# ANBI 139

Evolution of Human Disease

**Lecture 12: Diseases of Other primates**

Pascal Gagneux February 22, 2023

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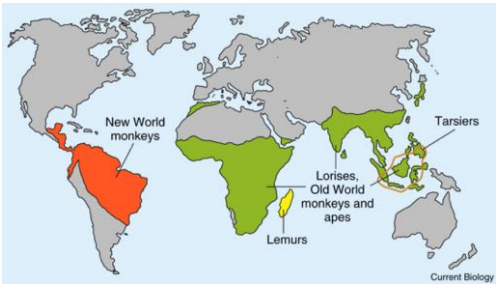
## Geography of non-human primates




Coloured areas indicate inclusive ranges of the five natural groups: lemurs, lorisiforms, tarsiers, New World monkeys, Old World monkeys and apes. Lorisiforms occupy most but not all of the region inhabited by Old World monkeys and apes.

Many important viruses and other diseases have an African primate origin:

Malaria, TB, Yellow fever, HIV1, HIV2, HTLV 1, HTLV2, HBV, Marburg, Dengue, Zika, Chikungunya

**Practice question:** Why are there so many zoonotic viruses with African origin?

**Answer:** Human are African primates which makes our species especially susceptible to African primate viruses.

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## Primates: Prosimians

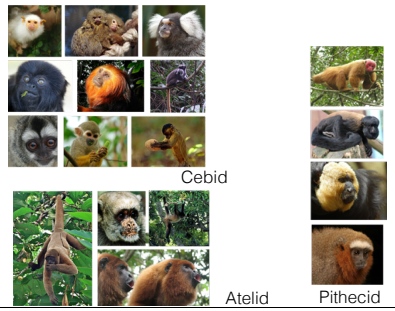
Galagos & Lorises

Tarsier

Lemurs

These primates are not “true” monkeys but rather surviving relatives of the common ancestor of all monkeys, apes and humans.

Primates: New World







Cebid and Atelid New world primates evolved prehensile tails in parallel (independently)

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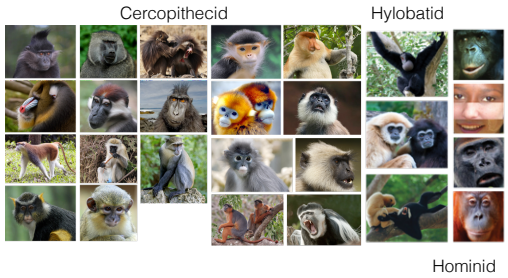
Primates: Old World




Cerco (tail) pithecid (monkey) are the tailed monkeys of Africa and Asia
Hylobatids are the lesser apes, gibbons and siamangs of South East Asia. Their genomes famously got massively rearranged via a novel transposon that only exists in the hylobatid genomes (LAVA element). Their chromosomes have been massively reshuffled. Hominids include the apes (lesser and great) and humans. Hominins are humans and their extinct bipedal relatives.
**Practice Question:** What is the difference between hominid and hominin?
**Answer:** Hominids include all other apes, hominin only living humans and extinct bipedal relatives.

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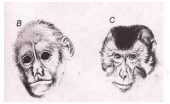
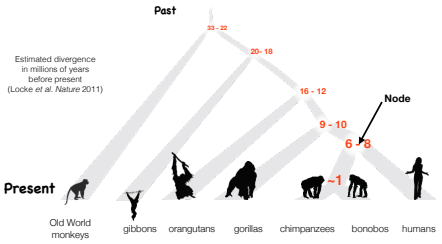
Taxonomy by Noses

- Strepsirrhine vs Haplorhine (curved, wet vs simple, dry nosed)
- Platyrrhine vs Catarrhine (flat nosed vs drooping nosed)
- rhinarium vs upper lip.


Nose shape has ben traditionally used to name the various primate species groups.
The evolution of a fused rhinarium, gave rise to the upper lip of monkeys and apes, allowing for novel facial expressions.
**Practice question:** Which body part figures prominently in the taxonomy of primates?
**Answer:** The nose.

## Humans and their Ape Relatives




A phylogenetic tree, from past to present. Think of it as the grand summary of past mating behavior, at least those sexual encounters

that led to successful reproduction and survival. Precise dating of divergence/speciation is problematic due to a number of unknowns e.g. mutation rate, population structure and incomplete divergence or rejoining of separate populations

**Practice question:** What do nodes in a phylogeny stand for?

**Answer:** Hypothetical common ancestors.

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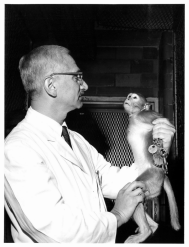
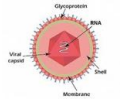
## Early polio vaccine experiments in monkey & ape central nervous system






Strains of each of the 3 types [of polio virus] which possess this limited virulence for monkeys by the spinal route were found to be completely avirulent when inoculated into the spinal cord of chimpanzees, producing neither paralysis nor lesions.

& brain tissue from human embryos

Albert Sabin

Semiannual Report, January 1-June 30, 1954. NFIP, Box 7, Folder 16. AS, WCHHP, UC, Ohio.

In 1936, Albert Sabin and Peter Olitsky at the Rockefeller Institute successfully grew poliovirus in a culture of brain tissue from a human embryo. The virus grew quickly, which was promising, but Sabin and Olitsky were concerned about using this as starting material for a vaccine, fearing nervous system damage for vaccine recipients. They tried to grow poliovirus in cultures using tissue that had been taken from other sources, but were unsuccessful.

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## B-Virus ( Herpesvirus simiae) HVB


A macaque virus very dangerous for humans!

This virus can kill people when it infects their central nervous system. There have been several casualties at US primate centers.

India Rhesus monkeys, used in the USA by the millions

Indian rhesus monkeys (*M. mulatta*) were imported at a rate of 200,000 per year for at least six years and by the tens of thousands for the next 20 years…until the ban by India in 1978.

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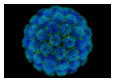
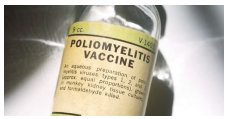
SV 40, another macaque virus…..

SV40 is dormant and is asymptomatic in rhesus monkeys






The discovery of SV40 revealed that between 1955 and 1963 around 90% of children and 60% of adults in USA were inoculated with SV40-contaminated polio vaccines

Shah, K; Nathanson, N (January 1976). "Human exposure to SV40: Review and comment". ***American Journal of Epidemiology.*** 103 (1): 1–12.

A contaminating macaque virus from preparations of vaccine in primary monkey kidney cells done in the 1960 for the Salk and the Sabin polio vaccines.

**Practice question:** How could a macaque virus (SV40) have ended up in the body of millions of American people?

**Answer:** Inadvertent contamination of polio vaccines produced in primary macaque kidney cells.

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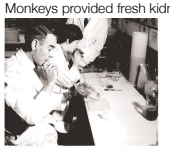
Early cell culture: limited growth

Monkeys provided fresh kidneys



Mouth pipetting of kidney cell suspension

1950's primary cultures of monkey kidney cells

Modern tissue culture hood

Long way from primary kidney cell culture to stable cell lines.

## Polio from humans to non-human primates

Faben, survived but lost use of his arms

1966: polio epidemic among Gombe chimpanzees

Unintended consequence of studying wild apes: infecting them with common human viruses.

**Practice question:** Why can polio virus infection result in paralysis?

**Answer:** The immune response to infection causes nerve damage.

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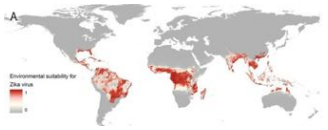
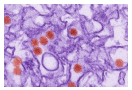
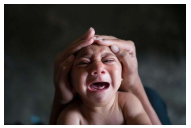
## ZIKA virus





Recent concern about the rapid spread of this novel global virus. The virus is toxic to developing neurons in the fetal brain. It effectively infects several species of New world primates.

