Biomedical Differences Between Human and Nonhuman Hominids: Potential Roles for Uniquely Human Aspects of Sialic Acid Biology

Nissi M. Varki,[1] Elizabeth Strobert,[2] Edward J. Dick Jr.,[3] Kurt Benirschke,[1] and Ajit Varki[1]

[1]Center for Academic Research and Training in Anthropogeny, Glycobiology Research and Training Center, University of California at San Diego, La Jolla, California 92093-0687; email: varkiadmin@ucsd.edu

[2]Yerkes National Primate Research Center, Emory University, Atlanta, Georgia 30022

[3]Southwest National Primate Research Center, Southwest Foundation for Biomedical Research, San Antonio, Texas 78245-0549

Annu. Rev. Pathol. Mech. Dis. 2011. 6:365–93

First published online as a Review in Advance on November 8, 2010

The *Annual Review of Pathology: Mechanisms of Disease* is online at pathol.annualreviews.org

This article's doi: 10.1146/annurev-pathol-011110-130315

1553-4006/11/0228-0365$20.00

Keywords

chimpanzees, human evolution

Abstract

Although humans are genetically very similar to the evolutionarily related nonhuman hominids (chimpanzees, bonobos, gorillas, and orangutans), comparative studies suggest a surprising number of uniquely human differences in the incidence and/or severity of biomedical conditions. Some differences are due to anatomical changes that occurred during human evolution. However, many cannot be explained either by these changes or by known environmental factors. Because chimpanzees were long considered models for human disease, it is important to be aware of these differences, which appear to have been deemphasized relative to similarities. We focus on the pathophysiology and pathobiology of biomedical conditions that appear unique to humans, including several speculative possibilities that require further study. We pay particular attention to the possible contributions of uniquely human changes in the biology of cell-surface sialic acids and the proteins that recognize them. We also discuss the metabolic incorporation of a diet-derived nonhuman sialic acid, which generates a novel xeno-autoantigen reaction, and chronic inflammation known as xenosialitis.

INTRODUCTION

Sialic acids: generic term for a family of sugars with a common 9-carbon backbone; they are typically found at the outermost end of glycan chains, which decorate all cell surfaces in vertebrates and so-called higher invertebrates

Mammals such as rodents are frequently used as experimental models for research into human disease. However, the shared common ancestor of humans with these species existed many tens of millions of years ago (Mya) (1), allowing ample time for genetic differences to develop and probably explaining the multiple instances wherein mouse studies do not translate well into studies on humans. Primate models are considered more representative. However, even among primates, our common ancestor with Old World monkeys was ~25 Mya (2). Our closest evolutionary cousins are the so-called great apes (chimpanzees, bonobos, gorillas, and orangutans), with whom we share more recent common ancestors (2). These nonhuman hominids (NHHs; see the sidebar entitled Updated Classification of African Primates) are thus often considered the best models for human disease. However, there are many fiscal and ethical issues that currently constrain the use of NHHs for research (3). Apart from these issues, humans appear to have several surprising differences in the severity and/or incidence of diseases and pathologies that cannot be explained by environmental factors (4–9). Although this situation poses a challenge to translating NHH studies into the human condition, it also provides an opportunity because of the extreme genetic similarities to humans (we are more closely related to NHHs than mice and rats are to each other).

In this review, we interface the existing background and knowledge base regarding NHH diseases with our own ongoing research, in which we have found multiple differences between humans and NHHs with regard to a family of cell-surface sugars known as sialic acids (10–12). We present interesting biomedical conditions, emphasizing the definite, probable, and possible differences between humans and NHHs and consider potential implications for our sialic acid–related research where appropriate. We realize that sialic acid–related changes are probably not the primary cause for most of the differences discussed. Also, there are many other genetic differences between humans and NHHs (13) that we do not consider here due to lack of space. Additionally, we realize that very little work has been done to compare the many other complex aspects of glycosylation between humans and NHHs. Finally, we know that monosaccharide modifications such as acetylation might alter the lectin- and antibody-binding specificities assumed in our results.

In deciding which biomedical conditions and diseases to discuss, we chose to be inclusive; we even mention many speculative possibilities. The reasons for this approach are twofold. First, given the relatively few NHHs in captivity that have been studied to date, there is a potential for observational bias in one direction or the other. Second, given that support of chimpanzee research by the National Institutes of Health was meant to provide models for human disease, the tendency in published studies has been to emphasize the similarities, rather than the differences, between NHHs and humans. Thus,

UPDATED CLASSIFICATION OF AFRICAN PRIMATES

The African Old World primates were traditionally classified into monkeys, apes, and humans. Apes in turn were subclassified into lesser apes (siamangs and gibbons) and great apes (chimpanzees, bonobos, orangutans, and gorillas). Because of apparently marked differences in morphology, behavior, and function, humans were previously classified separately. Modern genomics makes it clear that humans are basically a modified form of great ape. Thus, there is an emerging new classification (170) in which the term hominoid or Hominoidea continues to be used for all apes and humans and the lesser apes continue to be classified as Hylobatidae. The term hominid has been expanded to include not only humans but also the other great apes. The most distantly related great ape (the orangutan) is classified as Ponginae. The African great apes are now classified as Homininae and humans as Hominini. These new classifications are still under discussion and have not yet been accepted by all investigators in the field. For the purposes of this review, we replace the term great apes, which is no longer taxonomically valid, with the term nonhuman hominids (NHHs).

some of the apparent differences have been documented only minimally and/or not formally reported. Although this review describes both definitive facts and highly speculative considerations, we strive throughout to make clear when our comments are true, likely, or speculative. We first mention biomedical conditions that can be plausibly explained by anatomical differences between humans and other hominids. We then list diseases and biomedical conditions that apparently cannot be explained by anatomical differences. The latter are classified into definite, probable, and possible differences on the basis of the amount and type of information available.

NONHUMAN HOMINIDS ARE GENETICALLY VERY SIMILAR TO HUMANS BUT MAY NOT BE GOOD MODELS FOR SOME COMMON HUMAN DISEASES

As mentioned above, humans are remarkably similar to NHHs from the genetic perspective. Indeed, we shared a common ancestor with all these other hominids more recently than mice and rats did with each other: Our common ancestor with the orangutan lived ~13 Mya, that with the gorilla ~8 Mya, and that with the chimpanzee and the bonobo ~6 Mya (2). Furthermore, the chimpanzee-bonobo clade is closer to the human lineage than are all three species to gorillas and orangutans (2). Thus, the term great apes is no longer taxonomically correct; we use NHHs instead (see the sidebar entitled Updated Classification of African Primates). Despite these facts, there are remarkable similarities among the NHHs and obvious differences from humans not only in general phenotype but also in the pattern, severity, and incidence of various diseases (4–9).

Given these close genetic similarities, NHHs (particularly chimpanzees) were assumed to be good models for human diseases. As mentioned above, this may be why the extant literature is rather biased toward reporting instances in which similarities are present and pays limited attention to differences. However, understanding these disease differences represents a great opportunity. If humans and NHHs are genetically so similar, any genetic explanations for disease differences should be within reach. Such information could be collected simply by studying both NHHs and humans in a similar fashion, and the results would benefit the care or treatment of all these species.

BIOMEDICAL DIFFERENCES BETWEEN HUMANS AND NONHUMAN HOMINIDS THAT CAN PROBABLY BE EXPLAINED BY ANATOMICAL FACTORS

Some diseases that differ between humans and NHHs can be explained by anatomical differences. The following sections focus on such differences. In each instance, we briefly describe the disease and the anatomical differences that could explain it.

Sinusitis

Human skull bones have four air-containing sinus spaces lined by epithelium that secretes mucus (14). The reason for the prominence of sinuses in humans is unknown; it may be to lighten the weight of the skull during upright posture, or it may help with modulating sound during speech. Alternatively, sinuses may simply be a by-product of evolutionary changes in human facial anatomy (15). The epithelium lining of the sinuses has abundant cilia. However, inflammation resulting from allergies or infections causes mucosal swelling. This swelling blocks the exit channels for mucus, resulting in inflammation and chronic sinusitis—a bane for modern humans. Predisposing factors include ciliary impairment, allergy, nasal polyposis, and immune deficiency. Treatment is aimed at reducing mucosal inflammation and swelling, controlling infection, and restoring aeration of the nasal and sinus mucosa (14). In general, NHHs have smaller or nonexistent sinuses. For example, frontal sinuses in chimpanzees and gorillas tend to be smaller than in humans,

and orangutans do not have these sinuses at all (16). Perhaps for this reason and/or because of differential gravitational forces arising from humans' upright posture, chronic sinusitis and its complications appear uncommon in NHHs.

Air Sac Infections

Unlike humans, all NHHs have air sacs, which are extensions of the pharyngeal pouches of the upper airways. These sacs are best developed and most obvious in the orangutan. Although the air sacs may assist in sound production, their function is unknown. Given their location and connectivity to the upper airways, they are prone to infections, which can be acute or chronic. Cultures of such infected sacs can yield enteric organisms, and treatment with antibiotics and irrigation is often successful (17). However, surgical drainage may be necessary (18, 19). Humans do not have an anatomical equivalent of these structures.

Sleep Apnea

Humans commonly suffer from obstructive sleep apnea, which is characterized by periodic cessation of breathing during sleep and associated with snoring and upper airway obstruction. This syndrome has recently become more prominent with the epidemic of obesity (20). It does not seem to be a common feature of NHHs or of other mammals (20), with the exception of the English bulldog (21). Factors such as the anatomy of the skull, differences in placement of the foramen magnum, and a descended larynx as compared with NHHs have been proposed as contributors (20). The epiglottis and oropharyngeal region in humans may not have evolved specific musculature to maintain the dilation of the pharynx needed during sleep. Also, when humans assumed an upright posture and acquired the ability to speak, anatomic changes occurred, such as shortening of the mandible and descent of the larynx, klinorhynchy (posterior migration of the facial skeleton under the skull), and protrusion of the tongue into the larynx with a "lockup" of the epiglottis–soft palate region—all factors that contribute to obstructive sleep apnea (20). This problem may also precipitate or aggravate the metabolic syndrome, which is characterized by hypertension and a prediabetic state (22). Metabolic syndrome responds to weight loss and/or treatment with continuous positive airway pressure during nocturnal sleep.

Back Disorders

Taken together, current evidence indicates that the onset of bipedal upright posture in the human lineage may have occurred 6–7 Mya—relatively soon after the time of our common ancestor with the chimpanzee-bonobo clade (23, 24). As a consequence, the cervical, thoracic, and lumbar vertebrae of the human skeleton developed ventral (lordotic) curvatures that are not present in NHHs. Other anatomical alterations of vertebrae and supporting muscles appear unique to humans (25, 26). Upright walking imposes stresses and strains the spine and back muscles, which contribute to multifactorial causes for the chronic back pain and injury syndromes suffered by many humans. Evidently, despite the evolution of fully upright bipedal running >2 Mya (27), we are still not fully adjusted to our novel posture.

Obstetric and Perinatal Difficulties

The upright posture of human ancestors also caused a narrowing of the pelvic outlet. However until ~2 Mya, this narrowing probably did not pose an obstetric problem, because the size of the brain and head remained approximately the same as those of the chimpanzee. Beginning at ~2 Mya, and continuing up to a few hundred thousand years ago, the size of the human brain increased continuously. Thus, although human fetuses are born both with unfused skull sutures and before brain growth is complete, they still face great difficulty passing through the maternal pelvic canal (28, 29). This difficulty partly explains the very prolonged labor of humans compared with that of chimpanzees,

and it causes perinatal trauma to both mother and newborn. Details regarding these issues are not covered here.

Sudden Infant Death Syndrome

Sudden infant death syndrome (SIDS) is a diagnosis of exclusion. It occurs in sleeping human infants under one year of age, and its cause is unknown. Most such deaths occur between two and six months of age. Theories proposed include a delayed response to arousal; poorly developed cardiorespiratory control; immature upper airways; and prone positioning of the infant in the crib, especially on a soft surface. Other factors include maternal smoking, low birth weight, young maternal age, inadequate prenatal care, upper respiratory infections, fatty acid oxidation disorders, and so on. Interestingly, until the advent of civilization, mother-infant cosleeping was the norm, and SIDS appears to be rare in hunter-gatherers who follow this tradition. Thus, SIDS may be at least partly the consequence of the modern, false notion that it is best for the infant to learn to sleep apart from the mother beginning at an early age (30). Regardless, a great reduction in SIDS has been achieved by advising parents to position babies on their backs (supine position), rather than face-down, in the crib (31); again, this advice is contrary to that found in older infant-care manuals. Unfortunately, rare episodes in which overweight or inebriated mothers have accidentally smothered infants to death (32) led public health officials to advise against the natural evolutionary norm of mother-infant cosleeping. SIDS has not been formally reported in NHHs, in whom mother-infant cosleeping is the norm. However, occasionally neonatal NHHs are found dead in situations where not enough information is known to establish a cause of death or to rule SIDS in or out.

Inguinal Hernias

A hernia is an abnormal protrusion of an organ or structure that should be confined by normal anatomy. Of the various kinds of hernias, some are probably aggravated by the upright posture of humans and the resulting increase in pressure in the abdominal cavity. In particular, an inguinal hernia involves protrusion of peritoneal adipose tissue, and sometimes parts of the viscera, through the inguinal ligament in humans. This condition is observed more often in males than in females. In both humans and NHHs with inguinal hernias, there is a defect of the posterior rectus muscle sheath and a poorly developed transversalis fascia (33). In humans, the gravitational effects of upright posture probably increase the frequency of herniation through the inguinal canal (33).

Hemorrhoids

Hemorrhoids are dilated veins in the anorectal region that usually result from long-standing constipation involving straining during bowel movements, which causes increased intrarectal pressure and compensatory dilation of the loose-walled venules. Hemorrhoids may also arise from increased intra-abdominal pressure during pregnancy or from increased venous pressures secondary to liver cirrhosis. This condition is not commonly observed in NHHs, probably because of their high-fiber fruit and vegetable diet (which minimizes constipation) and/or perhaps because of the lack of high hydrostatic pressure caused by upright posture (34).

