic acids [8]. Since then many additional genetic differences between humans and great apes have been discovered [9,10], and there is a robust field of inquiry involving such questions.

However, most of these comparative studies are aimed at answering more fundamental and philosophical questions. Where did the human species

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originate from? How do we differ from the great apes? And how did these changes take place? It is time now to also apply this emerging knowledge about human-ape differences to our understanding of human disease. This brief overview considers questions in this arena and suggests approaches for the future. One related area of medicine presents clear examples of the evolutionary process at work – the biology of human pathogens and resistance development to various therapeutic agents such as antibiotics. It is curious to note that even microbiology literature typically uses the word 'emergence' rather than evolution [11], perhaps because of the lack of training of the relevant biomedical investigators in fundamental evolutionary principles. This article will not spend much time on evolutionary principles in infectious disease and microbiology, as this is a topic that is reasonably well discussed in other venues. Rather, it will focus on genetic differences between humans and our closest evolutionary cousins and their implications for disease.

3. Differences in the incidence and severity of diseases between humans and 'great apes'

Some disease differences between humans and 'great apes' are due to anatomical variations. The most obvious one relates to the upright striding bipedal posture of humans [12]. Evidence suggests that this unusual posture of humans is an ancient adaptation that occurred relatively soon after the divergence from our common ancestor with the chimpanzee about 6 million years ago [12]. While the evolutionary basis for the relatively sudden emergence of this unusual change in body posture remains unexplained, the consequences to the human body are still being felt today. These range from problems such as back muscle and spine disorders, (including major consequences for the spinal cord and the peripheral nervous system), the higher incidence of problems related to the increased hydrostatic pressure in blood vessels (e.g., varicose veins and hemorrhoids), and increased intrabdominal pressure (e.g., hernias). While these biomechanical consequences are not surprising, it is interesting to note that despite 6 million years of time for adaptation, we are still susceptible to such problems. This suggests that the original selection mechanism for bipedalism must have been rather intense, as it would have been associated with substantial deleterious consequences at the outset.

Conversely, there are anatomical differences between humans and apes in which the latter are the ones to suffer. Perhaps the most obvious one is infection of the pharyngeal pouches, which are particularly well developed in the orangutan, but are also present in the other great apes (but not humans) to varying extents. These so-called 'air sacs' are prone to infection, much in the same way that the human air sinuses are. These 'air sac' infections can be quite serious and have short and long-term consequences [13]. Other diseases related to anatomical differences are relatively less common, and will not be discussed here.

4. Differences not caused by purely anatomical factors

It has long been assumed that 'great apes', because of their close genetic similarity to us, also suffer from similar diseases. In fact, the chimpanzee has long been used for a model for the study of human diseases [14]. While there are now significant ethical issues constraining such work [15], there is a substantial body of existing information spanning almost a century, in which the chimpanzee was studied both as a model for human disease, and also cared for in captivity with excellent veterinary medical care, including autopsies, i.e., processes quite similar to those which gave rise to the current body of knowledge about human disease. However, there has been a strong tendency for such research to focus only on those aspects of chimpanzee diseases that are similar to that of humans, and not those that are different. Perhaps this is not surprising, as the funding agencies supporting the chimpanzees are interested in health issues, and not evolutionary ones.

Overall then, there has been a tendency to not discuss nor report on diseases and processes in which humans appear to be different than those of the great apes. Revisiting this issue from a utilitarian perspective shows many examples in which humans are actually rather different from chimpanzees and other 'great apes', in terms of disease profiles and severity [16–18]. In only a few instances are these differences well documented enough in the published literature to be considered as 'definite'. In many other instances, the published data is not as strong, and one must classify these as 'probable' and 'possible' differences. However, even in the case of the 'possible' differences the anecdotal evidence appears quite strong and should be taken seriously. A list of such differences based on examining all available data is summarized in table 1. Each of these disease differences is briefly considered in the following sections. Following this, our own work on sialic acid biology differences between humans and great apes is outlined

Table 1. Biomedical differences between humans and 'great apes' that cannot be explained by anatomical differences.