**Practice question:** Why does ZIKA virus cause microcephaly?

**Answer:** The virus kills brain precursor cells in the fetus.

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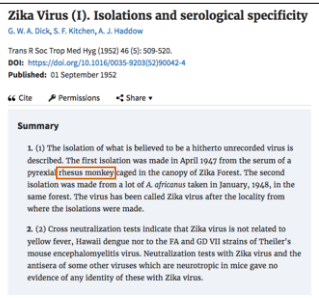
## ZIKA virus



**Zika Virus (1). Isolations and serological specificity**

G. W. A. Dick, S. F. Kitchen, A. J. Haddow

Trans R Soc Trop Med Hyg (1952) 46 (5): 509-520.

**DOI:** https://doi.org/10.1016/0035-9203(52)90042-4

**Published:** 01 September 1952

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**Summary**

1. (1) The isolation of what is believed to be a hitherto unrecorded virus is described. The first isolation was made in April 1947 from the serum of a pyrexial rhesus monkey caged in the canopy of Zika Forest. The second isolation was made from a lot of *A. africanus* taken in January, 1948, in the same forest. The virus has been called Zika virus after the locality from where the isolations were made.

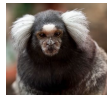
2. (2) Cross neutralization tests indicate that Zika virus is not related to yellow fever, Hawaii dengue nor to the FA and GD VII strains of Theiler's mouse encephalomyelitis virus. Neutralization tests with Zika virus and the antisera of some other viruses which are neurotropic in mice gave no evidence of any identity of these with Zika virus.

Scientists conducting surveillance in Uganda, discovered Zika virus in a sentinel monkey from an Asian species they had placed in  a cage in the trees of an African forest.

**Practice question:** What is surprising about a macaque in an African rain forest?

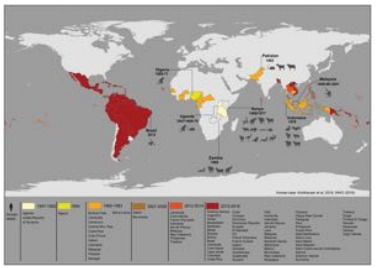
**Answer:** The only macaques in Africa live in Norther Africa (Barbary macaques), all other macaques are Asian.

Historical time-line of ZIKV spread in humans and animals in the world.



Marmoset

Red-bellied tamarin



Bueno MG, Martinez N, Abdalla L, Duarte dos Santos CN, Chame M (2016) Animals in the Zika Virus Life Cycle: What to Expect from Megadiverse Latin American Countries. ***PLOS Neglected Tropical Diseases*** 10(12)

Zika Virus has been spreading all arrow nether tropics and entered South American primates.
**Practice question:** What are the indictions that ZIKA virus entered a novel sylvatic cycle in South America?
**Answer:** Wild South American monkeys have been found to be infected.

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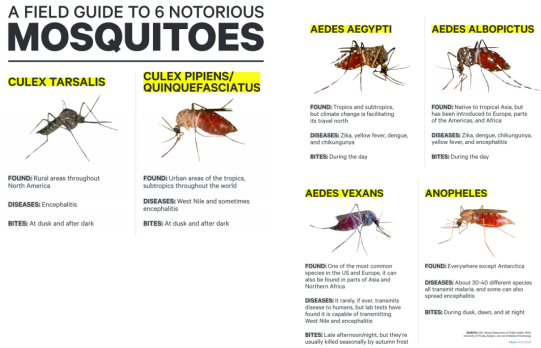


Different mosquito species carry a variety of infectious diseases.
Changes in the ecosystem strongly affect the abundance of these blood sucking insects.
**Practice Question:** What are the three most important genera of disease transmitting mosquitoes?
**Answer:** *Culex, Aedes, Anopheles.*

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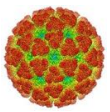
Chikungunya virus

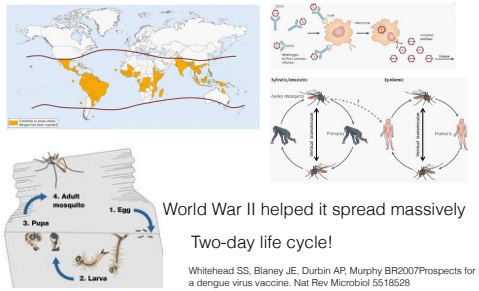
Another virus from forest primates of Africa, first isolated in America in 2013!



The disease was first identified in 1952 in Tanzania.The term is from the Kimakonde language and means "to become contorted". *Aedes albopictus* and *Aedes aegypti.*
They mainly bite during the day

Both mosquito species *Aedes albopictus* and *Aedes aegypti* live in Southern California. They bite during the day, unlike many other Anopheles mosquitos.
**Practice question:** What is especially troublesome about *Aedes albopictus* (tiger mosquito)?
**Answer:** These mosquitos fly very fast and bite during the day.

Dengue virus (breakbone fever)




World War II helped it spread massively

Two-day life cycle!

Whitehead SS, Blaney JE, Durbin AP, Murphy BR2007Prospects for a dengue virus vaccine. Nat Rev Microbiol 5518528

Female Aedes aegypti commonly lay eggs on the inner walls of artificial containers. When the containers fill with water, mosquito larvae hatch from the eggs. After developing through four larval stages, the larvae metamorphose into pupas. Like the larval stage, the pupal stage is also aquatic. After two days, a fully developed adult mosquito forms and breaks through the skin of the pupa. The adult mosquito can fly and has a terrestrial habitat.

Like Zika and Chikungunya, Dengue is also an African nonhuman primate virus.

Dengue virus can exploit antibody recognition of the host to infect host immune cells!!

**Practice Question:** How could World War II in South Asia have helped spread Dengue?

**Answer:** Massive movement of soldiers who were camping out and island hopping resulted in transfer of dengue into many new habitats.

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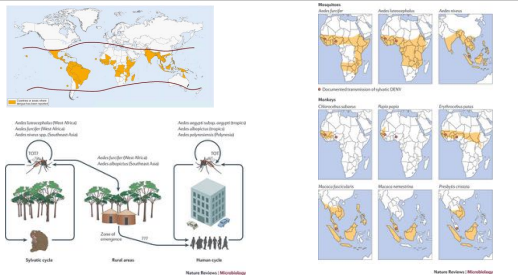
Dengue virus (breakbone fever)



Fever from the forest: prospects for the continued emergence of sylvatic dengue virus and its impact on public health
Nikos Vasilakis, Jane Cardosa, Kathryn A. Hanley, Edward C. Holmes & Scott C. Weaver ***Nature Reviews Microbiology*** 9, 532-541 (July 2011)

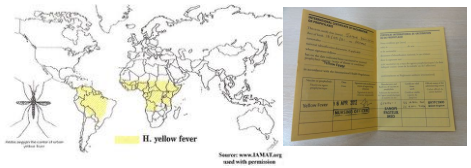
The sylvatic origins of dengue virus, and the 'zone of emergence', where sylvatic cycles contact human populations in rural areas of West Africa and Southeast Asia. In addition, dengue virus can persist in mosquito populations by transovarial transmission (TOT), in which virus-infected mosquitoes transfer the virus to their eggs (this has been shown to occur in some species but not in all).

The geographic range of known and putative mosquito vectors and non-human primate hosts for the transmission cycles of sylvatic dengue virus in Africa and Southeast Asia. Although the range of the guinea baboon (Papio papio) is limited to West Africa, closely related species such as *Papio anubis*, *Papio ursinus* and *Papio cynocephalus* are found across the continent and could also be involved in dengue virus transmission.

**Practice Question:** What is a sylvatic cycle?

**Answer:** Infectious cycle taking place in forests (often at elevation of the forest canopy, where monkeys spend most of the time)..

## Yellow fever






African primate virus now found across tropics.
Very effective vaccine exists!

**Practice question:** Which African primate virus can be stopped by an existing vaccine?
**Answer:** Yellow fever virus.