Varicose Veins

Varicose veins are superficial, enlarged, bulging, tortuous veins visible on the skin surface, typically in the lower legs (35), that are usually a result of poor valve function within the veins. The enlarged veins are visible under the skin and are associated with heredity, pregnancy, age, obesity, chronic venous insufficiency, or localized pathologies that cause blockages to flow. Complications include local thromboses and rupture, which lead to bruising and hemorrhaging under the skin. Areas of intimal hyperplasia and

smooth muscle proliferation—and sometimes areas of atrophy and reduced elastic content, upregulation of matrix metalloproteinases, and dysregulated smooth muscle apoptosis—have been observed. Although the causes of varicose veins are multifactorial, hydrostatic pressure due to upright posture contributes and may explain why this condition is uncommon in NHHs.

N-glycolylneuraminic acid (Neu5Gc): nonhuman sialic acid that differs by one oxygen atom from the human sialic acid *N*-acetylneuraminic acid (Neu5Ac); it cannot be synthesized by human cells because of a mutation that occurred in the human ancestors ~2–3 Mya. It can become incorporated into human tissues from the diet

Wound Healing

Although the difference between human and NHH wound healing has not been precisely documented, a common observation is that the wounds of monkeys and NHHs tend to heal rapidly, whereas human wounds often require suturing for closure and take a long time to heal. This difference could be due to the anatomical and histological differences between human and NHH skin (36), including differences in hair, subcutaneous fat, and sweat gland morphology. Interestingly, a mouse with a human-like defect in the sialic acid–modifying *CMAH* gene also demonstrates delayed wound healing (37), although the mechanism is unknown.

Acne Vulgaris

Acne is a common eruptive human skin condition that occurs most commonly in adolescents (38). It is characterized by the appearance of pilosebaceous lesions on the face, neck, and sometimes shoulder regions and involves blocked sebaceous sweat glands, closed comedones, inflammatory papules, and so on. Acne-like skin eruptions have not been reported in NHHs. Although the reason for this discrepancy is unknown, it may again relate to anatomical differences between human and NHH skin, particularly with regard to the type and distribution of sweat glands (36, 39). A role for milk consumption has been suggested (40). It would be interesting to know whether the bacterium commonly found in acne lesions (*Propionibacterium acnes*) (41) is specifically adapted to humans.

BIOMEDICAL DIFFERENCES BETWEEN HUMANS AND NONHUMAN HOMINIDS THAT ARE NOT EXPLAINED BY ANATOMICAL FACTORS

Biomedical differences between humans and NHHs that cannot be explained by anatomical differences are more intriguing (4, 5, 7–9, 42). In the following sections, we divide the candidate conditions into definite, probable, and possible differences. These categories were suggested by our own research and experience, by a survey of the literature, and by discussions with others with expertise (see Acknowledgments). Again, perhaps because of the history of the use of chimpanzees as models for human disease, extant literature tends to emphasize similarities rather than differences, so in this case the absence of published literature is not evidence for the absence of a difference. **Table 1** lists several of these conditions by category; each is discussed further below.

UNIQUELY HUMAN FEATURES OF SIALIC ACID BIOLOGY: MECHANISTIC CONNECTIONS TO BIOMEDICAL DIFFERENCES?

There are undoubtedly many reasons, including many that have yet to be discovered, for the nonanatomical biomedical differences observed between humans and NHHs. In our own research, we have found multiple differences between humans and NHHs in terms of the biology of sialic acids and sialic acid–recognizing proteins. These differences are summarized in **Table 2**, and detailed accounts can be found elsewhere (10–12). Given that fewer than 60 genes are involved in sialic acid biology, our finding that more than 10 of them show human-specific changes (12) suggests that this system represents a "hot spot" in human evolution. A dramatic change in the sialic acids of human cell surfaces, which occurred approximately ~2–3 Mya, is characterized by *Alu*-mediated inactivation of the *CMAH* gene that caused (*a*) a loss of synthesis of the common mammalian sialic acid *N*-glycolylneuraminic

Table 1 Apparent differences between humans and nonhuman hominids (NHHs) in the incidence and severity of biomedical conditions[a] and the potential role of sialic acid biology changes

Medical condition	Humans	NHHs	Potential roles of sialic acid biology changes
Definite differences			
Myocardial infarction	Common	Very rare	Low Siglecs: increased immune reactivity? Dietary Neu5Gc accumulation in endothelium and atheromas
Interstitial myocardial fibrosis	Rare	Common	Different patterns of cardiac sialylation?
Plasmodium falciparum malaria infection	Susceptible	Resistant	Neu5Ac is the preferred merozoite ligand
Sexually transmitted bacterial diseases	Common	Very rare	Bacterial Neu5Ac engages Siglecs?
HIV infection progressing to AIDS	Common	Very rare	Low Siglecs: increased immune reactivity?
Foamy virus (spumavirus) infection	Rare	Common	Did anti-Neu5Gc antibodies eliminate?
Probable differences			
Human influenza A susceptibility	Variable	Often mild	α2-6-linked Sias on upper airways Low Siglecs: increased immune reactivity?
Hepatitis B/C late complications	Variable	Often mild	Low Siglecs: increased reactivity?
Alzheimer's disease pathology	Common	Rare	Siglec expression in microglia?
Epithelial cancers (carcinomas)	Common	Rare?	Neu5Gc in carcinomas
Neu5Ac-expressing bacterial pathogens	Common	Rare?	Excess endogenous Siglec-1 ligands? Bacterial Neu5Ac engages inhibitory Siglecs?
Preeclampsia	Common	Rare?	Siglec-6 expression in placenta
Preterm labor	Common	Rare?	—
Possible differences			
Rheumatoid arthritis	Common	Rare?	Low Siglecs: increased immune reactivity? Neu5Gc in joints?
Bronchial asthma	Common	Rare?	Low Siglec: increased immune reactivity?
Early fetal wastage	Common	Rare?	—
Hydatidiform molar pregnancy	Common	Rare?	—
Endometriosis	Common	Rare?	Neu5Gc in endometrium?
Female iron deficiency	Common	Rare?	—
Major psychiatric diseases	Common	Rare?	—

[a]Excludes disease differences due to obvious anatomical differences. Abbreviations: Neu5Ac, *N*-acetylneuraminic acid; Neu5Gc, *N*-glycolylneuraminic acid.

acid (Neu5Gc) and (*b*) an accumulation of the precursor sialic acid *N*-acetylneuraminic acid (Neu5Ac). This transformation appears to have been followed by a variety of (probably linked) changes in other sialic acid–related genes, including increased expression of α2-6-linked Sias (probably due to increased expression of the *ST6GALI* gene) and multiple changes in genes encoding Sia-recognizing immunoglobin-like lectins (Siglecs), including binding-specificity changes (in Siglec-5, -7, -9, -11, and -12), gene conversion–based sequence changes (in Siglec-11), expression-pattern changes (in Siglec-1, -5, -6, and -11), and instances of deletion or partial pseudogenization (in *SIGLEC13*, *SIGLEC14*, and *SIGLEC16*) (12). An additional nongenetic outcome of the *CMAH* mutation is that Neu5Gc derived from the diet (particularly foods of mammalian origin) can become incorporated into human tissues, particularly endothelia and epithelia. This Neu5Gc-accumulation process can occur despite the presence of a broad spectrum of circulating anti-Neu5Gc antibodies, and the combination may lead to chronic inflammation (12). In the following sections on biomedical differences between NHHs and humans, we mention possible connections to these uniquely human changes in sialic acid biology. Several of these possibilities require much further

Sialic acid–recognizing immunoglobin-like lectins (Siglecs): constitute the largest known family of sialic acid–recognizing proteins

Table 2 Human-specific changes in sialic acid biology–related genes[a]

Gene	Human-specific changes	Possible consequences for humans
CMAH	Human-specific *Alu*-mediated deletion eliminates exon 6, resulting in frame-shift and truncated inactive enzyme	Loss of Neu5Gc and excess of Neu5Ac expression on cell surfaces
		Corresponding effects on pathogen recognition and invasion
		Metabolic incorporation of Neu5Gc from diet, despite anti-Neu5Gc antibodies
SIGLEC1	Increased endogenous Neu5Ac-rich ligands in humans; enhanced frequency and broader expression pattern in macrophages	Increased likelihood of masking by endogenous Neu5Ac-rich ligands?
		Altered phagocytosis of Neu5Ac-expressing pathogens?
		Increased uptake of hypersialylated viruses by macrophages?
SIGLEC5	Expression suppressed on T cells; likely restoration of essential arginine residue for sialic acid recognition	Hyperresponsive phenotype of human T cells
		Possible role in propensity for diseases associated with T cell activation
		Interactions with group B *Streptococcus* type Ia β protein?
SIGLEC14	Likely restoration of essential arginine residue for sialic acid recognition; fusion/deletion population polymorphism	Loss of leukocyte activatory potential in homozygous null individuals?
SIGLEC6	Placental trophoblast expression	Expression levels increase with progress of labor
		Expression is further upregulated in preeclampsia (a human-specific disease)
SIGLEC7 and *SIGLEC9*	Amino acid changes in V-set domain; adjusting of Neu5Gc to Neu5Ac recognition	Enhanced susceptibility to Neu5Ac-expressing pathogens that dampen innate leukocyte responsiveness?
SIGLEC11	Human-specific gene conversion; new expression in brain microglia	Altered interactions of microglia with neural cells?
		Altered response of microglia to infections?
SIGLEC12	Human-specific mutation of "essential arginine residue" for sialic acid recognition	Unknown
SIGLEC13	Human-specific deletion	Unknown
SIGLEC16	Human-specific inactivating mutation; population polymorphism	Altered interactions of microglia with neural cells?
		Altered response of microglia to infections?
ST6GAL1	Increased expression of Siaα2-6Galβ1-4GlcNAcβ1 termini in various cell types	Protection from avian influenza viruses, which prefer α2-3 sialic acid linkages, and susceptibility to human influenza viruses, which prefer α2-6 sialic acid linkages

[a]For details, see References 11 and 12. Abbreviations: Neu5Ac, *N*-acetylneuraminic acid; Neu5Gc, *N*-glycolylneuraminic acid.

research, and many other, unrelated factors are likely to be operative.

DEFINITE BIOMEDICAL DIFFERENCES BETWEEN HUMANS AND NONHUMAN HOMINIDS

Cardiovascular Disease: Myocardial Infarction Versus Interstitial Myocardial Fibrosis

The most common cause of death in both humans and captive chimpanzees was long thought to be cardiovascular disease that manifested either as sudden death due to heart attacks or as a slower death due to progressive heart failure (5, 43, 44). Older studies often assumed that cardiovascular disease was a human-chimpanzee similarity, although some studies noted different pathologies (45, 46). A more detailed comparison (47) indicates that the two diseases are indeed completely different. Human cardiovascular disease is caused primarily by progressive atherosclerosis, in which deposition of low-density lipoprotein–derived cholesterol causes gradual blockade of arteries, especially the coronary blood supply

to the heart. When complete blockage of coronary arteries occurs acutely, it causes the typical human heart attack, also known as a myocardial infarction. When ischemia to the myocardium occurs gradually, it gives rise to progressive, congestive heart failure.

Although NHHs suffer from a moderate degree of atherosclerosis in captivity and can be induced to have more severe disease via lipid feeding (48, 49), atherosclerosis only rarely leads to blockage of coronary arteries (although blockage of cerebral blood vessels leading to stroke can occur). There is one report of a gorilla in which coronary atherosclerotic occlusion was detected at necropsy (50). Recent reanalysis by several groups shows that early reports of sudden cardiac death or cardiomyopathy in NHHs were due to diffuse fibrosis that affected the myocardium; such interstitial myocardial fibrosis (IMF) is pathologically quite different from the human disease (**Figure 1**) (43, 44, 47, 51). Further analysis indicates that this type of pathology is common in all NHHs (particularly in males) and that it manifests either as a heart attack—that is, as sudden death, probably arising from a change in the cardiac rhythm—or as progressive heart failure due to loss of myocardial function.

Thus, there are two mysteries to unravel. First, why is it that humans do not get the common form of IMF observed in NHHs? Second, why is it that NHHs do not frequently get the coronary atherosclerotic blockage that causes the common human form of ischemic heart disease? The first question is difficult to answer, but our analysis reveals differences in terminal glycosylation of sialic acids and other glycans in the myocardium of the human versus chimpanzee heart, and there is additional evidence for a higher density of small blood vessels in the human myocardium as well as more fibrous septae in the normal NHH myocardium (**Figure 2**) (47). Regarding the second question, the likely explanation is that atherosclerosis in humans is more severe than in NHHs, although both groups share many of the same risk factors (47, 52–56). Our work on sialic acids suggests two possibilities that may contribute

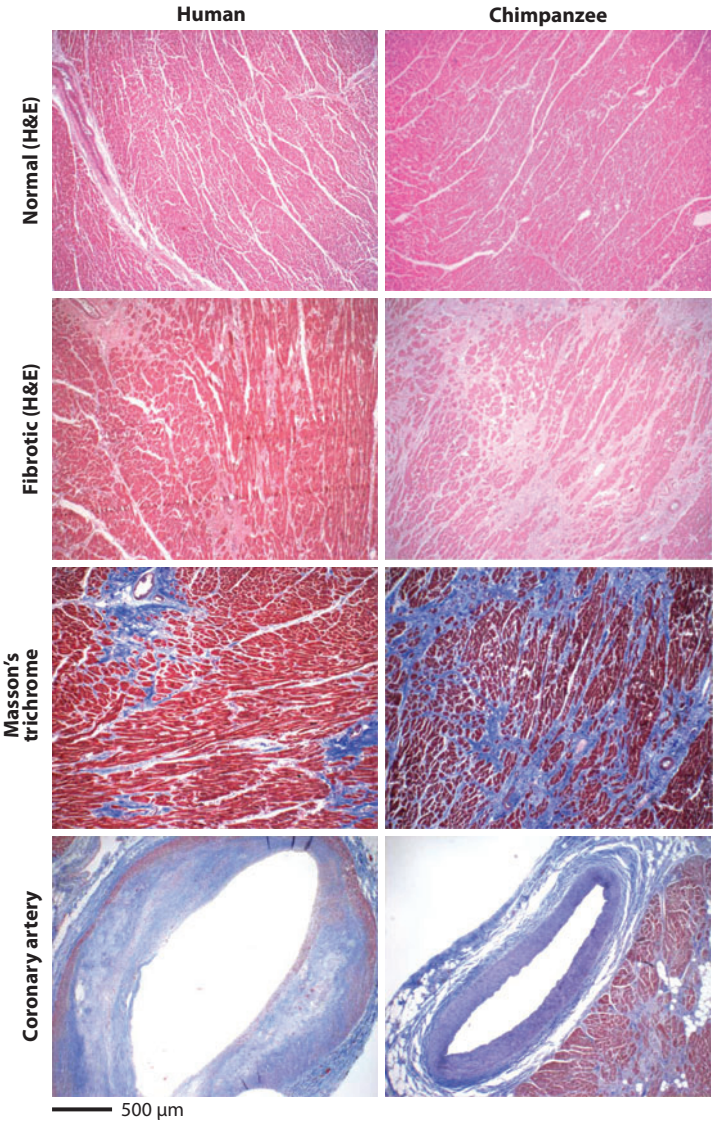

Figure 1

In humans and nonhuman hominids, different pathologies lead to cardiac disease. Shown are histological comparisons between human and chimpanzee hearts and coronary blood vessels. (*Top*) Hematoxylin and eosin (H&E) stains of normal myocardium sections from humans and chimpanzees appear very similar. (*Top middle*) An example of fibrosis immediately surrounding blood vessels, as observed in some human hearts, and an example of extensive interstitial myocardial fibrosis in a chimpanzee heart. (*Bottom middle*) Collagen fibrosis is more clearly seen with Masson's trichrome stain. (*Bottom*) Atherosclerotic coronary artery typically observed in humans (note the subendothelial plaques), compared with a typical uninvolved coronary artery in a chimpanzee, as observed using Masson's trichrome stain. Reproduced with permission from Reference 47.