Medical condition	Humans	'Great Apes'
Definite Differences		
HIV infection progression to AIDS	Common	Very rare
Hepatitis B/C late complications	Can be severe	Mild
P. falciparum malaria	Susceptible	Resistant
Myocardial infarction	Common	Very rare
Probable Differences		
Human influenza a susceptibility	Can be severe	Often mild
Epithelial cancers	Common	Rare?
Sia-expressing bacterial pathogens	Common	Rare?
Alzheimer's disease pathology	Complete	No tangles
Pre-eclampsia	Common	Rare?
Menopause	Universal	Rare?
Hydatidiform molar pregnancy	Common	Rare?
Possible Differences		
Rheumatoid arthritis	Common	Rare?
Bronchial asthma	Common	Rare?
Endometriosis	Common	Rare?
Autoimmune diseases	Common	Rare?

Data in this table are adapted and updated from references 16–18 and the citations therein.

and possible relationships to the disease differences are considered.

5. 'Definite' differences

Perhaps the best known of these disease differences relates to the effects of the human immunodeficiency virus (HIV) on humans and chimpanzees. Prior to the recent understanding that humans originally acquired HIV from chimpanzees [19,20], the chimpanzee was used as a host for transmission of the HIV virus from humans, as this was the only viable model [21]. Remarkably, after many hundreds of chimpanzees were infected with the virus, only one finally developed the full-blown syndrome of AIDS [22]. Even this case turned out to be one in which unusual mutations appear to have occurred in the virus itself, such that it was lethal to the few other chimpanzees into which it was transferred [23]. But this appears to have been an unusual variant that evolved in a chimpanzee infected with multiple strains of human immunodeficiency virus, and does not represent the wild type virus that normally infects chimpanzees. Meanwhile, it has been recently reported in meeting abstracts that wild chimpanzees chronically infected with the original virus can have milder versions of an AIDS-like syndrome. Regardless, the basic difference remains, that when the human immunodeficiency virus (which was derived from a chimpanzee virus) is put back into chimpanzees, it caused very little disease. The basis for this difference would certainly be worth knowing, and it may also help explain why chimpanzees infected with Hepatitis B or C viruses rarely progress onto chronic active hepatitis or liver cancer, outcomes that are relatively common in infected humans [24].

Another common disease in which there is a major difference between humans and chimpanzees is the malarial parasite *Plasmodium falciparum*, the major cause of malaria-related deaths worldwide. In experiments done a long time ago, it was shown that chimpanzees are practically resistant to infection with this parasite [25–27]. In contrast, chimpanzees are infected with a related form of malaria called *Plasmodium reichenowi*, which does not cause illness in humans [25,26]. Yet another dramatic difference between humans and great apes relates to cardiovascular disease. The most common cause of deaths in both humans and of great apes in captivity that are relatively free of infectious disease is heart disease, manifesting either as sudden heart attacks or as chronic heart failure [28]. Thus, at first glance it appears as if humans and chimpanzees are similar in this respect. In fact, careful analysis of the available data indicates that this is not the case. Remarkably, the cardiac disease that occurs in chimpanzees is quite different from that which occurs in humans [29–33]. In humans, as is well known, the most common cause of cardiac disease

is blockage of the coronary arteries due to the progression of atherosclerosis, eventually resulting in loss of blood supply to the cardiac muscle. In striking contrast, while chimpanzees can certainly have atherosclerotic cardiovascular disease, they very rarely develop blockade of the coronary arteries. Instead they often suffer from a chronic fibrotic process that involves the entire cardiac muscle [30–33]. This process can either generate sudden 'heart attacks' (likely due to changes in heart rhythm caused by the fibrosis), or chronic heart failure due to the replacement of heart muscle. Thus there are two mysteries to be solved. First, why is it that chimpanzees do not develop the severe chronic forms of coronary artery disease that plague humans? As discussed elsewhere, known dietary and genetic factors do not provide obvious answers [32]. Second, why is it that humans do not get this kind of common fibrotic heart disease that chimpanzees and other great apes suffer from? Nothing definite is known about this matter.