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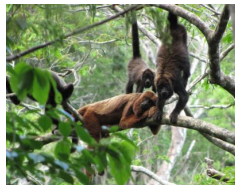
## Yellow fever

Muriqui (wooly spider monkeys)



Howler monkeys

Yellow fever epidemic 2016-2017

Spring 2017 has seen a violent epidemic of yellow fever in the Atlantic forests of Brazil

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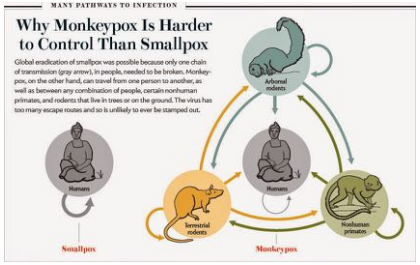
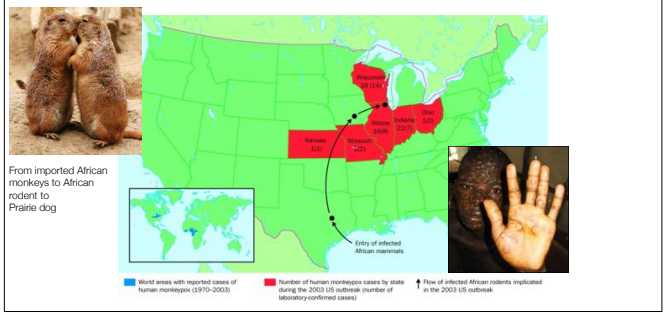
## Monkeypox virus




Monkey pox virus has a rodent reservoir (gliding squirrels) in Central Africa. Younger humans (your age) have not been immunized against smallpox and thus would be very susceptible to weaponized smallpox or monkeypox.

## Monkeypox virus




Accidental importation of Monkeypox to the USA in 2003.
In 2003, the crowded warehouse conditions of a US pet seller enabled a monkeypox virus, previously found only in Africa, to jump from imported rats to native prairie dogs. The prairie dogs carried the outbreak to six states and infected more than 40 people before health officials sorted out the infection. “Gaps in the statutory and regulatory framework across federal agencies increase the risk that some live animal imports will carry diseases into the United States,” notes the 2010 Government Accountability Office

**Practice question:** How did monkey pox arrive in the USA in 2013?

**Answer:** Via imported African rodents for the pet market.

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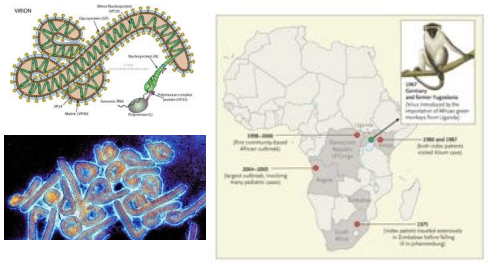
## Marburg Virus: hemorrhagic fever imported to Germany



Marburg hemorrhagic virus in vervet monkeys (African green/vervet monkeys) transported to Germany in 1967 killed a dozen people in research labs.

**Practice question:** What is the origin of the name Marburg virus?

**Answer:** Named after the city of Marburg, Germany where imported vervet monkeys infected researchers with this  East African hemorrhagic fever virus.

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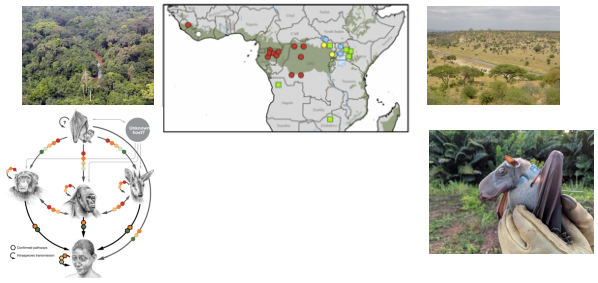
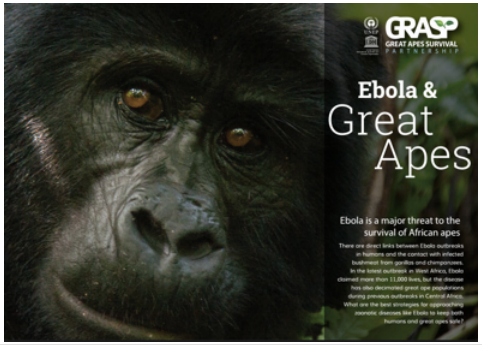
## Ebola versus Marburg Virus



Ebola (circles) seems more prevalent in wet forests, Marburg, another filovirus more in drier forest both appear to exist in reservoirs in different bat  (flying foxes) species, most likely the hammerhead bat *Hypsignathus monstrosus*

Ebola great ape die offs


Ebola represents a huge threat to African Great apes and through them a threat for humanity.





Ebola is one of the key examples of link between bushmeat hunting and emerging diseases.

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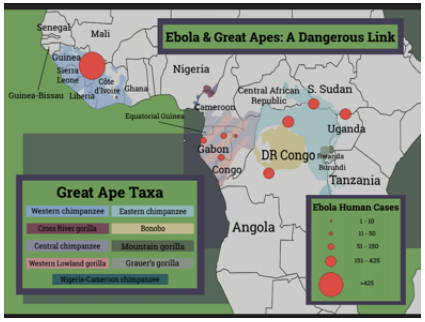


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Discussions are under way about the value of vaccinating/immunizing wild great apes.

## Oral anti-Ebola vaccine is being tested


Walsh, P., Kurup, D., Hasselschwert, D. *et al.* The Final (Oral Ebola) Vaccine Trial on Captive Chimpanzees?. ***Sci Rep* 7,** 43339 (2017).

Using a vaccine designed for humans is not necessarily safe in chimpanzees and gorillas. These there species each have uniquely evolved immune systems. In 2017 promising results were obtained with an oral vaccine.

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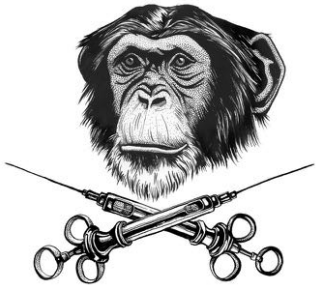
## NYT 2013: Apes need vaccines Too



The artist for the NY Times makes the unintended mistake of drawing old-fashioned reusable glass syringes of precisely the type associated with iatrogenic (medically caused) disease.

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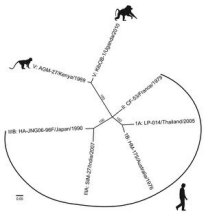
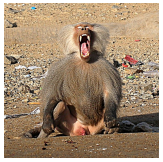
GRASP

## Dietary flexibility and survival

Hepatitis A Virus





Baboons and Macaques, among the few non-human primate species not to be endangered!

The African and Asian generalist monkey species that thrive even in heavily disturbed habitats with high human densities.
Baboons in South Africa have been found to have hight rates of Hepatitis A, Cytomegalovirus, and Eppstein Barr virus infections.

Macaque viruses of concern are primarily the very dangerous Herpes B virus, but also Hepatitis A, Simian retrovirus D and respiratory syncytial virus.

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## Alpha Die-Off 1982

Effects of monkey human (trash) contact in Masai Mara, Kenya

Robert Sapolsky, Stanford

Most aggressive males killed by bovine TB from discarded meat near tourist lodge.

What happened after all the most aggressive males died due to bovine TB these picked up in a tourist lodge trash pile. The baboon groups developed much more peaceful social systems. To read more: 2001 book: A Primate's Memoir by R. Sapolsky.

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## Junk Food Baboons?

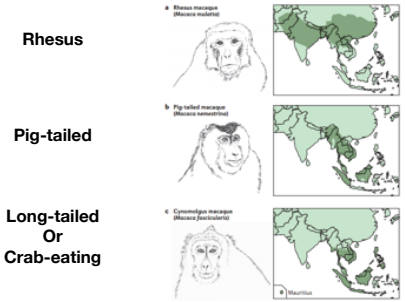
... fried drumsticks or a slab of beef left over by a tourist with eyes bigger than his stomach; fruit salad gone a bit bad, perhaps left too long on the sun-drenched buffet table; fragments of pies and cakes, and alarming yellow dollops of custard pudding, nibbled at by a disciplined dieter — processed sugars, fat, red meat and cholesterol, our modern Four Horsemen of the Apocalypse.