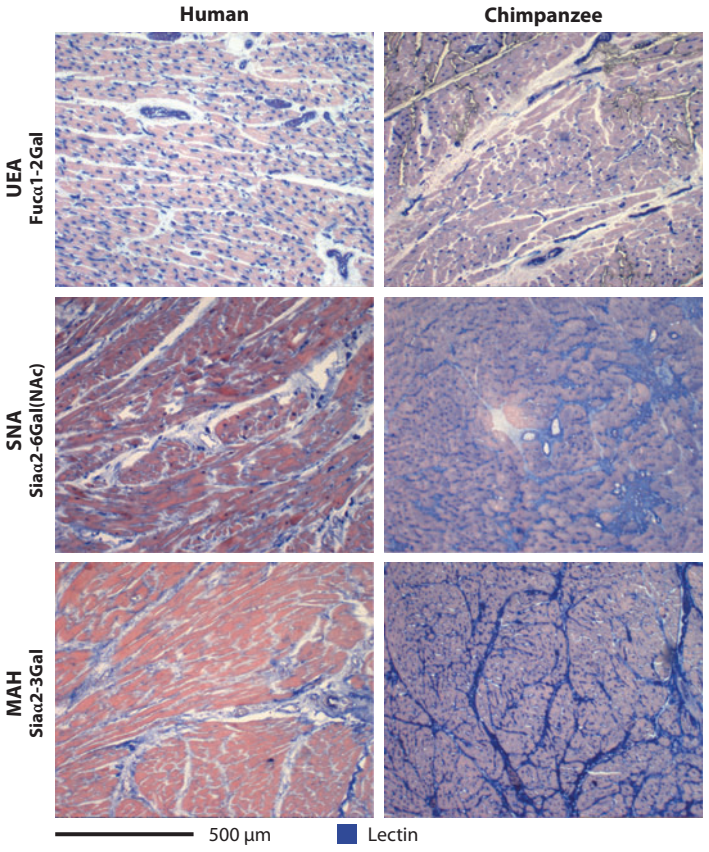

Figure 2

Uniquely human expression patterns of glycans in cardiac muscle: lectin staining of histologically normal–appearing myocardial sections from humans and nonhuman hominids. Shown are examples of typical lectin-staining patterns in human and chimpanzee myocardial sections using *Ulex europaeus* agglutinin (UEA), which recognizes terminal fucose residues in the sequence Fucα1-2Galβ1-4GlcNAcβ; *Sambucus nigra* agglutinin (SNA), which recognizes terminal Siaα2-6Galβ1-4GlcNAcβ units on N-linked glycan chains of glycoproteins; and *Maackia amurensis* hemagglutinin (MAH), which recognizes Siaα2-3Gal termini on various glycoconjugates (74, 75). The results shown are typical of those observed in 11 human and 7 chimpanzee samples. Three gorilla and four orangutan samples yielded results similar to those of the chimpanzee sections. Modified with permission from Reference 47.

to this difference. First, we found that human lymphocytes are more reactive than those of chimpanzees (57, 58), which may represent a potential mechanism for accelerating the inflammation observed in human atherosclerotic lesions. Second, we observed incorporation of the nonhuman sialic acid Neu5Gc into the endothelial cells of humans (**Figure 3**) (59), which occurs in the presence of circulating anti-Neu5Gc antibodies that can react with these immunogenic epitopes. In vitro studies using human endothelial cells fed with Neu5Gc support the notion that exposure of human endothelium expressing Neu5Gc to human sera bearing anti-Neu5Gc antibodies can trigger complement-mediated activation, monocyte adhesion, and inflammation (59)—mechanisms that are common to both early atherosclerosis and late stages of lesion progression. Our studies suggest possible mechanisms to be explored, although additional explanations remain likely.

Plasmodium falciparum Malaria

Human malaria is caused by various *Plasmodium* parasites that invade erythrocytes. *Plasmodium* sporozoites are injected from salivary glands of the mosquito vector into the host bloodstream, where they multiply in hepatocytes and are then released back into the bloodstream as merozoites. Merozoites bind to various surface receptors on erythrocytes, invading and eventually destroying them. Of the various *Plasmodium* parasites, *P. falciparum* has the greatest virulence in humans; it is known as malignant malaria because it is responsible for most malaria deaths worldwide. Interestingly, this parasite does not cause severe disease in chimpanzees (60), and it appears to be of relatively recent origin, estimated at only tens of thousands of years ago (61). What was its precursor? The most logical candidate is *P. reichenowi*, a similar organism that infects both chimpanzees and gorillas in Africa (62). Investigators initially believed that the two parasites speciated at the same time that the human and chimpanzee lineages split, which occurred ~6 Mya (62). However, this hypothesis does not accord with *P. falciparum* being a recently evolved pathogen. A potential explanation for this paradox, which relates to our work on sialic acids, was recently put forward.

Sialic acids are critical components of binding targets on erythrocytes that are used by *P. falciparum* merozoites, and the major carriers of sialic acids (the glycophorins) are rapidly evolving (63). The EBA-175 major binding

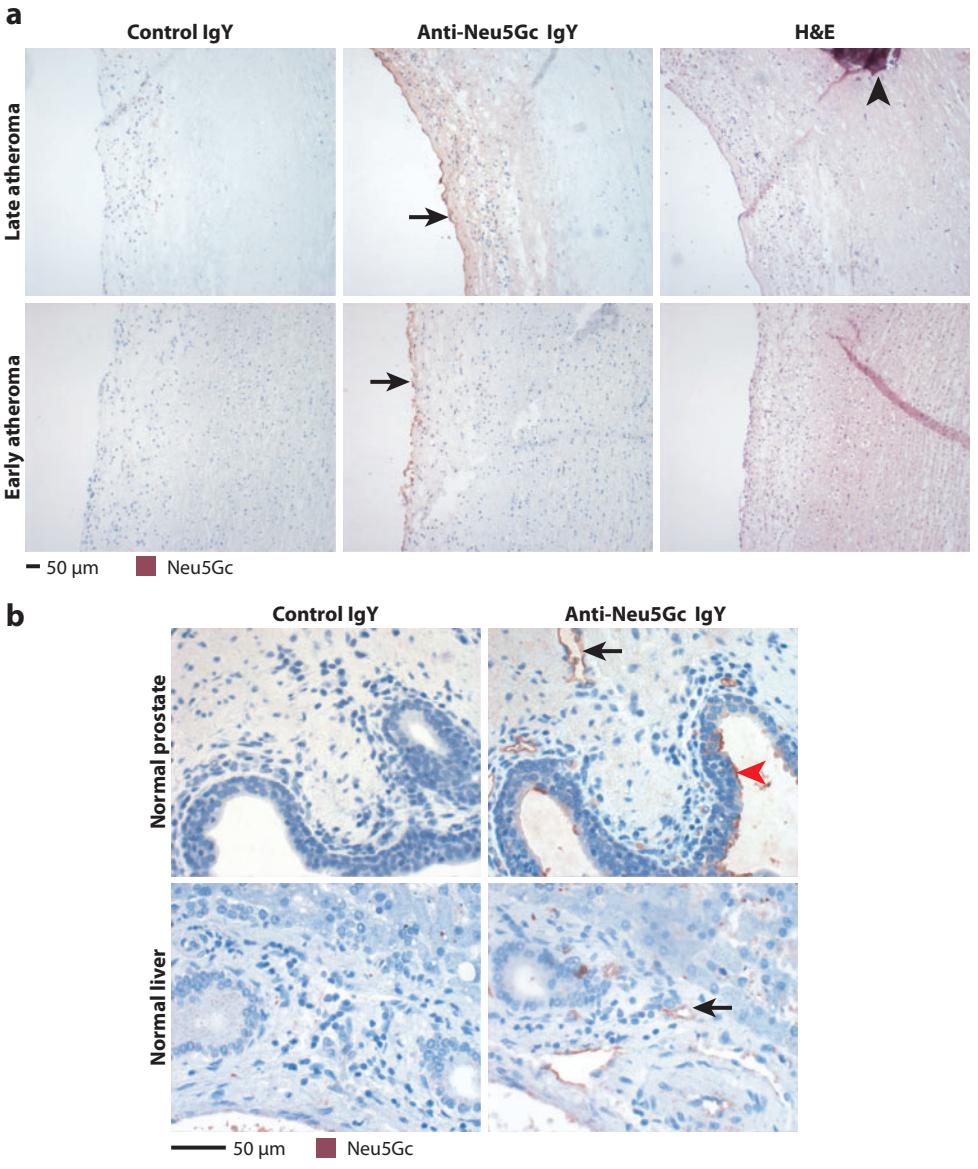

Figure 3

Human metabolic incorporation of dietary *N*-glycolylneuraminic acid (Neu5Gc) into normal and diseased endothelium. (*a*) Immunohistochemistry on frozen sections of aorta with the monospecific polyclonal chicken anti-Neu5Gc antibody and immunoglobin Y (IgY) control demonstrates expression of metabolically incorporated Neu5Gc (*red color*, *arrows*) along the endothelial surface of early and advanced atheromatous lesions; calcification is indicated by the arrowhead. Note the infiltration of Neu5Gc into the subintimal areas of the late lesion. Magnification: 200×. (*b*) Immunohistochemistry with a monospecific polyclonal chicken anti-Neu5Gc antibody and IgY control on paraffin sections of normal tissues demonstrates expression of metabolically incorporated Neu5Gc in the endothelia of capillaries (*arrows*). Note the expression along the luminal edge of the epithelial cells of the prostate gland (*red arrowhead*). For other examples, see References 59 and 174. Magnification: 400×.

Acquired immune deficiency syndrome (AIDS): disease characterized by loss of immune function following infection with HIV; not every human with HIV infection progresses to AIDS, and it is very rare among NHHs

protein of *P. reichenowi* merozoite prefers to recognize Neu5Gc, the sialic acid missing in humans (64). Thus, when ancestral hominins lost their Neu5Gc expression, they may have become relatively resistant to the existing *P. reichenowi* malaria. Indeed, this might even have been the selection mechanism that eliminated Neu5Gc synthesis from the lineage leading to humans. Thereafter, our ancestors may have enjoyed a period of relative freedom from this form of malaria. However malarial parasites evolve more rapidly than humans do, and new data indicate that one strain of *P. reichenowi* eventually switched over to binding the Neu5Ac-rich sialic acids of human erythrocytes, perhaps even in a single NHH-human transfer (65). Although such a transfer would be difficult to date precisely, it may have occurred somewhere in Africa, probably prior to the origin of modern humans. Thereafter, the advent of the Neolithic age, followed by agriculture and civilization, would have allowed the mosquito vector to proliferate, thereby facilitating expansion of what we now know as *P. falciparum* malaria (66). Further work is needed to confirm and extend these observations, but so far all information is consistent with this scenario.

Sexually Transmitted Bacterial Diseases

Chimpanzees and bonobos display promiscuous sexual behavior, albeit in different patterns of mating. Such behavior undoubtedly accounts for the transmission of retroviruses and perhaps other, as-yet-undiscovered diseases. Sexually transmitted bacterial diseases common in humans have not been reported in NHHs. These diseases include gonorrhea caused by *Neisseria gonorrhoeae* (67, 68), syphilis caused by *Treponema pallidum* (69), and chancroid caused by *Hemophilus ducreyi* (70). These organisms probably entered into human populations after the time of our last common ancestor with the chimpanzee. It is difficult to ascertain when this transfer occurred, and how and why humans acquired these diseases, but notably, two of these organisms (*Neisseria gonorrhoeae* and *Hemophilus ducreyi*) express sialic acids on their surfaces. Expression of sialic acids by bacteria can allow engagement of human Siglecs (which prefer Neu5Ac, the sialic acid produced by the bacterium), thereby dampening the innate immune system and allowing for the establishment of infection (71). Thus, the human loss of Neu5Gc and the adjustment of inhibitory human Siglecs to recognize Neu5Ac (72) may have facilitated the emergence of these bacterial sexually transmitted diseases in humans. In the case of gonorrhea, additional mechanisms for human species specificity have been described (67, 68).

Human Immunodeficiency Virus Infection Progressing to Acquired Immune Deficiency Syndrome

When the human immunodeficiency virus (HIV) epidemic first became evident in the early 1980s, the only animal found to support in vivo virus growth was the chimpanzee (73). Subsequently, more than 100 chimpanzees in the United States and Europe were experimentally infected with HIV. Surprisingly, after more than 10 years, only one chimpanzee progressed to a full-blown acquired immune deficiency syndrome (AIDS)-like syndrome (74), and infected blood from this chimpanzee caused similar outcomes in other individuals into whom it was transferred (75). Since then, numerous other infected chimpanzees developed low CD4 counts, but often without an AIDS-like syndrome (76). Moreover, all of these cases occurred in animals that were infected with multiple HIV isolates, which suggests the existence of unusual variants that evolved within the captive chimpanzee hosts. Overall, humans appear to be more susceptible to progression to AIDS from HIV infection. The exact reasons for this difference are unclear, despite many studies on the subject (e.g., 77–84), but apparently it is not due to any cellular protection from primary or secondary infection, and asymptomatic infected chimpanzees may carry a viral load similar to that of humans with AIDS.