6. Probable differences

Chimpanzees are clearly quite susceptible to some human viruses, such as respiratory syncytial virus [34]. However, when chimpanzees were deliberately infected with human influenza viruses, they required relatively large doses of virus to generate symptomatic infections, and even then did not have severe consequences [35,36]. Another remarkable finding is the rarity of reports of carcinomas (cancers arising from the epithelial lining of hollow organs) in chimpanzees [16,28]. These are the commonest cancers in humans, and yet have hardly ever been reported in any of the great apes. To some extent the difference maybe age-related, in that most apes die at a relatively young age. However, given the high frequency of some of these cancers even in relatively young humans, it is noteworthy that none have been reported in the chimpanzees, who are now living longer in captivity. It is unlikely it is just a matter of lack of reporting, as this difference is so well known in the veterinary and primate pathology communities that any case would very likely have been considered 'reportable'. Another interesting difference appears to be in the frequency of infections with bacteria that express sialic acids [37,38]. While such organisms are very commonly isolated from humans, infections have simply not been reported as spontaneous occurrences in any of the great apes. Interestingly, many of the relevant bacteria are human-specific obligate commensals/facultative pathogens [37,38]. Another difference is in the prevalence of the pathology of Alzheimer's disease, a chronic degenerative condition affecting older humans, which manifests as progressive neuronal loss associated with the deposition of amyloid plaques and neurofibrillary tangles. While age-matched brains from great apes have been shown to contain typical amyloid plaques, the neurofibrillary tangles are quite rare [39–41]. Likewise, the extensive neuronal loss and cerebral atrophy that occurs in Alzheimer's disease of humans does not seem to occur in any of the great apes. Again, one possibility is simply that this is an age-related phenomenon. However, a sufficient number of apes have lived into an age span where at least the pathology might have been noted – and as indicated, age-matched sample comparisons did not show obvious neurofibrillary tangles.

There also appear to be multiple differences in female reproductive biology. For example, preeclampsia is a common problem of pregnant humans, manifesting as loss of protein in the urine and consequent edema, elevated blood pressure, etc., associated with placental insufficiency, a process which eventually can result in fetal loss or a requirement for early delivery because of progression of symptoms in the mother [42]. To date, this syndrome has not been reported in any pregnant great apes, although it can be artificially induced in an experimental fashion in monkeys [43–46]. Another human condition that appears to be rare in great apes is menopause, i.e., the sudden cessation of menstrual periods and fertility in otherwise healthy, middle-aged females [47,48]. To some extent this maybe again related to the fact that chimpanzees and other 'great apes' do not live as long. However, there is sufficient data to indicate that while hormonal changes similar to menopause may occur in elderly female chimpanzees [49–51], full-blown loss of fertility occurring at a time when the female is otherwise healthy is likely a unique human condition. Another surprise is the almost complete absence of reports of hydatidiform molar pregnancy in non-human primates. This is a very common problem in humans, characterized by fertilization of the blighted ovum by a sperm, followed by duplication of the male haploid genome giving a homozygous state at all loci and abnormal imprinting [52,53]. Essentially no fetus is present in most of these cases – rather the extra embryonic fetal tissues instead of developing into a placenta get converted into aberrant large grape-like clusters of tissue. This common disorder has never been reported in any of the other primates and the reasons for this difference remain unknown.

7. Possible differences

In this category of differences are diseases wherein anecdotal evidence suggests a marked difference

between humans and apes, but for which there is no documented, published enumeration of risk difference. Perhaps the most dramatic example is that of bronchial asthma, an extremely common disease in humans, and which is increasing in prevalence in recent times. Discussions with great ape veterinarians indicate that bronchial asthma has yet to be seen as a problem in any great ape in captivity. This noticeable difference has not been documented carefully, but needs to be further investigated. Another surprise is the almost complete absence of cases of rheumatoid arthritis (RA), a disease that is easy to diagnose by direct physical examination. While sero-negative spondyloarthropathy is common in humans and old world primates [54], the very common RA disease of humans has not so far been reported in most great apes in captivity (an exception may be gorillas). Another curiosity has to do with the very low frequency of endometriosis in the apes. This disease affects about 10% of women of child-bearing age [55–57] but is rare in great apes – although it has been reported in monkeys [58]. Finally, there seems to be a general paucity of autoimmune disorders such as systemic lupus in the apes. This is surprising also, but the frequency of these diseases is relatively low in humans.