The "garbage dump" diet reliably produced pathology in baboons, with two distinct metabolic patterns. What in the diet was the culprit? I'm betting that it was the sugar from the fruit salad, pies, cakes and custard. That would be most compatible with what we know about sugar's toxicity in humans. It's also in keeping with the human research outcomes, which have linked sugar to multiple pathological pathways leading to diabetes, heart attacks, strokes, hypertension, cancer, obesity, fatty liver disease and death from heart disease.

***Am J Primatol.*** 2002 May;57(1):13-9.
Effects of food availability on serum insulin and lipid concentrations in free-ranging baboons.
Kemnitz JW1, Sapolsky RM, Altmann J, Muruthi P, Mott GE, Stefanick ML.

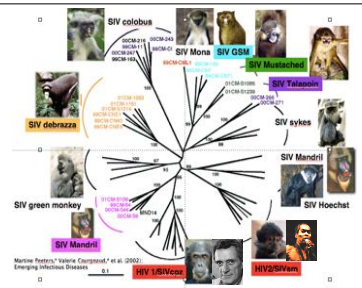
Ecological disturbances often provide the opportunity to study "natural" experiments.
In this case: junk food is bad for you if you are a primate, baboon or human.

## Macaques in AIDS research why?




Macaque species commonly used in AIDS research, and their geographical ranges. a | The geographical range of the rhesus macaque (Macaca mulatta) exceeds that of all other primate species except humans, extending from western India and Pakistan across China. Distinct populations of rhesus macaques can be differentiated on the basis of mitochondrial DNA sequences or SNPs203,204. Captive-breeding programmes in the United States were initially established using animals imported from India, contributing to the widespread use of Indian-origin rhesus macaques in AIDS research. However, owing to the increasing demand for rhesus macaques and an embargo on the exportation of these animals from India since 1978, there has been a substantial decline in their availability and a sharp increase in their cost. This has led to greater dependence on rhesus macaques imported from China and Burma. b | The pig-tailed macaque (Macaca nemestrina) is native to Southeast Asia, Malaysia and Indonesia, and last shared a common ancestor with rhesus macaques approximately 3.5 million years ago. c | The cynomolgus macaque (Macaca fascicularis), also known as the long-tailed or crab-eating macaque, is native to regions of Indochina, Malaysia, Indonesia and the Philippines. Genetic evidence suggests that cynomolgus and rhesus macaques diverged from a common ancestor approximately 1.9 million years ago

## SIV in > 40 species of primates




Peeters *et al.* 2002. ***Emerg. Infect. Dis.***

SIVs have long history of co-evolution with non -human primate host species in Africa.

**Practice question:** If SIV and HIV have African origins, why are macaques used as model animal for HIV research?

**Answer:** Accidental infection of a rhesus macaque with mangabey SIV resulted in rapid AIDS like symptoms.

There are no large biomedical research colonies of African monkeys.

## SIVmac?



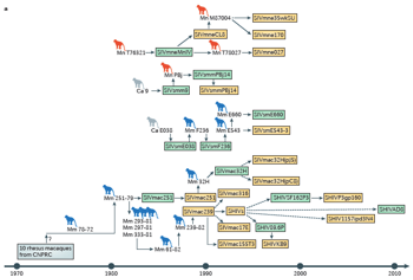


Apetrei, C. et al. Kuru experiments triggered the emergence of pathogenic SIVmac. ***AIDS*** 20, 317–321 (2006).

Accidental infection of an Asian macaque (*M. mulatta* or rhesus macaque) at the National primate center at UC Davis in the early 1970s. The researchers were trying to study prion disease by infecting a macaque with tissue from a sooty mangabey (a west African monkey).

The Macaque did not develop Kuru but rather a severe form of acquired immunodeficiency syndrome (AIDS). The virus was related to HIV2, itself having its origin in sooty mangabeys. These monkeys can produce high levels of circulating viruses, but do not show any signs of disease.

SIVmac?



Derivation of common simian immunodeficiency virus and simian–human immunodeficiency virus strains. a | Monkey cartoons indicate animals from which simian immunodeficiency virus (SIV) isolates were derived. Green boxes represent uncloned biological isolates, and yellow boxes represent infectious molecular clones. Solid arrows represent direct viral transmission or isolation steps, and dotted arrows indicate passage and/or cloning steps omitted for simplicity. b | Schematic representation of HIV-1, SIV and chimeric viral genomes. Maroon and blue boxes indicate HIV-1-and SIV-derived sequences, respectively. Ca, *Cercocebus atys* (sooty mangabey); CNPRC, California National Primate Research Center (Davis, California, USA); Env, envelope glycoprotein; LTR, long terminal repeat; Mm, *Macaca mulatta* (rhesus macaque); Mn, *Macaca nemestrina* (pig-tailed macaque); SHIV, simian–human immunodeficiency virus; SIVmac, macaque SIV; SIVmne, pig-tailed macaque SIV; SIVsmm, sooty mangabey SIV; stHIV-1, simian-tropic HIV-1; RT, reverse transcriptase.

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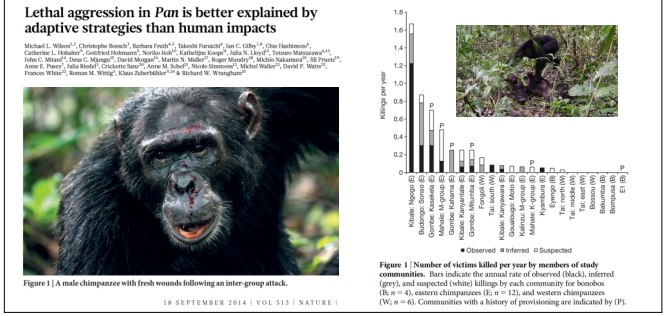
Male violence as disease?



**Lethal aggression in *Pan* is better explained by adaptive strategies than human impacts**

Michael L. Wilson[1,2], Christophe Boesch[3], Barbara Fruth[4,5], Takeshi Furuichi[6], Ian C. Gilby[7,8], Chie Hashimoto[9], Catherine L. Hohmann[1], Gottfried Hohmann[3], Noriko Itoh[10], Katherine Knapp[1], Julia N. Lloyd[11], Tetsuro Matsuzawa[9,12], John C. Mitani[13], Dena C. Mjungu[14], David Morgan[15], Martin N. Muller[13], Roger Mundry[16], Michio Nakamura[17], Jill Pruetz[18], Anne E. Pusey[7], Julia Riedel[3], Crickette Sanz[19], Anne M. Scheff[1], Nicole Simmons[20], Michel Walker[21], David P. Watts[22], Frances White[23], Roman M. Wittig[3], Klaus Zuberbühler[3,24] & Richard W. Wrangham[25]



Figure 1 | A male chimpanzee with fresh wounds following an inter-group attack.




**Figure 1 | Number of victims killed per year by members of study communities.** Bars indicate the annual rate of observed (black), inferred (grey), and suspected (white) killings by each community for bonobos (B; $n = 4$), eastern chimpanzees (E; $n = 12$), and western chimpanzees (W; $n = 6$). Communities with a history of provisioning are indicated by (P).

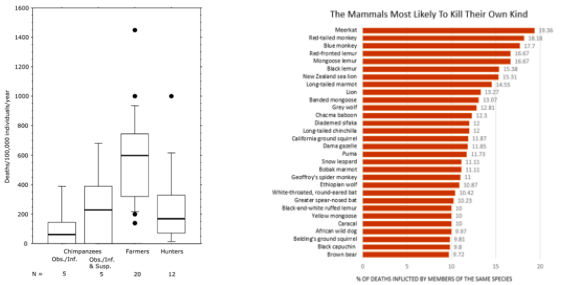


Observations of chimpanzees (Pan troglodytes) and bonobos (Pan paniscus) provide valuable comparative data for understanding the significance of conspecific killing. Two kinds of hypothesis have been proposed. Lethal violence is sometimes concluded to be the result of adaptive strategies, such that killers ultimately gain fitness benefits by increasing their access to resources such as food or mates. Alternatively, it could be a non-adaptive result of human impacts, such as habitat change or food provisioning. To discriminate between these hypotheses we compiled information from 18 chimpanzee communities and 4 bonobo communities studied over five decades. Our data include 152 killings (n =58 observed, 41 inferred, and 53 suspected killings) by chimpanzees in 15 communities and one suspected killing by bonobos. We found that males were the most frequent attackers (92% of participants) and victims (73%);most killings (66%)involved intercommunity attacks; and attackers greatly outnumbered their victims (median 8:1 ratio). Variation inkilling rateswas unrelated tomeasures ofhumanimpacts. These results are compatible with previously proposed adaptive explanations for killing by chimpanzees, whereas the human impact hypothesis is not supported.