These findings are especially surprising because we now know that (*a*) HIV is derived from

chimpanzee simian immunodeficiency viruses (SIVs) that were transmitted into humans on rare occasions during the past century (85) and (*b*) similar viruses are common in some West African chimpanzee populations and apparently do not cause progress to AIDS (86). Notably, East African chimpanzees in which HIV did not originate carry an SIV that causes a mild to moderate immune deficiency and leads to decreased life span (87). However, even in those cases, the immunodeficiency appears to be milder than in untreated human HIV infections.

Differences in the activity of molecules such as APOBEC3G and TRIM5α between humans and chimpanzees cannot account for the differences in AIDS susceptibility observed in these two species, as the molecules are essentially identical in sequence (88, 89). Many other explanations have been suggested, and the most recent review of the topic concludes "that a critical factor that differentiates nonprogressive from progressive HIV infection is the maintenance of T cell immune competence in the face of a virus that infects and kills $CD4^+$ T cells" (see the abstract of Reference 90). The explanation currently considered the most likely is that the human immune system overreacts to the virus, which causes the eventual exhaustion and elimination of $CD4^+$ T cells (78–80, 82, 91, 92). A related possibility is overreactivity of human T cells to defective HIV virions (84). Natural SIV hosts may avoid the generalized immune system activation that is associated with disease progression in HIV-infected individuals (83, 90). A specific mechanism is the structural and immunological damage to the gastrointestinal tract that occurs during the acute phase of HIV infection in humans, breaching the mucosal barrier and leading to generalized immune activation by bacterial products (93). However, human T lymphocytes are more reactive than their chimpanzee counterparts; decreased expression of inhibitory Siglecs on human lymphocytes may explain this relative overreactivity (57, 58). Regardless of the underlying mechanism, the relative overreactivity of the human T cell may contribute to the excessive responses to the virus. This hypothesis is testable and is currently under study.

Foamy Virus (Spumavirus) Infection

All known primate lineages (and, in fact, most mammals) harbor endemic infectious retroviruses known as spumaviruses (foamy viruses) that are often present in the majority of individuals in a species and seem to cospeciate with each lineage (94). The same is true of NHHs (95, 96). As mentioned above, NHHs also have other endemic retroviruses, such as SIVs and simian T cell leukemia viruses. Thus, the common ancestral population of humans and chimpanzees must have harbored many of these endemic viruses. However, current human populations did not have endemic spumaviruses or any of the other retroviruses mentioned—until the emergence of the HIV epidemic and the geographically localized detection of human T lymphotropic viruses over the past century. Human infections with these viruses can occur; that is, humans did not escape them by developing resistance (97, 98).

Again, there are two mysteries to be solved. First, how did the human lineage purge itself of these endemic viruses? Second, despite continuing (and increasing) contact with humans in recent times (due to the bush-meat trade), why is it that repeated transmissions of these viruses into humans do not occur on a regular basis? Interestingly, enveloped viruses carry sialic acids from the host cell in which they originate. Thus, it is speculated (P. Gagneux, personal communication) that enveloped viruses produced in NHHs, or other Old World primates, that express Neu5Gc might be killed upon contact with human body fluids, which contain antibodies directed against Neu5Gc-expressing viruses. This hypothesis may also explain why there have been no recently documented episodes of transfer of these viruses into the human population, despite increasing exposure of African hunters and bush-meat vendors to SIV-infected chimpanzee carcasses. This issue is under study.

PROBABLE BIOMEDICAL DIFFERENCES BETWEEN HUMANS AND NONHUMAN HOMINIDS

Human Influenza A Susceptibility

Influenza A viruses infect humans by attaching to sialic acid receptors on upper airway epithelial cells. The ciliated columnar epithelial cells of humans express cell-surface glycans with an abundance of terminal α2-6-linked sialic acids, and human influenza A viruses have a binding specificity for this linkage (99). In contrast, bird influenza viruses prefer to bind to α2-3-linked sialic acids, which may explain why these viruses do not easily transfer into humans. The upper airways of chimpanzees and other NHHs are more similar to those of birds in that they do not express an abundance of terminal α2-6-linked sialic acids (**Figure 4**) (100). The latter may be the ancestral condition, and at some point in human evolution, a switch to expression of α2-6-linked sialic acids may have occurred. A possible scenario is that this selection was mediated by the malarial parasite merozoite EBA-175 protein, which also prefers to bind to α2-3-linked sialic acids (66). The same episode of selection that eliminated Neu5Gc from humans may have simultaneously selected for a switch in preference to expressing α2-6-linked sialic acids (12). Although further studies are needed, we note that relatively large doses of human influenza virus were given to chimpanzees and did not cause severe illness (101, 102). Given that complications of influenza can be caused not only by the virus but also by an excessive immune response, another plausible reason is that chimpanzee T cells are less reactive (57, 58).

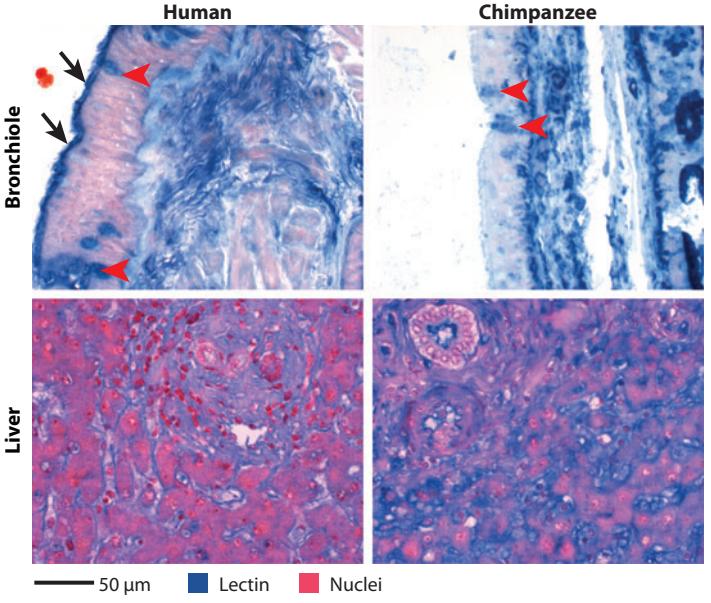

Figure 4

Uniquely human patterns of α2-6-linked sialic acid expression in upper airway and other tissues. Paraffin sections of respiratory epithelium and liver using *Sambucus nigra* lectin. (*Top*) Respiratory epithelium of human and chimpanzee bronchioles, highlighting the cilia and the basal bodies to which they are attached (*arrows*), as well as the mucin-containing goblet cells (*red arrowheads*). Note that the cilia are *Sambucus nigra* positive only in humans. Only some goblet cells are *Sambucus nigra* positive. (*Bottom*) Human and chimpanzee liver sections. Staining of endothelium-lined sinusoids is observed in both species, but in the chimpanzee, it is also observed within hepatocytes. The blue substrate demonstrates *Sambucus nigra* binding; in contrast, the nuclei are identified with nuclear fast red. For other examples, see References 100 and 175. Magnification: 400×.

Hepatitis B and C Late Complications

Hepatitis B and C virus infections are common in humans, and a significant percentage of such infections eventually progress to chronic active hepatitis and/or liver cirrhosis, which sometimes terminate in hepatocellular carcinomas. NHHs, and particularly chimpanzees, have long been recognized as hosts for these diseases, and in the case of hepatitis C, they are apparently the only available model (103–109). Interestingly, although cases of chronic hepatitis and/or hepatocellular carcinoma have been reported in chimpanzees, animals infected with these viruses rarely develop the types of complications commonly seen in humans (103, 107, 109). There are two possible interpretations of these findings, which are not mutually exclusive. First, there may indeed be a difference between human and chimpanzee responses to the virus, in accord with the observation that many late complications of the hepatitis viruses may be caused not by any cytopathic effect of the viruses per se but rather by an overexuberant immune response (110). This observation

would also accord with our finding of excessive reactivity of human T lymphocytes compared with chimpanzee T lymphocytes (57, 58). Second, these chimpanzee infections are not natural (i.e., they are induced by injecting a bolus dose of viruses derived from humans), and the immune response may thus be skewed in a manner that is favorable for the experimental chimpanzee. Overall, a review of the literature does not indicate which of these two possibilities is correct, and both may be true to some extent. Regardless, these diseases should be placed in the category of probable differences between humans and NHHs; further studies are needed.

Epithelial Cancers

The most common malignancies of humans are carcinomas, which arise from epithelial cells that line various hollow organs and the skin. Aside from skin carcinomas, which are often diagnosed early enough for curative resection, other carcinomas (e.g., head and neck, esophagus, breast, lung, stomach, pancreas, colon, ovary, prostate, and endometrium) constitute the bulk of human cancers worldwide in terms of both incidence and mortality (111). Although skin carcinomas are not commonly reported in NHHs, there are vast differences in skin histology among humans and NHHs, as well as in protection from direct exposure to sunlight by hair. It is more difficult to explain why the other common carcinomas of humans have not been found in NHHs (4, 5, 112), even in captive populations that live to age 40 and beyond, whereas a significant frequency of carcinomas is observed in humans. This relative rarity of carcinomas in NHHs extends to captive nonhuman primates in general (9), with the exception of cases in which a clear risk factor can be identified (e.g., colon carcinoma in the setting of ulcerative colitis in the cottontop tamarin) (113) and cases of hepatocellular carcinoma associated with chronic *Schistosoma mansoni* infection (114). This difference is probably not an ascertainment bias, given that high-quality necropsy and tissue reports show that NHHs suffer from some of the less common cancers of humans (112, 115–117). Additional data against ascertainment bias include frequent detection of benign tumors in NHH necropsies (4, 5, 112).

Increasing age is a risk factor for human carcinomas, and significant numbers of NHHs are reaching an advanced age in captivity now that early mortality from other factors such as infectious diseases is decreased. Additionally, captive NHH populations are less exposed to certain human risk factors, such as smoking, dietary red meat, and potential environmental carcinogens. However, although these risk factors vary substantially across human populations, baseline rates of these carcinomas across the world are still significant worldwide (111). Data on hunter-gatherers are consistent but very limited (118, 119).

The most recent retrospective analysis of this issue concluded that although neoplasia in general is not uncommon in the chimpanzee, it is generally benign and occurs primarily in the urogenital system in females (112). Incidence of carcinomas (malignant tumors of epithelial origin) may fall into the category of probable differences between humans and NHHs. If so, what might explain this difference? Notably, the hallmark feature of all these carcinomas is multiple chromosomal abnormalities (120). Also, such multiple chromosomal abnormalities are also a feature of early fetal wastage (see below) (121), a common and possibly human-unique feature that has also been observed in human embryos fertilized in vitro (122). Perhaps the human chromosomal segregation processes are more prone to the generation of such abnormalities, thereby increasing the risk of carcinomas. It may be relevant that, at some unknown time in human evolution, two ancestral NHH chromosomes underwent a telomeric fusion that resulted in the creation of human chromosome 2, which still has residual telomeric sequences in the fusion region (123), and that aneuploidies can be induced in yeast through the addition of extra telomeres (124).

Also, many recent studies have emphasized a critical role for chronic inflammation in carcinoma progression (125–127). We found one potentially human-specific variation of this

mechanism for aggravation of carcinoma risk that involves two phenomena. The first is the metabolic incorporation of the nonhuman sialic acid Neu5Gc from dietary sources (principally red meat) into epithelia as a xeno-autoantigen, a novel term we coined, referring to the fact that Neu5Gc enters the body from dietary sources and becomes incorporated into human tissues even in the presence of an ongoing immune response that recognizes the molecule as foreign. The molecule can be described as xeno, that is, as originating from other animals, as well as auto, that is, expressed on human cell surfaces as an antigen (see **Figure 5** for examples). The resulting mechanism is chronic inflammation resulting from interactions with circulating anti-Neu5Gc antibodies (128). The second mechanism is the relative overreactivity of human lymphocytes to stimulation (57, 58), which may also contribute to such chronic inflammation.

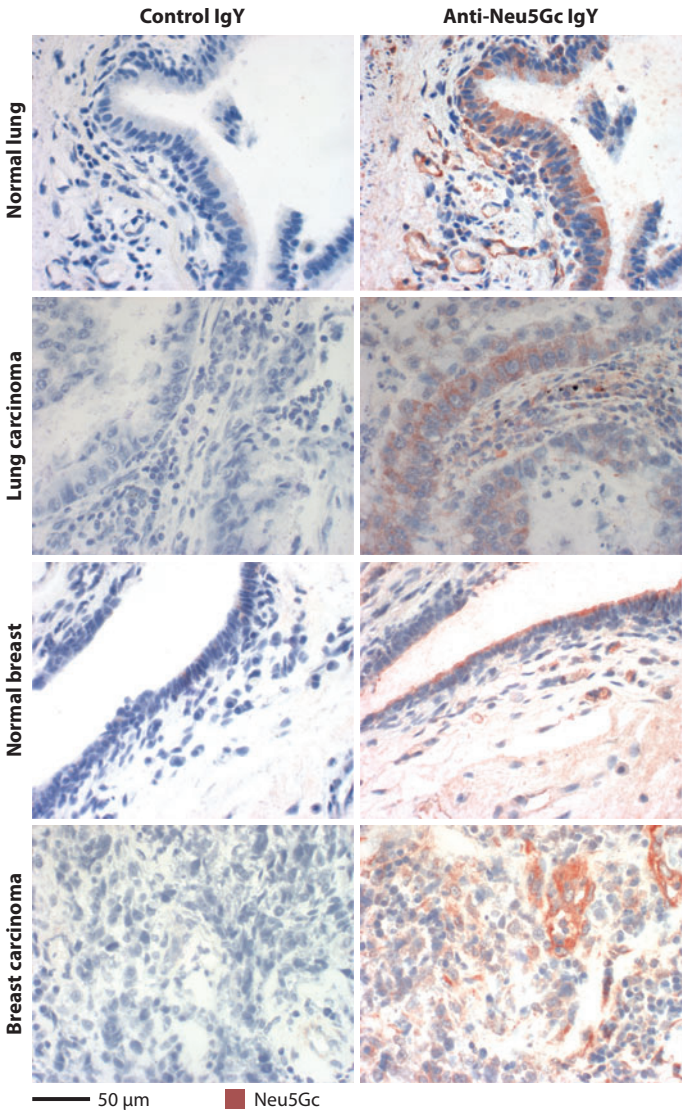

Figure 5

Human metabolic incorporation of dietary *N*-glycolylneuraminic acid (Neu5Gc) into normal and malignant epithelial cells. Immunohistochemistry using the monospecific polyclonal chicken anti-Neu5Gc antibody with immunoglobin Y (IgY) control on paraffin sections of human samples. The red color identifies binding of the anti-Neu5Gc IgY to the microvasculature, to the luminal edge of normal bronchial and breast duct epithelium, and to malignant cells of lung carcinoma and breast carcinoma. For other examples, see References 164 and 174. Magnification: 400×.