8. What might explain these differences?

In each instance discussed above, several possible explanations can be offered. One of greatest concerns is simply that of ascertainment bias, i.e., just a failure to detect the disease in the apes because of the low numbers studied. This certainly can be used as an explanation for diseases that are relatively rare in the human population. However, many of those mentioned above are quite common, and ascertainment bias seems unlikely, given that several thousand apes have been observed in captivity over a >50 year period. Thus it is reasonable to consider genetic and/or environmental differences between humans and great apes that might explain these unexpected observations. Clearly there is also a need to investigate further by review of medical records and discussions with veterinarians.

9. Potential roles of sialic acid biology in explaining some of the differences

As discussed in detail elsewhere, we have discovered multiple changes in sialic acid biology that appear to be uniquely human [59,60]. In a biological system with less than 60 known genes [61], more than 10 have shown human-specific differences from the great apes [59,60]. This suggests that sialic acid biology was a 'hot spot' in human evolution. With regard to the disease differences between humans and great apes, we are pursuing the possibility that some of these changes in sialic acid biology may have contributed. Three general categories of mechanisms can be considered. First of all, the change in the cell surface sialic acids, i.e., the loss of Neu5Gc sialic acid and an excess of the Neu5Ac sialic acid would create a situation wherein pathogens or toxins that prefer to bind to Neu5Gc would not be able to infect humans. In contrast, those that prefer to bind to Neu5Ac would find humans cells to be particularly attractive targets. Several examples of these possibilities have surfaced and one particularly striking one is the potential role in affecting the *P. falciparum* malaria differences between humans and chimpanzees. We have shown that the major binding protein of the *P. falciparum* merozoite prefers to bind to Neu5Ac, in contrast to the corresponding protein of the chimpanzee parasite, which prefers Neu5Gc [62]. The second category of differences arises from the unusual phenomenon of incorporation of dietary Neu5Gc sialic acid into human tissues via metabolic incorporation and re-utilization in the face of circulating anti-Neu5Gc antibodies [60,63–69]. This combination could trigger chronic inflammation in tissues such as epithelial cells (potentially exacerbating the progression of carcinomas) or endothelial cells (potentially aggravating processes such as inflammatory vasculitidies including atherosclerosis) or incorporation into inflamed tissues such as arthritic joints, potentially aggravating the arthritis process. These possibilities are currently being pursued. Alternatively, metabolic incorporation of Neu5Gc into human tissues could make us sensitive to toxins that prefer to bind Neu5Gc [70]. In a third mechanism, humans appear to have altered the expression of Siglecs (Sialic acid binding Ig superfamily lectins) [71,72] in various tissues. The relative or absolute loss of Siglec expression on lymphocytes [73] could perhaps explain the propensity of humans to develop disorders associated with excessive lymphocyte activation such as AIDS, chronic active hepatitis and the severe consequences of human influenza virus infection. On the other hand Siglec-6 shows expression in the human placenta, which is not present in the great apes [74]. Interestingly the expression of Siglec-6 is also markedly up-regulated in the human specific disease pre-eclampsia [75]. Several other examples could be cited of potential interactions between changes in sialic acid biology and the initiation or aggravation of so-called human-specific diseases. However, much further work needs to be done before this can be made definitive for most of the suggested cases.

10. Conclusions and perspectives

This brief overview has provided some attention to the serious lack of teaching of evolutionary biology and human evolution in medical curriculum. I have then used differences between humans and great apes as an example of where research could provide useful knowledge. Our own work in this area is focused on human-specific changes in sialic acid biology. However, there are obviously many other biological systems that have or are likely to have undergone human-specific changes, and all of these need to be considered. Finally, although not addressed in this review, another important aspect of human origins and evolution has to do with the marked 'mismatch' between our modern human condition and that of our hunter-gatherer ancestors [76–79], and these mismatches can help account for some of our propensity to certain types of diseases.

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