Killings involved a median of five male attackers (range: 0–19) and no females (range: 0–6). Considering all cases for which the number of
attackers was observed (n=58) or could be inferred (n=6), males constituted 92% of participants in attacks (338/366). Controlling for
observation time andcommunitycomposition,males were much more likely to participate in killings than females (negative binomial mixed
model: n536 observations (fixed effects: sex with 2 levels; random effects: community with 18 levels); b0526.960.98; bmales52.660.59,
z54.42, P,0.0001). Females sometimes joined males in attacking grown individuals (n=3), but when acting without males, females
killed only young infants (n=8). Most victims were members of different communities from the

attackers (n=62 of 99 cases; 63%) and thus not likely to be close kin

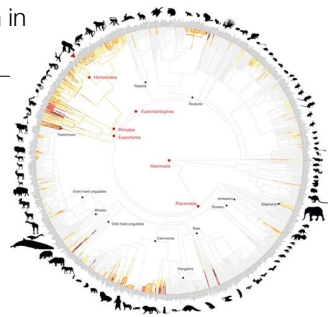
Male violence as disease?




Wrangham *et al* 2006 ***Primates***

Box plots illustrating the death rate from intergroup aggression for chimpanzees and humans in subsistence societies. Boxes enclose the 25th, 50th and 75th percentile of each data set. The 50th percentile (median) is indicated by a thick horizontal line. Whiskers indicate the 10th and 90th percentiles, and dots indicate more extreme outliers. The number of populations for each data set (N) is given below the graph. Two estimates are shown for chimpanzees: one based strictly on observed or inferred cases, and one that also includes suspected cases. Human data are shown for subsistence farmers and hunter–gatherers

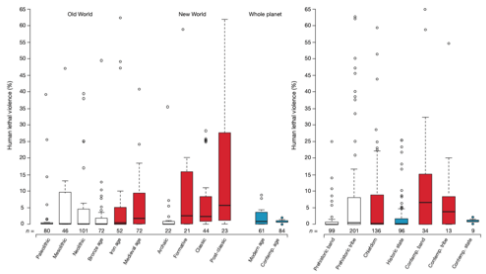
Evolution of lethal aggression in non-human mammals



Gómez, J., Verdú, M., González-Megías, A. *et al.* The phylogenetic roots of human lethal violence. *Nature* **538,** 233–237 (2016)

Tree showing the phylogenetic estimation of the level of lethal aggression in mammals (n = 1,024 species) using stochastic mapping. Lethal aggression increases with the intensity of the colour, from yellow to dark red. Light grey indicates the absence of lethal aggression. Mammalian ancestral nodes compared with human lethal violence are shown in red, whereas main placental lineages are marked with black nodes. The red triangle indicates the phylogenetic position of humans. The silhouettes of representative mammals (downloaded from http://www.phylopic.org) illustrate the main mammalian clades.

Human lethal violence across time and societies




Gómez, J., Verdú, M., González-Megías, A. *et al.* The phylogenetic roots of human lethal violence. *Nature* **538,** 233–237 (2016)

**right**, Human lethal violence during different temporal periods of human history, according to the Old World and New World chronologies
**left**, Human lethal violence in different socio-political organizations28. In all cases the boxplots show median values, 50th percentile values (box outline), 95th percentile values (whiskers), and outlier values (circles). We tested whether the level of lethal violence observed in each ancestral node, human period and human socio-political organization differed significantly from the phylogenetic inferences in a. Colour indicates whether the observed lethal violence was statistically similar (white), higher (red), or lower (blue) than the phylogenetic inferences (Extended Data Tables 2, 3). In a and b, n indicates the number of iterations and in c and d it indicates the number of human populations (see Supplementary Information sections 7, 9c for the number of deaths)

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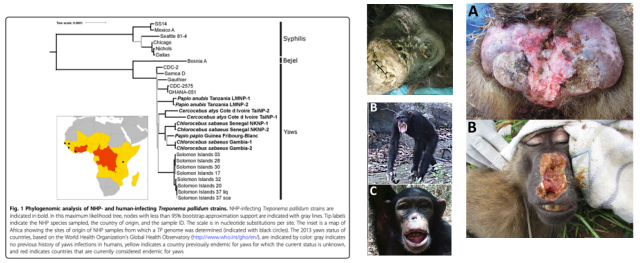
Yaws/ Syphillis in non-human primates?







Knauf et al. Emerging ***Microbes & Infections*** (2018)7:157

Mubemba B, Chanove E, Mätz-Rensing K, Gogarten JF, Düx A, Merkel K, et al. Yaws Disease Caused by Treponema pallidum subspecies pertenue in Wild Chimpanzee, Guinea, 2019. ***Emerg Infect Dis.*** 2020;26(6):1283-1286

*Treponema pallidum*–induced clinical manifestations affecting olive baboons (Papio anubis), Tanzania. A). Lesions on the anogenital area of animal at Lake Manyara National Park. B) Facial lesions of animal at Tarangire National Park. Orofacial lesions were found only in olive baboons.

Geographic proximity between human yaws and endemic syphilis, as estimated by the World Health Organization, and locations in which treponemal infection has been identified in nonhuman primates (NHPs), Africa, 1990s. Red dots indicate infection in NHPs confirmed by sensitive and specific treponemal serologic tests (TPI/FTA-ABS/MHA-TP [Treponema-pallidum-immobilization reaction/fluorescence-Treponema-antibody-absorption test/Treponema pallidum microhemagglutination assay]) and, in some cases, PCR. Stars indicate suspected infection (i.e., sightings of NHPs with lesions consistent with infection). Sources include the following: 1) Cameroon: Gorilla gorilla, observation (W. Karesh, pers. comm.); Pan troglodytes, G. gorilla, and Papio sp., skeletal analysis and serology (4;11 in Technical Appendix. 2) Chad: Erythrocebus patas, serology (4). 3) Democratic Republic of Congo (DRC): Pan troglodytes, serology (4). 4) Gabon: G. gorilla, observation (W. Karesh, pers. comm.). 5) Guinea: Papio sp., serology and PCR (4,8). 6) Kenya: Papio anubis and Chlorocebus sp., observation and serology (J. Fischer, pers. comm.); 12 in Technical Appendix). 7) Nigeria, Papio anubis (J. Wallis, pers. comm.). 8) Republic of Congo: G. gorilla, serology and observation (W. Karesh, unpub. data; 5). 9) Tanzania: P. anubis; observation, serology, PCR (6,7; 13 in Technical Appendix; S. Knauf, unpub. data). 10) Senegal: Papio sp., Chlorocebus sp., colobus monkeys, and Erythrocebus patas; serology (S. Knauf, unpub. data; 4; 14 in Technical Appendix). Scale bar = 1,000 km.

Another recent study has documented a similar bacterial pathogen on wild chimpanzees.

## Monkey virus jumps to humans in California

TMAdV (titi monkey adenovirus)

In May 2009, a deadly outbreak of respiratory illness spread through a colony of titi monkeys at the California National Primate Research Center in Davis. Of the 65 monkeys housed in one building, 23 developed symptoms, including pneumonia. As a result, 19 died or were put down.

A novel adenovirus, named TMAdV (titi monkey adenovirus), infected both a titi monkey colony and a human scientist and her family.

In May 2009, a deadly outbreak of respiratory illness spread through a colony of titi monkeys at the California National Primate Research Center in Davis. Of the 65 monkeys housed in one building, 23 developed symptoms, including pneumonia. As a result, 19 died or were put down.