Alzheimer's Disease Pathology

Alzheimer's disease is the most common cause of dementia in older humans. Although pathologic examination is necessary for definitive diagnosis, imaging studies and clinical assessment can be reasonably accurate. Examination of the brain shows cortical atrophy, and classic histological findings are characterized by accumulation of amyloid plaques and neurofibrillary tangles, along with extensive synaptic and neuronal loss. These features of full-blown Alzheimer's disease have not been reported in any other animal, including chimpanzees and other NHHs. Age-matched studies of NHH and human brains showed that although amyloid plaques are observed at a frequency similar to that in humans, neurofibrillary tangles in NHHs (with one unusual exception; see Reference 129), or indeed in any other animal, have never been reported (130, 131). A possible explanation is that NHHs simply do not live long enough for these events to accumulate. However, whereas asymptomatic humans ranging in age from 40 to 60 may show some of these early pathologies, age-matched NHH brains in the same age range do not (130). The number of older NHH brains studied is small, but the pathology of Alzheimer's disease falls into the probable difference category; further work is needed to define the extent of this

difference and the mechanisms involved. Notably, activated microglia play an important role in inflammation and damage caused by Alzheimer's disease (132, 133), and humans are unique in expressing Siglec-11 in microglia (**Figure 6**) (134, 135) and possibly the activatory counterpart Siglec-16; the latter is partially pseudogenized in the human population (136). The possibility that excess microglial activation by Siglec-16 plays a role in some humans should be investigated.

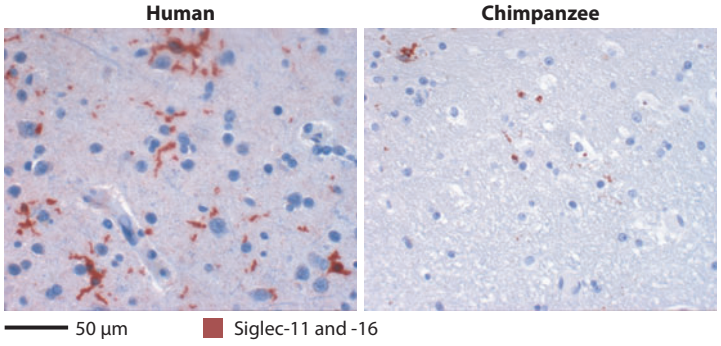

Figure 6

Uniquely human expression of Siglec-11 and -16 in the brain. Immunohistochemistry, using mouse antihuman Siglec-11 and -16 monoclonal antibody 4C4 on paraffin sections of brain, shows expression within many human microglia (*red*) but only rarely in the chimpanzee brain. For other examples and double staining, see References 134 and 135. Magnification: 400×.

Infections with Neu5Ac-Expressing Bacterial Pathogens

Several bacteria have independently reinvented the human sialic acid Neu5Ac (137, 138) and use this coating of a native glycan to subvert the human immune system by regulating complement deposition, dampening adaptive immune responses, and/or subverting inhibitory Siglecs to reduce reactivity of the innate immune system (71). Interestingly, of the pathogens known to produce Neu5Ac, the majority are human pathogens and several are human specific (137). Given the extent and high quality of current veterinary microbiology, it seems unlikely that this apparent difference is merely an ascertainment bias. A more likely possibility is that humans are particularly prone to be exploited by such organisms because our Siglecs have adjusted to the loss of Neu5Gc and preferentially recognize Neu5Ac as self (12, 72); importantly, no bacterium has ever reinvented Neu5Gc. It would be interesting to study the interactions of Neu5Ac-expressing bacteria with neutrophils from NHHs, whose major Siglecs prefer to bind Neu5Gc (72).

Several of these pathogens affect fetuses, newborns, infants, children, and young adults, and they may have had a marked effect on reproductive fitness. Thus, the emergence of these pathogens may have followed the human loss of Neu5Gc and the adjustment of Siglecs to bind Neu5Ac, and it could be an ongoing process. Our current data concerning multiple changes of CD33-related Siglecs in humans (12) support this scenario. Also consistent with this idea is the finding that the nonsignaling phagocytotic Siglec on macrophages (known as Siglec-1 or sialoadhesin) has apparently undergone upregulation and a change of distribution in humans (**Figure 7**) (139).

Preeclampsia

A trio of abnormalities define the apparently human-specific disease of preeclampsia: new-onset hypertension, proteinuria, and edema. This disease occurs after ~20 weeks of gestation in 3% to 5% of human pregnancies (more often in primiparous women) (140). Some patients develop full-blown eclampsia, which is characterized by convulsions and disseminated intravascular coagulation. The only cure is delivery of the placenta. Development of preeclampsia has been correlated with incomplete trophoblast penetration into the endometrial spiral arterioles during the time of implantation, which results in altered blood flow and an ischemic placenta. Placental antiangiogenic factors are also upregulated (140), and the maternal spiral artery endothelium is disrupted. Additionally, the increase in human brain size and the prolonged labor process may be connected in a way that is distinctly human (141). The cause of the disease and why it is specific to humans are unknown.

Xeno-autoantigen: refers to the nonhuman sialic acid *N*-glycolylneuraminic acid, which enters the body from dietary sources and becomes incorporated into human tissues (particularly endothelia and epithelia), even in the face of an ongoing immune response that recognizes the molecule as foreign

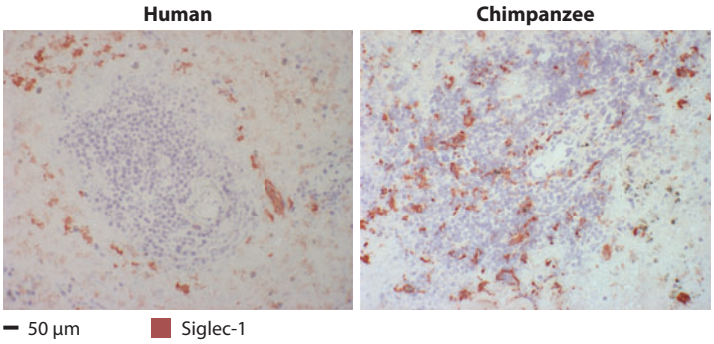

Figure 7

Uniquely human expression pattern of Siglec-1 in the spleen. Immunohistochemistry on frozen sections of spleen, using mouse anti-CD169/Siglec-1 antibody (AbCam), shows differences in Siglec-1 expression patterns (*red*). In the human spleen, anti-Siglec-1 identifies cells only outside the lymphoid follicles, whereas in chimpanzee spleen, the Siglec-1-marked cells infiltrate into the lymphoid follicle. For other examples and double staining, see Reference 139. Magnification: 100×.

Although Siglec-6 is expressed on the B cells of both humans and chimpanzees, it shows placenta-specific expression only in humans (**Figure 8**) (142). Intriguingly, the human-specific trophoblast expression of Siglec-6 is further upregulated in preeclampsia (143).

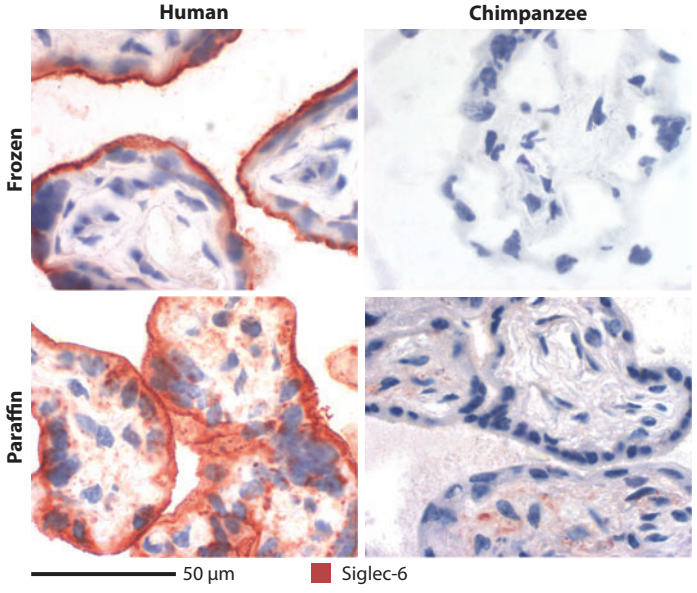

Figure 8

Uniquely human expression of Siglec-6 in placenta. Immunohistochemistry using mouse anti–human Siglec-6 antibody (BD Pharmingen) shows Siglec-6 expression on the trophoblast of human placenta only (*red*). For other examples and staining of Siglec-6 ligands, see Reference 142. Magnification: 1,000×.

Preterm Labor

Pregnancy and parturition in humans are rather unusual compared with those of other mammals, including NHHs (144, 145). Some investigators have suggested that "human parturition is a distinctly human event" (145, p. 271). It is difficult to accurately predict a delivery date for human infants, given that normal-term gestation ranges from 37 to 42 weeks (146). In contrast, the chimpanzee gestation period varies by only 10–12 days (147). In light of these findings and the human-specific tendency to develop preeclampsia (see the previous section), it is not surprising that spontaneous preterm labor is common in humans (148) compared with NHHs. Although multiple factors (including evolutionary ones) probably contribute (148), the uniquely human expression of Siglec-6, which seems to increase in levels during the process of labor, may play a role in the placenta (142).

POSSIBLE DISEASE DIFFERENCES BETWEEN HUMANS AND NONHUMAN HOMINIDS

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune process characterized by progressive bilateral arthritis and erosive inflammation of the synovial lining. RA affects up to 1% of the human population (149, 150). Its cause is unknown, and treatment generally aims to reduce inflammation and/or antibody production. With the exception of a few gorillas at one institution (46) that developed what appeared to be a mild form of this disease, RA seems rare in captive NHHs, probably because of environmental and/or genetic differences between humans and NHHs. There are two hypotheses regarding the role of sialic acids. First, the human propensity for relative lymphocyte overreactivity

(57, 58) could contribute to the difference between human RA and NHH RA. Second, RA was originally associated with an increase in circulating anti-Neu5Gc antibodies (151), and whether or not Neu5Gc accumulates in synovium and interacts with these antibodies is unknown. In this regard, increases in RA in several European countries were observed as more meat was added to national diets (152), and additional studies support a role for red meat in the risk of RA (150). Clinical experience suggests that fasting, followed by adoption of a vegetarian diet, can help treat some patients with RA (153).

Bronchial Asthma

Bronchial asthma is an allergic, hyperreactive, chronic inflammatory disease of the airways that is characterized by recurrent episodes of bronchospasm and breathlessness, which can be triggered in response to cold, exercise, or exposure to an allergen to which previous sensitization has occurred (154). Remarkably, there are no reported cases of bronchial asthma in captive NHHs. The symptomatology of asthma (wheezing and rapid breathing) is so obvious that the condition, if it occurred, would be easily diagnosed in NHHs. The reason for this surprising difference is unclear, but the human propensity for relative lymphocyte overreactivity (57, 58) is of interest. There are confounding factors. First, NHHs are often infected with parasites (which seem to be difficult to eliminate from the colonies), and such infections may reduce the frequency of asthma. Second, the now-popular hygiene hypothesis suggests that the incidence of asthma in developed countries has increased during the past several decades due to increased cleanliness. Notably, other allergic responses occur in chimpanzees, for instance, in the form of nasal polyps (155, 156).

Hydatidiform Molar Pregnancy

Hydatidiform moles are placental abnormalities that present with cystically swollen placental villi and a variably proliferative trophoblast that are associated with the partial or complete replacement of normal placental structure (157). This condition is usually identified during the fourth or fifth month of pregnancy if the uterus appears larger than expected, with abnormally high levels of serum human gonadotropic hormone levels (ultrasound examination can identify it earlier). Incidence in humans is 0.6–2 per 1,000 pregnancies, with higher rates in the Far East. Genetic studies show that most complete moles have a 46XX diploid pattern in which all 46 chromosomes are derived from a single sperm, which evidently fertilizes a blighted ovum and then duplicates the paternal genome. The occurrence of hydatidiform moles appears to be restricted to humans, with the exception of one case of a partial mole observed at necropsy of a pregnant chimpanzee that died of other causes (158). A possible explanation is that concealed ovulation of humans (159) results in a high frequency of mistimed copulations: The sperm may arrive after the ovum has begun to degenerate.

Endometriosis

Endometriosis arises from the abnormal presence of endometrial glands and stroma at sites other than the lining of the uterus (160, 161). These ectopic rests of endometrial tissue have been observed in the ovaries and peritoneum and are observed during laparoscopies in almost 10% of women of childbearing age (162). The disease contributes to infertility and morbidity due to recurrent episodes of pain during menstrual bleeding that eventually lead to scarring and intestinal adhesions, among other complications. Medical treatment includes hormonal therapy and surgery to remove the lesions; recurrence is common. The spontaneous occurrence of endometriosis has been observed in the baboon, which has been used as an animal model. However, with the exception of two cases of adenomyosis (endometriosis within the wall of the uterus) (163), this disease has not been reported in NHHs. The reasons for this disparity are unknown. The presence of diet-derived Neu5Gc in the endometrium and endometrial vasculature (164) could interact with

ETHICAL AND PRACTICAL ISSUES IN STUDYING NONHUMAN HOMINID DISEASES

Because at least some nonhuman hominids (NHHs) (e.g., the chimpanzee and orangutan) recognize themselves in mirrors and may have a simplified theory of mind (169), new concerns have arisen regarding the ethics of doing unlimited research on them. On one hand, the National Institutes of Health (NIH) and other health research agencies have invested considerable funding over recent years to use NHHs as models of human disease. On the other hand, these ethical concerns raise valid questions. Opinions on this matter fall along a spectrum. On one end of the spectrum, some investigators believe that NHHs should continue to be used for research that will save human lives (especially for conditions such as hepatitis C, for which no other model exists) (171); on the other end, members of the so-called Great Ape Project (172) seek to ban all future research on these species. As is always the case in a subject with wide-ranging opinions, the two extremes appear to have garnered the most attention; the Great Ape Project currently has the upper hand (173). Indeed, NHHs in captivity (at least those supported by the NIH) cannot be euthanized to reduce population size, and they also must be "retired" after a certain period of time to long-term care facilities (173). The debate is still under way, and further legislation to limit research is under consideration. Meanwhile, some investigators have adopted the middle position, arguing that although NHHs are certainly not equivalent to mice, rats, or even monkeys in terms of what might be allowable in terms of research, they deserve to be studied in a similar manner to humans. Much can be learned about humans and NHHs by subjecting both to the same types of research following generally similar principles (3). Ironically, although the NIH has decided to support the long-term retirement of chimpanzees, the agency does not support the need for extensive record keeping and for collection of samples during medical care. Tragically, there is not enough support for systematic collection and archiving of tissue samples from NHHs at the time of death from natural causes or from euthanasia for terminal suffering. These precious resources are being lost forever. Indeed, this review—which aims to improve our understanding of both human and NHH disease—could not have been written without prior research on NHHs in captivity and, to some extent, in the wild.

anti-Neu5Gc antibodies to increase the inflammatory component.