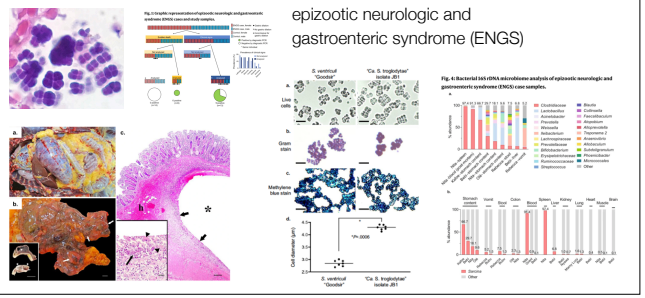
Chiu and his colleagues analysed tissue taken from the affected monkeys, and identified a previously unknown virus. Genetic sequencing revealed it to be an adenovirus, although its genome was substantially different to those of all known related viruses. But what tipped the researchers off that there was something unusual about this virus, says Chiu, was what happened when they tried to culture it. "It was unusual to see it grow well in human cell lines, but not monkey" cells, he says. This suggested that the virus could infect humans as well as titi monkeys. "After we interviewed all of the staff, the only person who said they had been sick was one researcher — the one who had

## Cousin of Anthrax

*B. Cereus in West African chimpanzees*

Back in 2001, Leendertz and his colleagues thought the chimps had died of the familiar form of anthrax, caused by B. anthracis. But that is known to kill many wild animals in arid regions, not rainforests, and in 2010 the researchers linked the deaths to the closely related B. cereus, a common and usually benign soil microbe. (Some strains do cause diarrhea and vomiting in humans.) They also discovered that the Taï strain has acquired two plasmids, or circles of DNA, possibly from B. anthracis, encoding most of the genes that make anthrax a formidable killer.

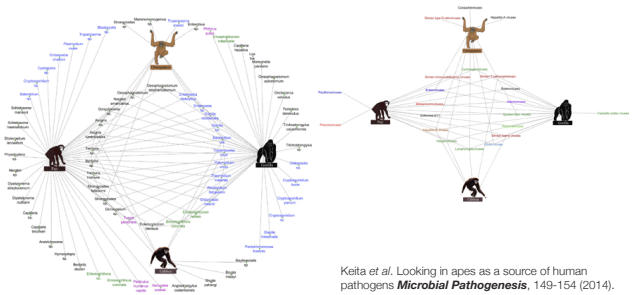
## Sarcina: a newly discovered chimpanzee pathogen



epizootic neurologic and gastroenteric syndrome (ENGS)

Photographic images from an adult male chimpanzee who died of ENGS showing moderate to severe gastric dilation (a), hemorrhagic diathesis (b), and emphysematous typhlocolitis (c; arrows point to gas-filled pockets within the cecum wall, which has reddened areas [in inset, white arrowheads point to gas bubbles in the cut surfaces of the formalin-fixed cecum]; scale bars = 1 cm). On histology (c), gas-filled space (*) in the cecal submucosa, surrounded by inflammatory infiltrates (arrows) and hemorrhage (h) were visualized by hematoxylin and eosin staining (inset depicts inflammatory infiltrates, which include eosinophils [arrow] and multinucleate giant cells [arrowheads]; scale bars = 300 µm [main image] and 30 µm [inset]; micrograph is a representative image of three similar sections obtained from the same individual).

## Apes as reservoirs for human parasites and pathogens



Keita *et al*. Looking in apes as a source of human pathogens ***Microbial Pathogenesis***, 149-154 (2014).

Parasitic reservoir of apes (chimpanzees, gibbons, gorillas and orangutans). Helminths (black), Protozoa (blue), Fungi (green) and Arthropods (pink). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Apes (chimpanzees, gibbons, gorillas and orangutans) serving as viral reservoirs. Viral genera and species are distributed into the following nine families: Retroviridae (dark red), Herpesviridae (green), Hepadnaviridae (orange), Adenoviridae (purple), Papillomaviridae (blue), Filoviridae (light blue), Picornaviridae (black), Paramyxoviridae (red) and Polyomaviridae (light green).

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## Avoiding studying apes to death in the wild!

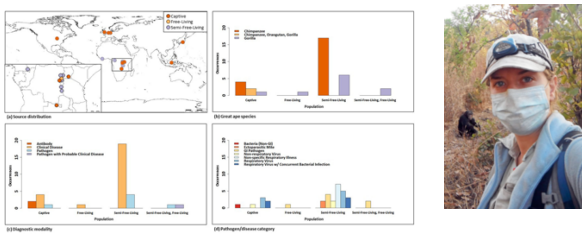

**Fig. 2.** Reported occurrences of zoonotic transmission from humans to great apes by population. **a** Source distribution, **b** great ape species, **c** diagnostic modality, and **d** pathogen/disease category.



NHP primate researcher are taking new precautions to protect the animals they study.

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## Summary

- Humans share the planet with over 300 species of other primates.
- Non-human primates have many diseases including viral, bacterial, protozoal, fungal and helminth related.
- Monkeys and apes of Africa and Asia share many of the diseases with humans, they can be important reservoirs.
- Some innocuous monkey viruses can kill humans (B-virus and monkey pox), others accidentally made it into humans via polio vaccines.
- Wild primates can die from human diseases: measles, polio, respiratory viruses, bovine TB.
- Primates of the Americas (New World Primates) are susceptible to many Old World primate diseases (malaria, dengue, yellow fever, chikungunya, zika)
- The exchange of viruses between distantly related primate species can have disastrous consequences: SIVmc causing monkey AIDS.

# Criteria for a “Human Specific” Disease

Very common in humans but rarely reported in closely related species such as “Great Apes” (even in captivity) and/or could not be experimentally reproduced in such species (in the days when such studies were allowed).

Caveat:
Reliable information is limited to data on a few thousand “Great Apes” in captivity:
BUT
cared for in NIH-funded facilities, with full veterinary care and thorough necropsies

## Candidates for “Human-Specific” Diseases

| “Definite”? |
|---|
| Myocardial Infarction (Coronary Thrombosis) |
| Malignant Malaria (*P. Falciparum*) |
| Typhoid Fever (*Salmonella Typhi*) |
| Cholera (*Vibrio Cholerae*) |
| Mumps (Epidemic Parotitis) |
| Whooping Cough (Pertussis/Diphtheria) |
| Measles (Rubeola) |
| German Measles (Rubella) |
| Smallpox (Variola) |
| Poliomyelitis |
| Pneumococcal Infections |
| Gonorrhea (*Neisseria Gonorrhoea*) |
| Group B Streptococcal Infections |
| *E. coli* K1 Septicemia/Meningitis |
| Meningococcal Meningitis |
| Non-typeable *Hemophilus Influenzae* infections |
| Missing Endemic Transmissible Retroviral Infections e.g., Spumaviruses |
| Type 1 Diabetes? |
| Rheumatoid Arthritis? |

| Probable |
|---|
| Human-Influenza A infections |
| Alzheimer’s Disease |
| Carcinoma (Cancers of Epithelial Origin) |
| Rapid Progression of HIV Infection to AIDS |
| Hepatitis B/C Complications (Cirrhosis, Cancer) |
| Muscular Dystrophy Severity |
| Preeclampsia (Pregnancy-induced Hypertension, PIH) |

| Possible |
|---|
| Frequency of Early Fetal Wastage? |
| Frequency of Premature Labor and Birth |
| Frequency of Chronic Female Iron Deficiency |
| Bronchial Asthma? |
| Hydatidform Molar Pregnancy? |
| Schizophrenia |
| Bipolar Disorders |
| Autism Spectrum Disorders |
| Polycystic Ovarian Disease (PCOS) |

There are countless diseases that seem to be human specific. What could be the reasons?

## Candidates for “Human-Specific” Diseases

| “Definite”? |
|---|
| Myocardial Infarction (Coronary Thrombosis) |
| Malignant Malaria (*P. Falciparum*) |
| Typhoid Fever (*Salmonella Typhi*) |
| Cholera (*Vibrio Cholerae*) |
| Mumps (Epidemic Parotitis) |
| Whooping Cough (Pertussis/Diphtheria) |
| Measles (Rubeola) |
| German Measles (Rubella) |
| Smallpox (Variola) |
| Poliomyelitis |
| Pneumococcal Infections |
| Gonorrhea (*Neisseria Gonorrhoea*) |
| Group B Streptococcal Infections |
| *E. coli* K1 Septicemia/Meningitis |
| Meningococcal Meningitis |
| Non-typeable *Hemophilus Influenzae* infections |
| Missing Endemic Transmissible Retroviral Infections e.g., Spumaviruses |
| Type 1 Diabetes? |
| Rheumatoid Arthritis? |

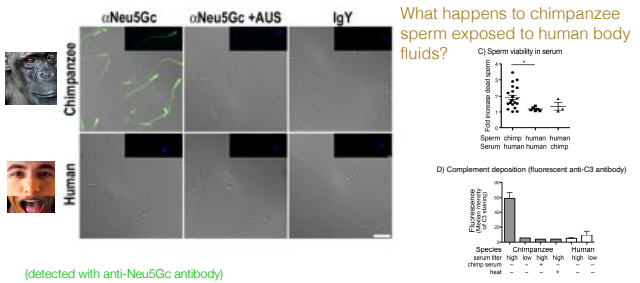
Spontaneous coronary thrombosis due to atherosclerosis seems to be very rare in other animals - in the absence of experimental genetic or dietary manipulations

Possible human-specific mechanisms:

- behavioral and dietary changes associated with “civilization”.
- Amino acid changes resulting in derived proatherogenic human forms of APOE4 and Lp(a).
- Genetic loss of CMAH: hyperactive innate immune cells and effects of red meat consumption.

one can divide such diseases into definite probable and possible.

## Neu5Gc on chimpanzee but not human sperm cells




(detected with anti-Neu5Gc antibody)

What happens to chimpanzee sperm exposed to human body fluids?







Ghaderi *et al. **PNAS***, 2011

Illustration of species-specific “biochemical flavor”. Humans lack. endogenous Neu5Gc sialic acid. Antibodies specific for this non-human sugar are present in most humans.

These antibodies can tag chimpanzee sperm for destruction.

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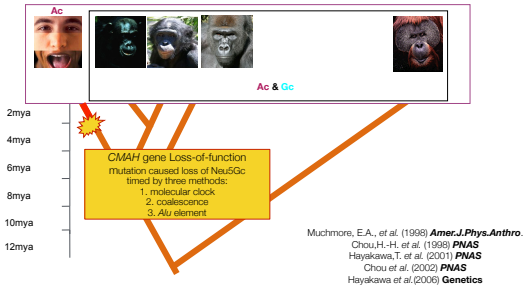
## Human-specific loss of the sialic acid Neu5Gc ~2-3mya




Muchmore, E.A., *et al.* (1998) ***Amer.J.Phys.Anthro.***
Chou,H.-H. *et al.* (1998) ***PNAS***
Hayakawa,T. *et al.* (2001) ***PNAS***
Chou *et al.* (2002) ***PNAS***
Hayakawa *et al.*(2006) **Genetics**

Humans are knock-outs for CMAH enzyme and lack endogenous Neu5Gc

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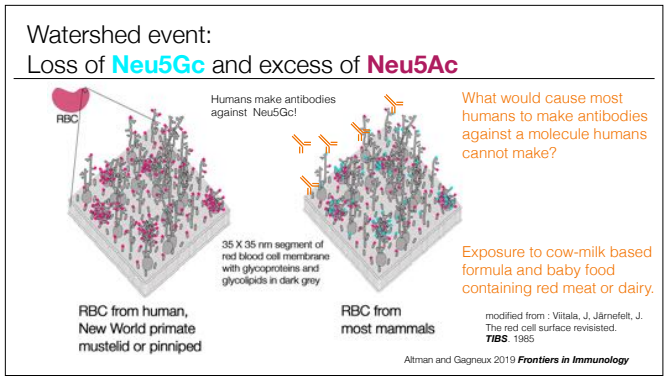
## Watershed event:
## Loss of **Neu5Gc** and excess of **Neu5Ac**

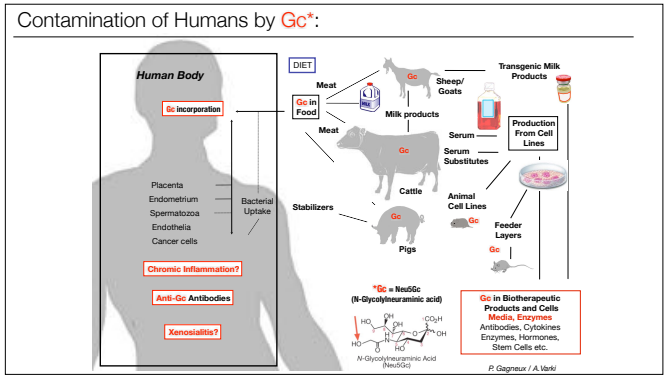

Deletion of 478 pb
in human genome
including 92 bp of exon 6
of the CMAH gene

Altman and Gagneux 2019 ***Frontiers in Immunology***

Modification of CMP-Neu5Ac to CMP-Neu5Gc. The enzyme CMAH, encoded by a single gene in all mammals, catalyzes the modification of Neu5Ac to Neu5Gc in the form of their sugar nucleotides, cytidine monophosphate (CMP).



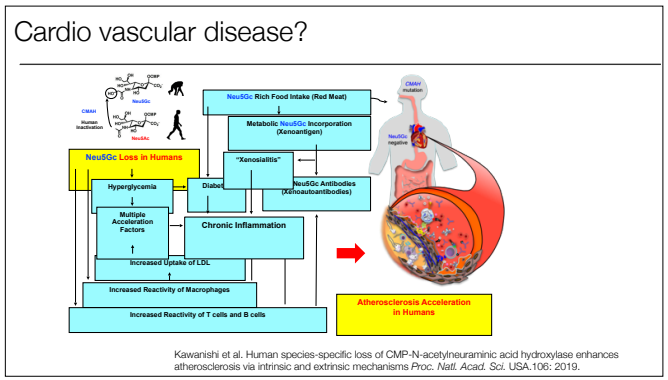

Due to the large number of sialic acids terminating many of the glycan chains on the glycocalyces of most cells, the loss of function of the *CMAH* gene leads to a drastic change in the molecular identity or “flavor” of the glycocalyx, as indicated by a small fraction of a red blood cell membrane.




The non-human sugar Neu5Gc (a sialic acid) can be incorporated into the human body where it then reacts with pre-existing antibodies that recognize this foreign sugar: it becomes a xenoautoantigen.

**Practice question:** What is a xenoautoantigen?

**Answer:** A molecule that comes from the outside the body (e.g. diet) and then becomes incorporated into the body but still is recognized by antibodies (i.e. is antigenic).




Plaque, the accumulation of cholesterol on the inside of blood vessels also involves accumulation of Neu5Gc.

## Candidates for “Human-Specific” Diseases

| “Definite”? |
|---|
| Myocardial Infarction (Coronary Thrombosis) |
| **Malignant Malaria (*P. Falciparum*)** |
| Typhoid Fever (*Salmonella Typhi*) |
| Cholera (*Vibrio Cholerae*) |
| Mumps (Epidemic Parotitis) |
| Whooping Cough (Pertussis/Diphtheria) |
| Measles (Rubeola) |
| German Measles (Rubella) |
| Smallpox (Variola) |
| Poliomyelitis |
| Pneumococcal infections |
| Gonorrhea (*Neisseria Gonorrhoea*) |
| Group B Streptococcal Infections |
| *E. coli* K1 Septicemia/Meningitis |
| Meningococcal Meningitis |
| Non-typeable *Hemophilus Influenzae* infections |
| Missing Endemic Transmissible Retroviral Infections e.g., Spumaviruses |
| Type 1 Diabetes? |
| Rheumatoid Arthritis? |

(Horrible!) Studies done in 1920-40s

- Two-way cross-transfusions between Chimpanzees and Humans infected or non-infected with malaria.
- No evidence of cross-infection!
- Conclusion: parasites look the same, but are different.