Female Iron Deficiency

In the absence of good nutritional sources of iron (especially red meat), women are frequently iron deficient (165). Indeed, even in developed countries the frequency of iron deficiency in premenopausal women is high. The obvious cause is loss of iron-rich blood during menstrual periods. The frequency of iron deficiency in captive chimpanzees appears to be much lower. However, their standardized food is well fortified with iron. Although the amount of blood loss during human versus NHH menstrual periods has not been quantified, anecdotal evidence suggests that blood loss is significantly greater in humans (165). Notably, red meat, which is one of the richest sources of absorbable iron, played a prominent role in the emergence of the *Homo* lineage and can help ameliorate the severity of iron deficiency in women.

Varicella

Varicella zoster, a DNA virus of the *Herpes viridae* family, typically manifests in childhood infections as chicken pox and in adults as shingles. In humans, primary chicken pox is much less severe in younger individuals than in adults who have never been exposed (166). Limited studies of experimental varicella in adult NHHs reported mild symptoms (167). Anecdotal observations suggest that when adult NHHs in captivity do contract chicken pox due to transmission from a keeper with an infected child at home, the disease tends not to be severe but rather manifests relatively limited symptoms. In the absence of further data, it is impossible to know whether this difference is real, but it does accord with the notion that an excessive T cell response to the virus in adult humans may worsen symptoms (57, 58).

Major Psychiatric Diseases

NHHs in captivity can manifest many neurotic behaviors, such as obsessive rocking, coprophagy, and depilation (168). Whether the major psychiatric diseases found in humans, such as schizophrenia and bipolar disorder, exist in NHHs is difficult to ascertain because many diagnostic features require linguistic interactions between psychiatrist and patient. However, to date there are no reports of lifetime behavioral patterns in NHHs that are consistent with such disorders, which afflict a significant fraction (>1%) of all human populations. As for autism spectrum disorders, some of their cardinal features (e.g., deficits in social interaction and communication) may be attributed to the failure to fully develop a theory of mind. If so, NHHs could be considered functionally autistic (H.A. Lurie, personal communication), as studies suggest that they stop short of developing a full theory of mind (169).

CONCLUSIONS, CAVEATS, AND FUTURE PROSPECTS

This wide-ranging and somewhat speculative survey of definite, probable, and possible biomedical differences between humans and our closest evolutionary relatives departs from the usual model of this journal, which tends to provide authoritative summaries of established facts. Although we have focused on our own related research, our broader purpose has been to generate interest in this poorly studied area, which deserves much more attention both for the benefit of human medical knowledge and for the proper veterinary care of NHHs. Ultimately, some suggested differences that stand the test of time and further study probably have genetic explanations. Such genetic approaches are becoming very accessible with the increasing availability of the genomes of all the species in question.

SUMMARY POINTS

1. Humans are genetically very closely related to NHHs, also known as great apes.
2. The disease profile of NHHs has long been assumed to be similar to that of humans. Although in some cases this is true, there appear to be many striking differences in terms of disease incidence and severity.
3. Because only a few NHHs in captivity have undergone complete veterinary evaluation and necropsies, we cannot draw any conclusions about diseases that are rare in humans, that is, that occur with a frequency of less than one in several hundred.
4. Given the history of support for NHH research by the National Institutes of Health, investigators have tended to emphasize similarities rather than differences between NHHs and humans.
5. On the basis of the amount and quality of information available, we classify differences between NHHs and humans as definite, probable, or possible. However, even among the possible differences, anecdotal evidence suggests that many do exist and simply have not yet been reported.
6. These differences involve diseases that span a wide spectrum of systems and mechanisms.
7. Genetic and/or environmental factors must account for any major differences. We suggest some potential explanations on the basis of uniquely human changes in sialic acid biology.
8. Further exploration is constrained by restrictions on the study of NHHs (see the sidebar entitled Ethical and Practical Issues in Studying Nonhuman Hominid Diseases).

DISCLOSURE STATEMENT

Two authors (N.M.V. and A.V.) are cofounders of Sialix, Inc. (formerly Gc-Free, Inc.), a start-up biotechnology company with an interest in the biomedical significance of Neu5Gc and anti-Neu5Gc antibodies.

ACKNOWLEDGMENTS

The authors gratefully acknowledge both the opportunities provided by the Yerkes National Primate Center and the Primate Foundation of Arizona (PFA) to learn about NHH diseases firsthand and the many samples provided for study. We also acknowledge helpful comments from Dan Anderson and James Else at Yerkes, Jo Fritz at PFA, Jon Cohen at *Science*, James McKenna at the University of Notre Dame, and Carl W. Dieffenbach at the National Institute of Allergy and Infectious Diseases/National Institutes of Health.

LITERATURE CITED

1. Murphy WJ, Pevzner PA, O'Brien SJ. 2004. Mammalian phylogenomics comes of age. *Trends Genet.* 20:631–39
2. **Goodman M. 1999. The genomic record of humankind's evolutionary roots. *Am. J. Hum. Genet.* 64:31–39**
3. Gagneux P, Moore JJ, Varki A. 2005. The ethics of research on great apes. *Nature* 437:27–29
4. McClure HM. 1973. Tumors in nonhuman primates: observations during a six-year period in the Yerkes primate center colony. *Am. J. Phys. Anthropol.* 38:425–29
5. Schmidt RE. 1978. Systemic pathology of chimpanzees. *J. Med. Primatol.* 7:274–318
6. Benirschke K, Adams FD. 1980. Gorilla diseases and causes of death. *J. Reprod. Fertil. Suppl.* 28:139–48
7. **Varki A. 2000. A chimpanzee genome project is a biomedical imperative. *Genome Res.* 10:1065–70**
8. Lowenstine LJ. 2003. A primer of primate pathology: lesions and nonlesions. *Toxicol. Pathol.* 31(Suppl.):92–102
9. **Finch CE. 2010. Evolution in health and medicine Sackler colloquium: evolution of the human lifespan and diseases of aging: roles of infection, inflammation, and nutrition. *Proc. Natl. Acad. Sci. USA* 107:1718–24**
10. Varki A. 2009. Multiple changes in sialic acid biology during human evolution. *Glycoconj. J.* 26:231–45
11. Varki A. 2007. Glycan-based interactions involving vertebrate sialic-acid-recognizing proteins. *Nature* 446:1023–29
12. Varki A. 2010. Uniquely human evolution of sialic acid genetics and biology. *Proc. Natl. Acad. Sci. USA* 107:8939–46
13. Varki A, Geschwind DH, Eichler EE. 2008. Explaining human uniqueness: genome interactions with environment, behaviour and culture. *Nat. Rev. Genet.* 9:749–63
14. Marple BF, Stankiewicz JA, Baroody FM, Chow JM, Conley DB, et al. 2009. Diagnosis and management of chronic rhinosinusitis in adults. *Postgrad. Med.* 121:121–39
15. Keir J. 2009. Why do we have paranasal sinuses? *J. Laryngol. Otol.* 123:4–8
16. Blaney SP. 1986. An allometric study of the frontal sinus in *Gorilla*, *Pan* and *Pongo*. *Folia Primatol.* 47:81–96
17. Strobert EA, Swenson RB. 1979. Treatment regimen for air sacculitis in the chimpanzee (*Pan troglodytes*). *Lab. Anim. Sci.* 29:387–88
18. Hill LR, Lee DR, Keeling ME. 2001. Surgical technique for ambulatory management of airsacculitis in a chimpanzee (*Pan troglodytes*). *Comp. Med.* 51:80–84
19. Hastings BE. 1991. The veterinary management of a laryngeal air sac infection in a free-ranging mountain gorilla. *J. Med. Primatol.* 20:361–64
20. Davidson TM, Sedgh J, Tran D, Stepnowsky CJJ. 2005. The anatomic basis for the acquisition of speech and obstructive sleep apnea: evidence from cephalometric analysis supports The Great Leap Forward hypothesis. *Sleep Med.* 6:497–505

2. Uses DNA data to show that humans are more closely related to chimpanzee and bonobos than they are to gorillas.

7. Justifies the chimpanzee genome project on the basis of major disease differences between humans and NHHs.

9. Discusses the genes affecting infection, inflammation, and nutrition: Compared with humans, chimpanzees have lower incidences of cancer, coronary atherosclerosis, and neurodegeneration.

21. Hendricks JC, Kline LR, Kovalski RJ, O'Brien JA, Morrison AR, Pack AI. 1987. The English bulldog: a natural model of sleep-disordered breathing. *J. Appl. Physiol.* 63:1344–50
22. Kato M, Adachi T, Koshino Y, Somers VK. 2009. Obstructive sleep apnea and cardiovascular disease. *Circ. J.* 73:1363–70
23. Harcourt-Smith WE, Aiello LC. 2004. Fossils, feet and the evolution of human bipedal locomotion. *J. Anat.* 204:403–16
24. Lovejoy CO, Suwa G, Spurlock L, Asfaw B, White TD. 2009. The pelvis and femur of *Ardipithecus ramidus*: the emergence of upright walking. *Science* 326:71
25. Haeusler M, Martelli SA, Boeni T. 2002. Vertebrae numbers of the early hominid lumbar spine. *J. Hum. Evol.* 43:621–43
26. Filler AG. 2007. Emergence and optimization of upright posture among hominiform hominoids and the evolutionary pathophysiology of back pain. *Neurosurg. Focus* 23:E4
27. Bramble DM, Lieberman DE. 2004. Endurance running and the evolution of *Homo*. *Nature* 432:345–52
28. Wittman AB, Wall LL. 2007. The evolutionary origins of obstructed labor: bipedalism, encephalization, and the human obstetric dilemma. *Obstet. Gynecol. Surv.* 62:739–48
29. Trevathan WR. 1996. The evolution of bipedalism and assisted birth. *Med. Anthropol. Q.* 10:287–90
30. McKenna JJ, Ball HL, Gettler LT. 2007. Mother-infant cosleeping, breastfeeding and sudden infant death syndrome: what biological anthropology has discovered about normal infant sleep and pediatric sleep medicine. *Am. J. Phys. Anthropol.* 45(Suppl.):133–61
31. Kinney HC, Thach BT. 2009. The sudden infant death syndrome. *N. Engl. J. Med.* 361:795–805
32. Blair PS, Sidebotham P, Evason-Coombe C, Edmonds M, Heckstall-Smith EM, Fleming P. 2009. Hazardous cosleeping environments and risk factors amenable to change: case-control study of SIDS in southwest England. *Br. Med. J.* 339:B3666
33. McArdle G. 1997. Is inguinal hernia a defect in human evolution and would this insight improve concepts for methods of surgical repair? *Clin. Anat.* 10:47–55
34. Acheson AG, Scholefield JH. 2008. Management of haemorrhoids. *Br. Med. J.* 336:380–83
35. Lim CS, Davies AH. 2009. Pathogenesis of primary varicose veins. *Br. J. Surg.* 96:1231–42
36. Montagna W, Yun JS. 1963. The skin of primates. X. The skin of the chimpanzee (*Pan satyrus*). *Am. J. Phys. Anthropol.* 21:189–203
37. Hedlund M, Tangvoranuntakul P, Takematsu H, Long JM, Housley GD, et al. 2007. *N*-glycolylneuraminic acid deficiency in mice: implications for human biology and evolution. *Mol. Cell. Biol.* 27:4340–46
38. Kurokawa I, Danby FW, Ju Q, Wang X, Xiang LF, et al. 2009. New developments in our understanding of acne pathogenesis and treatment. *Exp. Dermatol.* 18:821–32
39. Hiley PG. 1976. The thermoreculatory responses of the galago (*Galago crassicaudatus*), the baboon (*Papio cynocephalus*) and the chimpanzee (*Pan stayrus*) to heat stress. *J. Physiol.* 254:657–71
40. Melnik BC, Schmitz G. 2009. Role of insulin, insulin-like growth factor 1, hyperglycaemic food and milk consumption in the pathogenesis of acne vulgaris. *Exp. Dermatol.* 18:833–41
41. Lolis MS, Bowe WP, Shalita AR. 2009. Acne and systemic disease. *Med. Clin. N. Am.* 93:1161–81
42. Varki A, Nelson D. 2007. Genomic differences between humans and chimpanzees. *Annu. Rev. Anthropol.* 36:191–209
43. Seiler BM, Dick EJ Jr, Guardado-Mendoza R, Vandeberg JL, Williams JT, et al. 2009. Spontaneous heart disease in the adult chimpanzee (*Pan troglodytes*). *J. Med. Primatol.* 38:51–58
44. Lammey ML, Baskin GB, Gigliotti AP, Lee DR, Ely JJ, Sleeper MM. 2008. Interstitial myocardial fibrosis in a captive chimpanzee (*Pan troglodytes*) population. *Comp. Med.* 58:389–94
45. Hansen JF, Alford PL, Keeling ME. 1984. Diffuse myocardial fibrosis and congestive heart failure in an adult male chimpanzee. *Vet. Pathol.* 21:529–31
46. Munson L, Montali RJ. 1990. Pathology and diseases of great apes at the national zoological park zoo. *Zoo Biol.* 9:99–105
47. Varki N, Anderson D, Herndon JG, Pham T, Gregg CJ, et al. 2009. Heart disease is common in humans and chimpanzees, but is caused by different pathological processes. *Evol. Appl.* 2:101–112
48. Vastesaeger M, Peeters H, Blaton V, Petrovas C, Mortelmans J. 1975. Somes aspects of the chimpanzee as a model for experimental atherosclerosis. *Adv. Exp. Med. Biol.* 63:359–69

49. Blaton V, Peeters H. 1976. The nonhuman primates as models for studying human atherosclerosis: studies on the chimpanzee, the baboon and the rhesus macacus. *Adv. Exp. Med. Biol.* 67:33–64
50. Gray R, O'Neal RM, Jordan FB. 1981. Sudden death associated with atherosclerosis in a gorilla. *J. Am. Vet. Med. Assoc.* 179:1306–7
51. Lammey ML, Lee DR, Ely JJ, Sleeper MM. 2008. Sudden cardiac death in 13 captive chimpanzees (*Pan troglodytes*). *J. Med. Primatol.* 37(Suppl. 1):39–43
52. McClure HM, Keeling ME, Guilloud NB. 1972. Hematologic and blood chemistry data for the gorilla (*Gorilla gorilla*). *Folia Primatol.* 18:300–316
53. Doucet C, Huby T, Chapman J, Thillet J. 1994. Lipoprotein[a] in the chimpanzee: relationship of apo[a] phenotype to elevated plasma Lp[a] levels. *J. Lipid. Res.* 35:263–70
54. Steinetz BG, Randolph C, Cohn D, Mahoney CJ. 1996. Lipoprotein profiles and glucose tolerance in lean and obese chimpanzees. *J. Med. Primatol.* 25:17–25
55. Schmidt DA, Ellersieck MR, Cranfield MR, Karesh WB. 2006. Cholesterol values in free-ranging gorillas (*Gorilla gorilla gorilla* and *Gorilla beringei*) and Bornean orangutans (*Pongo pygmaeus*). *J. Zoo Wildl. Med.* 37:292–300
56. Videan EN, Heward CB, Chowdhury K, Plummer J, Su Y, Cutler RG. 2009. Comparison of biomarkers of oxidative stress and cardiovascular disease in humans and chimpanzees (*Pan troglodytes*). *Comp. Med.* 59:287–96
57. Nguyen DH, Hurtado-Ziola N, Gagneux P, Varki A. 2006. Loss of Siglec expression on T lymphocytes during human evolution. *Proc. Natl. Acad. Sci. USA* 103:7765–70
58. Soto PC, Stein LL, Hurtado-Ziola N, Hedrick SM, Varki A. 2010. Relative over-reactivity of human versus chimpanzee lymphocytes: implications for the human diseases associated with immune activation. *J. Immunol.* 184:4185–95
59. Pham T, Gregg CJ, Karp F, Chow R, Padler-Karavani V, et al. 2009. Evidence for a novel human-specific xeno-auto-antibody response against vascular endothelium. *Blood* 114:5225–35
60. Taylor DW, Wells RA, Vernes A, Rosenberg YJ, Vogel S, Diggs CL. 1985. Parasitologic and immunologic studies of experimental *Plasmodium falciparum* infection in nonsplenectomized chimpanzees (*Pan troglodytes*). *Am. J. Trop. Med. Hyg.* 34:36–44
61. Tishkoff SA, Varkonyi R, Cahinhinan N, Abbes S, Argyropoulos G, et al. 2001. Haplotype diversity and linkage disequilibrium at human G6PD: recent origin of alleles that confer malarial resistance. *Science* 293:455–62
62. Escalante AA, Barrio E, Ayala FJ. 1995. Evolutionary origin of human and primate malarias: evidence from the circumsporozoite protein gene. *Mol. Biol. Evol.* 12:616–26
63. Wang HY, Tang H, Shen CK, Wu CI. 2003. Rapidly evolving genes in human. I. The glycophorins and their possible role in evading malaria parasites. *Mol. Biol. Evol.* 20:1795–804
64. Martin MJ, Rayner JC, Gagneux P, Barnwell JW, Varki A. 2005. Evolution of human-chimpanzee differences in malaria susceptibility: relationship to human genetic loss of *N*-glycolylneuraminic acid. *Proc. Natl. Acad. Sci. USA* 102:12819–24
65. Rich SM, Leendertz FH, Xu G, LeBreton M, Djoko CF, et al. 2009. The origin of malignant malaria. *Proc. Natl. Acad. Sci. USA* 106:14902–7
66. Varki A, Gagneux P. 2009. Human-specific evolution of sialic acid targets: explaining the malignant malaria mystery? *Proc. Natl. Acad. Sci. USA* 106:14739–40
67. Ngampasutadol J, Ram S, Gulati S, Agarwal S, Li C, et al. 2008. Human factor H interacts selectively with *Neisseria gonorrhoeae* and results in species-specific complement evasion. *J. Immunol.* 180:3426–35
68. Ngampasutadol J, Tran C, Gulati S, Blom AM, Jerse EA, et al. 2008. Species-specificity of *Neisseria gonorrhoeae* infection: Do human complement regulators contribute? *Vaccine* 26(Suppl. 8):62–66
69. Zetola NM, Engelman J, Jensen TP, Klausner JD. 2007. Syphilis in the United States: an update for clinicians with an emphasis on HIV coinfection. *Mayo Clin. Proc.* 82:1091–102
70. Janowicz DM, Li W, Bauer ME. 2010. Host-pathogen interplay of *Haemophilus ducreyi*. *Curr. Opin. Infect. Dis.* 23:64–69
71. Carlin AF, Uchiyama S, Chang YC, Lewis AL, Nizet V, Varki A. 2009. Molecular mimicry of host sialylated glycans allows a bacterial pathogen to engage neutrophil Siglec-9 and dampen the innate immune response. *Blood* 113:3333–36

65. Presents evidence that *Plasmodium falciparum* evolved from preexisting *P. reichenowi* by a single NHH-to-human transfer.

72. Sonnenburg JL, Altheide TK, Varki A. 2004. A uniquely human consequence of domain-specific functional adaptation in a sialic acid–binding receptor. *Glycobiology* 14:339–46
73. Alter HJ, Eichberg JW, Masur H, Saxinger WC, Gallo R, et al. 1984. Transmission of HTLV-III infection from human plasma to chimpanzees: an animal model for AIDS. *Science* 226:549–52
74. Novembre FJ, Saucier M, Anderson DC, Klumpp SA, O'Neil SP, et al. 1997. Development of AIDS in a chimpanzee infected with human immunodeficiency virus type 1. *J. Virol.* 71:4086–91
75. Juompan LY, Hutchinson K, Montefiori DC, Nidtha S, Villinger F, Novembre FJ. 2008. Analysis of the immune responses in chimpanzees infected with HIV type 1 isolates. *AIDS Res. Hum. Retrovir.* 24:573–86
76. O'Neil SP, Novembre FJ, Hill AB, Suwyn C, Hart CE, et al. 2000. Progressive infection in a subset of HIV-1-positive chimpanzees. *J. Infect. Dis.* 182:1051–1062
77. Nara PL, Robey WG, Arthur LO, Asher DM, Wolff AV, et al. 1987. Persistent infection of chimpanzees with human immunodeficiency virus: serological responses and properties of reisolated viruses. *J. Virol.* 61:3173–80
78. Gougeon ML, Lecoeur H, Heeney J, Boudet F. 1996. Comparative analysis of apoptosis in HIV-infected humans and chimpanzees: relation with lymphocyte activation. *Immunol. Lett.* 51:75–81
79. Heeney J, Bogers W, Buijs L, Dubbes R, ten Haaft P, et al. 1996. Immune strategies utilized by lentivirus infected chimpanzees to resist progression to AIDS. *Immunol. Lett.* 51:45–52
80. Gougeon ML, Lecoeur H, Boudet F, Ledru E, Marzabal S, et al. 1997. Lack of chronic immune activation in HIV-infected chimpanzees correlates with the resistance of T cells to Fas/Apo-1 (CD95)-induced apoptosis and preservation of a T helper 1 phenotype. *J. Immunol.* 158:2964–76
81. Pischinger K, Zimmermann K, Eibl MM, Mannhalter JW. 1998. Comparison of early events during infection of human and chimpanzee peripheral blood mononuclear cells with HIV-1. *Arch. Virol.* 143:2065–76
82. Rutjens E, Balla-Jhagjhoorsingh S, Verschoor E, Bogers W, Koopman G, Heeney J. 2003. Lentivirus infections and mechanisms of disease resistance in chimpanzees. *Front. Biosci.* 8:1134–45
83. Paiardini M, Pandrea I, Apetrei C, Silvestri G. 2009. Lessons learned from the natural hosts of HIV-related viruses. *Annu. Rev. Med.* 60:485–95
84. Finzi D, Plaeger SF, Dieffenbach CW. 2006. Defective virus drives human immunodeficiency virus infection, persistence, and pathogenesis. *Clin. Vaccine Immunol.* 13:715–21
85. Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, et al. 1999. Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*. *Nature* 397:436–41
86. Keele BF, Van Heuverswyn F, Li Y, Bailes E, Takehisa J, et al. 2006. Chimpanzee reservoirs of pandemic and nonpandemic HIV-1. *Science* 313:523–26
87. Keele BF, Jones JH, Terio KA, Estes JD, Rudicell RS, et al. 2009. Increased mortality and AIDS-like immunopathology in wild chimpanzees infected with SIVcpz. *Nature* 460:515–19
88. Mariani R, Chen D, Schrofelbauer B, Navarro F, Konig R, et al. 2003. Species-specific exclusion of APOBEC3G from HIV-1 virions by Vif. *Cell* 114:21–31
89. Song B, Javanbakht H, Perron M, Park DH, Stremlau M, Sodroski J. 2005. Retrovirus restriction by TRIM5α variants from Old World and New World primates. *J. Virol.* 79:3930–37
90. Brenchley JM, Silvestri G, Douek DC. 2010. Nonprogressive and progressive primate immunodeficiency lentivirus infections. *Immunity* 32:737–42
91. Heeney J, Haaksma T, Ten HP, Niphuis H, Kuebler D, et al. 1995. Resistance to the development of AIDS in chimpanzees is associated with maintenance of Th1 responses and preservation of MHC class II regions in lymphoid tissues during HIV-1 infection. *J. Med. Primatol.* 24:204
92. Ehret A, Westendorp MO, Herr I, Debatin KM, Heeney JL, et al. 1996. Resistance of chimpanzee T cells to human immunodeficiency virus type 1 Tat-enhanced oxidative stress and apoptosis. *J. Virol.* 70:6502–7
93. Brenchley JM, Douek DC. 2008. The mucosal barrier and immune activation in HIV pathogenesis. *Curr. Opin. HIV AIDS* 3:356–61
94. Switzer WM, Salemi M, Shanmugam V, Gao F, Cong ME, et al. 2005. Ancient cospeciation of simian foamy viruses and primates. *Nature* 434:376–80
95. Liu W, Worobey M, Li Y, Keele BF, Bibollet-Ruche F, et al. 2008. Molecular ecology and natural history of simian foamy virus infection in wild-living chimpanzees. *PLoS Pathog.* 4:e1000097

83. Discusses the major role of chronic immune activation in the progression of HIV infection to AIDS.

94. Presents evidence that simian foamy viruses cospeciated with all primates studied, except humans.

96. Morozov VA, Leendertz FH, Junglen S, Boesch C, Pauli G, Ellerbrok H. 2009. Frequent foamy virus infection in free-living chimpanzees of the Tai National Park (Côte d'Ivoire). *J. Gen. Virol.* 90:500–6
97. Schweizer M, Turek R, Hahn H, Schliephake A, Netzer KO, et al. 1995. Markers of foamy virus infections in monkeys, apes, and accidentally infected humans: Appropriate testing fails to confirm suspected foamy virus prevalence in humans. *AIDS Res. Hum. Retrovir.* 11:161–70
98. Goepfert PA, Ritter GDJ, Peng X, Gbakima AA, Zhang Y, Mulligan MJ. 1996. Analysis of West African hunters for foamy virus infections. *AIDS Res. Hum. Retrovir.* 12:1725–30
99. Couceiro JNSS, Paulson JC, Baum LG. 1993. Influenza virus strains selectively recognize sialyloligosaccharides on human respiratory epithelium: the role of the host cell in selection of hemagglutinin receptor specificity. *Virus Res.* 29:155–65
100. Gagneux P, Cheriyan M, Hurtado-Ziola N, Brinkman–Van Der Linden ECM, Anderson D, et al. 2003. Human-specific regulation of α2–6-linked sialic acids. *J. Biol. Chem.* 278:48245–50
101. Snyder MH, London WT, Tierney EL, Maassab HF, Murphy BR. 1986. Restricted replication of a cold-adapted reassortant influenza A virus in the lower respiratory tract of chimpanzees. *J. Infect. Dis.* 154:370–71
102. Murphy BR, Hall SL, Crowe J, Collins P, Subbarao K, et al. 1992. The use of chimpanzees in respiratory virus research. In *Chimpanzee Conservation and Public Health: Environments for the Future*, ed. J Erwin, JC Landon, pp. 21–27. Rockville, MD: Diagnon/Bioqual
103. Walker CM. 1997. Comparative features of hepatitis C virus infection in humans and chimpanzees. *Springer Semin. Immunopathol.* 19:85–98
104. Bassett SE, Brasky KM, Lanford RE. 1998. Analysis of hepatitis C virus–inoculated chimpanzees reveals unexpected clinical profiles. *J. Virol.* 72:2589–99
105. Lanford RE, Bigger C, Bassett S, Klimpel G. 2001. The chimpanzee model of hepatitis C virus infections. *ILAR J.* 42:117–26
106. Bukh J. 2004. A critical role for the chimpanzee model in the study of hepatitis C. *Hepatology* 39:1469–75
107. Gagneux P, Muchmore EA. 2004. The chimpanzee model: contributions and considerations for studies of hepatitis B virus. *Methods Mol. Med.* 96:289–318
108. Bowen DG, Walker CM. 2005. Mutational escape from $CD8^+$ T cell immunity: HCV evolution, from chimpanzees to man. *J. Exp. Med.* 201:1709–14
109. Bettauer RH. 2010. Chimpanzees in hepatitis C virus research: 1998–2007. *J. Med. Primatol.* 39:9–23
110. Guidotti LG, Chisari FV. 2006. Immunobiology and pathogenesis of viral hepatitis. *Annu. Rev. Pathol. Mech. Dis.* 1:23–61
111. Parkin DM, Bray FI, Devesa SS. 2001. Cancer burden in the year 2000. The global picture. *Eur. J. Cancer* 37(Suppl. 8):S4–66
112. Brown SL, Anderson DC, Dick EJ Jr, Guardado-Mendoza R, Garcia AP, Hubbard GB. 2009. Neoplasia in the chimpanzee (*Pan* spp.). *J. Med. Primatol.* 38:137–44
113. Johnson LD, Ausman LM, Sehgal PK, King NWJ. 1996. A prospective study of the epidemiology of colitis and colon cancer in cotton-top tamarins (*Saguinus oedipus*). *Gastroenterology* 110:102–115
114. Abe K, Kagei N, Teramura Y, Ejima H. 1993. Hepatocellular carcinoma associated with chronic *Schistosoma* mansoni infection in a chimpanzee. *J. Med. Primatol.* 22:237–39
115. Greenwood AG, Lowe JW, Gaunt L. 1995. Renal carcinoma in a chimpanzee (*Pan troglodytes*). *Vet. Rec.* 137:380–81
116. Binhazim AA, Lee DR, Bernacky BJ, Rizvi TA. 1997. Spontaneous anaplastic large cell lymphoma in a chimpanzee: a clinicopathological and immunohistochemical study. *J. Med. Primatol.* 26:260–66
117. Bommineni YR, Dick EJ Jr, Hubbard GB. 2009. Gastrointestinal stromal tumors in a baboon, a spider monkey, and a chimpanzee and a review of the literature. *J. Med. Primatol.* 38:199–203
118. Eaton SB, Konner M, Shostak M. 1988. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. *Am. J. Med.* 84:739–49
119. Gage TB. 2005. Are modern environments really bad for us? Revisiting the demographic and epidemiologic transitions. *Am. J. Phys. Anthropol.* 41(Suppl.):96–117
120. Rajagopalan H, Lengauer C. 2004. Aneuploidy and cancer. *Nature* 432:338–41
121. Macklon NS, Geraedts JP, Fauser BC. 2002. Conception to ongoing pregnancy: the 'black box' of early pregnancy loss. *Hum. Reprod. Update* 8:333–43

107. Review by investigators not involved in hepatitis research concludes that chimpanzees suffer less from late complications of hepatitis infection.

122. Vanneste E, Voet T, Le Caignec C, Ampe M, Konings P, et al. 2009. Chromosome instability is common in human cleavage-stage embryos. *Nat. Med.* 15:577–83
123. Fan Y, Linardopoulou E, Friedman C, Williams E, Trask BJ. 2002. Genomic structure and evolution of the ancestral chromosome fusion site in 2q13–2q14.1 and paralogous regions on other human chromosomes. *Genome Res.* 12:1651–62
124. Ganem NJ, Godinho SA, Pellman D. 2009. A mechanism linking extra centrosomes to chromosomal instability. *Nature* 460:278–82
125. Tan TT, Coussens LM. 2007. Humoral immunity, inflammation and cancer. *Curr. Opin. Immunol.* 19:209–16
126. Mantovani A, Allavena P, Sica A, Balkwill F. 2008. Cancer-related inflammation. *Nature* 454:436–44
127. Naugler WE, Karin M. 2008. The wolf in sheep's clothing: the role of interleukin-6 in immunity, inflammation and cancer. *Trends Mol. Med.* 14:109–19
128. Hedlund M, Padler-Karavani V, Varki NM, Varki A. 2008. Evidence for a human-specific mechanism for diet and antibody-mediated inflammation in carcinoma progression. *Proc. Natl. Acad. Sci. USA* 105:18936–41
129. Rosen RF, Farberg AS, Gearing M, Dooyema J, Long PM, et al. 2008. Tauopathy with paired helical filaments in an aged chimpanzee. *J. Comp. Neurol.* 509:259–70
130. Gearing M, Rebeck GW, Hyman BT, Tigges J, Mirra SS. 1994. Neuropathology and apolipoprotein E profile of aged chimpanzees: implications for Alzheimer disease. *Proc. Natl. Acad. Sci. USA* 91:9382–86
131. Gearing M, Tigges J, Mori H, Mirra SS. 1997. β-Amyloid (A β) deposition in the brains of aged orangutans. *Neurobiol. Aging* 18:139–46
132. Minagar A, Shapshak P, Fujimura R, Ownby R, Heyes M, Eisdorfer C. 2002. The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. *J. Neurol. Sci.* 202:13–23
133. Streit WJ. 2004. Microglia and Alzheimer's disease pathogenesis. *J. Neurosci. Res.* 77:1–8
134. Angata T, Kerr SC, Greaves DR, Varki NM, Crocker PR, Varki A. 2002. Cloning and characterization of human Siglec-11. A recently evolved signaling molecule that can interact with SHP-1 and SHP-2 and is expressed by tissue macrophages, including brain microglia. *J. Biol. Chem.* 277:24466–74
135. Hayakawa T, Angata T, Lewis AL, Mikkelsen TS, Varki NM, Varki A. 2005. A human-specific gene in microglia. *Science* 309:1693
136. Cao H, Lakner U, de Bono B, Traherne JA, Trowsdale J, Barrow AD. 2008. SIGLEC16 encodes a DAP12-associated receptor expressed in macrophages that evolved from its inhibitory counterpart SIGLEC11 and has functional and nonfunctional alleles in humans. *Eur. J. Immunol.* 38:2303–15
137. Crocker PR, Varki A. 2001. Siglecs, sialic acids and innate immunity. *Trends Immunol.* 22:337–42
138. Lewis AL, Desa N, Hansen EE, Knirel YA, Gordon JI, et al. 2009. Innovations in host and microbial sialic acid biosynthesis revealed by phylogenomic prediction of nonulosonic acid structure. *Proc. Natl. Acad. Sci. USA* 106:13552–57
139. Brinkman–Van der Linden ECM, Sjoberg ER, Juneja LR, Crocker PR, Varki N, Varki A. 2000. Loss of *N*-glycolylneuraminic acid in human evolution—implications for sialic acid recognition by siglecs. *J. Biol. Chem.* 275:8633–40
140. Young BC, Levine RJ, Karumanchi SA. 2010. Pathogenesis of preeclampsia. *Annu. Rev. Pathol. Mech. Dis.* 5:173–92
141. Rosenberg KR, Trevathan WR. 2007. An anthropological perspective on the evolutionary context of preeclampsia in humans. *J. Reprod. Immunol.* 76:91–97
142. Brinkman–Van der Linden ECM, Hurtado-Ziola N, Hayakawa T, Wiggleton L, Benirschke K, et al. 2007. Human-specific expression of Siglec-6 in the placenta. *Glycobiology* 17:922–31
143. Winn VD, Gormley M, Paquet AC, Kjaer-Sorensen K, Kramer A, et al. 2009. Severe preeclampsia-related changes in gene expression at the maternal-fetal interface include sialic acid–binding immunoglobulin-like lectin-6 and pappalysin-2. *Endocrinology* 150:452–62
144. Bernal AL. 2001. Overview of current research in parturition. *Exp. Physiol.* 86:213–22
145. Smith R. 2007. Parturition. *N. Engl. J. Med.* 356:271–83

130. Shows, using age-matched samples of human and NHH brains, that the complete pathology of Alzheimer's disease is missing in the latter.

146. Liao JB, Buhimschi CS, Norwitz ER. 2005. Normal labor: mechanism and duration. *Obstet. Gynecol. Clin. N. Am.* 32:145–64
147. Keeling MR, Roberts JR. 1972. *The Chimpanzee*, vol. 5: *Histology, Reproduction and Restraint*, ed. GH Bourne, pp. 127–52. New York: Karger
148. Muglia LJ, Katz M. 2010. The enigma of spontaneous preterm birth. *N. Engl. J. Med.* 362:529–35
149. Firestein GS. 2005. Immunologic mechanisms in the pathogenesis of rheumatoid arthritis. *J. Clin. Rheumatol.* 11:S39–44
150. Oliver JE, Silman AJ. 2006. Risk factors for the development of rheumatoid arthritis. *Scand. J. Rheumatol.* 35:169–74
151. Nishimaki T, Kano K, Milgrom F. 1978. Studies on heterophile antibodies in rheumatoid arthritis. *Arthritis Rheum.* 21:634–38
152. Grant WB. 2000. The role of meat in the expression of rheumatoid arthritis. *Br. J. Nutr.* 84:589–95
153. Muller H, de Toledo FW, Resch KL. 2001. Fasting followed by vegetarian diet in patients with rheumatoid arthritis: a systematic review. *Scand. J. Rheumatol.* 30:1–10
154. Cohn L, Elias JA, Chupp GL. 2004. Asthma: mechanisms of disease persistence and progression. *Annu. Rev. Immunol.* 22:789–815
155. Jacobs RL, Lux GK, Spielvogel RL, Eichberg JW, Gleiser CA. 1984. Nasal polyposis in a chimpanzee. *J. Allergy Clin. Immunol.* 74:61–63
156. Dumonceaux GA, Lamberski N, Clutter D, Nagy SMJ, Burek K, Phillips LG. 1997. Treatment of bilateral nasal polyposis and chronic refractory inhalant allergic rhinitis in a chimpanzee (*Pan troglodytes*). *J. Zoo Wildl. Med.* 28:215–19
157. Berkowitz RS, Goldstein DP. 2009. Clinical practice. Molar pregnancy. *N. Engl. J. Med.* 360:1639–45
158. Debyser IW, Soma H, Zwart P. 1993. Partial hydatidiform mole in a pregnant chimpanzee (*Pan troglodytes*). *Zoo Biol.* 12:299–305
159. Burt A. 1992. 'Concealed ovulation' and sexual signals in primates. *Folia Primatol.* 58:1–6
160. Giudice LC, Kao LC. 2004. Endometriosis. *Lancet* 364:1789–99
161. Hompes PG, Mijatovic V. 2007. Endometriosis: the way forward. *Gynecol. Endocrinol.* 23:5–12
162. Eskenazi B, Warner ML. 1997. Epidemiology of endometriosis. *Obstet. Gynecol. Clin. N. Am.* 24:235–58
163. Barrier BF, Allison J, Hubbard GB, Dick EJ Jr, Brasky KM, Schust DJ. 2007. Spontaneous adenomyosis in the chimpanzee (*Pan troglodytes*): a first report and review of the primate literature: case report. *Hum. Reprod.* 22:1714–17

164. Tangvoranuntakul P, Gagneux P, Diaz S, Bardor M, Varki N, et al. 2003. Human uptake and incorporation of an immunogenic nonhuman dietary sialic acid. *Proc. Natl. Acad. Sci. USA* 100:12045–50

165. Denic S, Agarwal MM. 2007. Nutritional iron deficiency: an evolutionary perspective. *Nutrition* 23:603–14
166. Chen TM, George S, Woodruff CA, Hsu S. 2002. Clinical manifestations of varicella zoster virus infection. *Dermatol. Clin.* 20:267–82
167. Cohen JI, Moskal T, Shapiro M, Purcell RH. 1996. Varicella in chimpanzees. *J. Med. Virol.* 50:289–92
168. Nash LT, Fritz J, Alford PA, Brent L. 1999. Variables influencing the origins of diverse abnormal behaviors in a large sample of captive chimpanzees (*Pan troglodytes*). *Am. J. Primatol.* 48:15–29
169. Call J, Tomasello M. 2008. Does the chimpanzee have a theory of mind? 30 years later. *Trends Cogn. Sci.* 12:187–92
170. Harrison T. 2010. Anthropology. Apes among the tangled branches of human origins. *Science* 327:532–34
171. VandeBerg JL, Zola SM. 2005. A unique biomedical resource at risk. *Nature* 437:30–32
172. Cavalieri P, Singer P. 1995. The Great Ape Project: premises and implications. *Altern. Lab Anim.* 23:626–31
173. Cohen J. 2007. Biomedical research. The endangered lab chimp. *Science* 315:450–52

164. Reports that human tissues contain traces of Neu5Gc, which is derived from red meat in diet, and that all humans have anti-Neu5Gc antibodies.

174. Diaz SL, Padler-Karavani V, Ghaderi D, Hurtado-Ziola N, Yu H, et al. 2009. Sensitive and specific detection of the nonhuman sialic acid *N*-glycolylneuraminic acid in human tissues and biotherapeutic products. *PLoS ONE* 4:e4241
175. Altheide TK, Hayakawa T, Mikkelsen TS, Diaz S, Varki N, Varki A. 2006. System-wide genomic and biochemical comparisons of sialic acid biology among primates and rodents: evidence for two modes of rapid evolution. *J. Biol. Chem.* 281:25689–702
176. Liu W, Li Y, Learn GH, Rudicell RS, Robertson JD, et al. 2010. Origin of the human malaria parasite *Plasmodium falciparum* in gorillas. *Natur* 467:420–25
177. Glintborg D, Andersen M. 2010. An update on the pathogenesis, inflammation, and metabolism in hirsutism and polycystic ovary syndrome. *Gynecol. Endocrinol.* 26:281–96
178. Zhou R, Bird IM, Dumesic DA, Abbott DH. 2005. Adrenal hyperandrogenism is induced by fetal androgen excess in a rhesus monkey model of polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 90:6630–37

NOTE ADDED IN PROOF

A recent paper by Hahn and colleagues (176) confirms that *Plasmodium falciparum* arose from a single transfer of an NHH malarial parasite and that the transfer occurred specifically from a gorilla, rather than from a chimpanzee. Furthermore, this paper describes the ongoing multiple transfers between chimpanzees and gorillas. In striking contrast, there was only one ape-to-human transfer, and no reverse transfers were found. Overall, there is strong evidence for the initial loss of such parasites from the human lineage, a single reverse transfer to humans, and the persistence of a major evolutionary barrier minimizing human-to-ape and ape-to-human transfers. The loss of the sialic acid Neu5Gc in humans is at present the best explanation for the two-way barrier.

Polycystic ovarian syndrome, a common endocrinopathy associated with reproductive, metabolic, and cardiovascular problems, is also thought to be a human-specific disease (177) that can be induced only experimentally in other primates (178).

Annual Review of Pathology: Mechanisms of Disease

Volume 6, 2011

Contents

Indexes

Errata

An online log of corrections to *Annual Review of Pathology: Mechanisms of Disease* articles may be found at http://pathol.annualreviews.org