Malignant malaria caused the *Plasmodium falciparum* is a uniquely human disease

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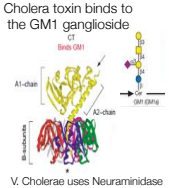
Robert Koch (1884) British Medical Journal:

“…although these experiments were constantly repeated with material from fresh cholera cases, our mice remained healthy. We then made experiments on monkeys, cats, poultry, dogs and various other animals […] but we were never able to arrive at anything in animals similar to the cholera process”

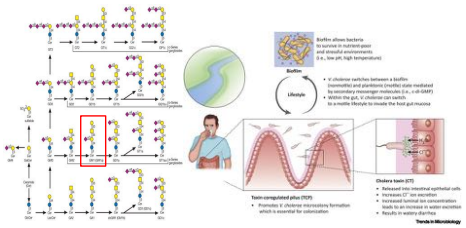
*V. cholerae* does not induce diarrhea in adult mammals other than humans.

## V. cholerae Neuraminidase Digests down Complex Intestinal Gangliosides to GM1 — the Cholera Toxin Ligand!

Cholera toxin binds to the GM1 ganglioside




V. Cholerae uses Neuraminidase to generate GM1 from complex ganglioside mixture

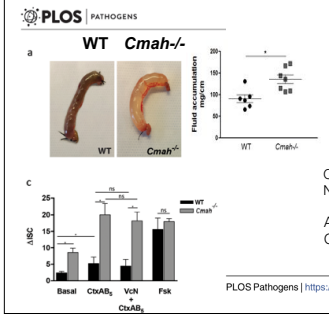


*V. cholerae* Neuraminidase Works much slower on Neu5Gc-containing glycans

Cholera toxin (Ctx) binds to the glycolipid ganglioside GM1, but, GM1 is not present em high levels in the intestine mucosa. Instead, the most abundant gangliosides are GM3 (~80%), GD1b, GT1b and GQ1b (in this order). If we look carefully to the ganglioside structures, we can see that they have a conserved core with Glc, Galactose, GalNAc and Galactose, only differing by how many units of sialic acid they present. Here is when the bacteria Neuraminidase comes into play. The bacteria uses its own enzyme: Vibrio cholera neuraminidase (VcN) to generate GM1 structures from the Polysialogangliosides.

The bacterium gives the molecules a “haircut” to create its own sticky landing pad!!

## Cholera Toxin induces higher fluid accumulation and Cl- ion secretion in small intestine of human-like Neu5Gc-deficient Cmah-/- mice.




CFTR= Cystic Fibrosis Transmembrane Regulator!
Need to study Cmah-/- CFTR -/- mice!

A second as yet unexplained mechanism involving CFTR

PLOS Pathogens | https://doi.org/10.1371/journal.ppat.1007133 June 18, 2018

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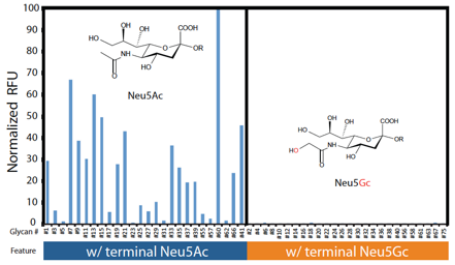
More Horrible Studies done in 1960s

Large doses of Salmonella typhi did not result in severe and complicated forms of typhoid fever in chimpanzees.

Survival of S.typhi in infected chimpanzees limited in time as well as sites affected.

Chimpanzees less sensitive to the typhoid toxin than humans.

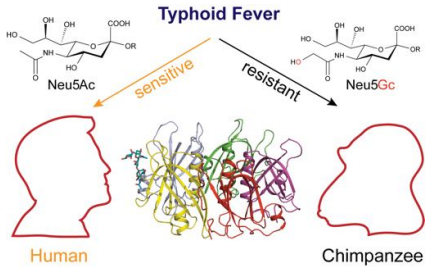
## Typhoid Toxin Cannot Recognize the Non-human/Chimpanzee Sialic Acid Neu5Gc




Deng et al. *Cell*. 159:1290, 2014.

Glycan array: synthetic sugar chains of defined composition printed on a glass slide allow testing different toxins, bacteria, viruses and even human proteins for their affinity to defined glycans.

## Candidates for “Human-Specific” Diseases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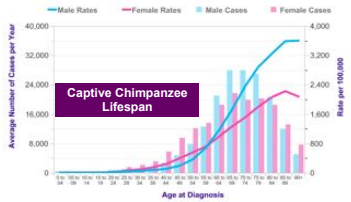
“Molecular Mimicry”
Bacterial Capsule Sialic Acids Perfectly Mimic Common Motifs on Sialoglycans of Mammalian Cells

**Number of New Cases Per Year and Age-Specific Incidence Rates per 100,000 Population, UK**

**All Cancers Excluding Non-Melanoma Skin Cancer 2011-2013**





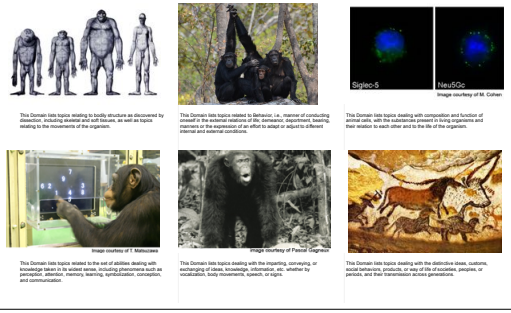

CANCER RESEARCH UK

## Comparative Anthropogeny


## The Matrix of Comparative Anthropogeny (MOCA)


The Matrix of Comparative Anthropogeny (MOCA), which is a collection of comparative information regarding humans and our closest evolutionary cousins, with an emphasis on uniquely human features.

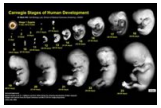
## Matrix of Comparative Anthropogeny MOCA



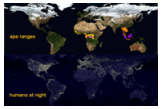
## Matrix of Comparative Anthropogeny MOCA cont'd

Image courtesy of Bill Calvin

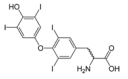
This Domain lists topics dealing with the teeth.




This Domain lists topics dealing with growth and unfolding of organs and organisms.




This Domain lists topics dealing with relationships between living organisms and their environment.




This Domain lists topics dealing with the physiology or study of the endocrine glands, having an internal secretion, which is poured into blood or lymph and acts at distance.

Image Courtesy of Tara Stoinski

This Domain lists topics dealing with key maturational and reproductive characteristics defining the life course. The history of changes undergone by an organism from conception to death.

This Domain lists topics dealing with inherited variation in living organisms, and some of the genetic processes responsible for this.

## Matrix of Comparative Anthropogeny MOCA cont'd

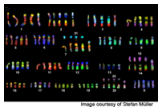
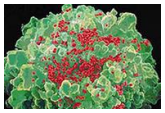
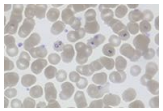


Image courtesy of Stefan Muller

This Domain lists topics dealing with the structure, function and evolution of genomes.

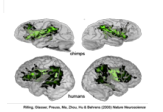


This Domain lists topics dealing with the structure and function of the immune system.



This Domain lists topics dealing with medicine, i.e., conditions requiring treatment or diagnosis by a physician.

This Domain lists topics dealing with temporary or permanent impairment of the mind due to inherited defect, injury, illness, or environment, usually needing special care or rehabilitation.




Rilling, Glasser, Preuss, Ma, Zhou, Hu & Behrens (2008) Nature Neuroscience

This Domain lists topics dealing with the structure or function of the nervous system.

Image courtesy of Pascal Gagneux

This Domain lists topics dealing with the action or process of supplying, or of receiving, nourishment or food.

## Matrix of Comparative Anthropogeny MOCA cont'd

Image courtesy of Cary Wolinsky, PNAS

This Domain lists topics dealing with the normal functioning of living organisms and their systems and organs.

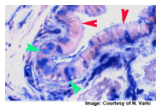


Image: Courtesy of R. Vialet

This Domain lists topics dealing with the causes and nature of diseases and abnormal anatomical and physiological conditions.

Image courtesy of Mike Huffman

This Domain lists topics dealing with drugs and their uses; as well as the physiological response of an organ or its function to drugs or other pharmacologically active substances.

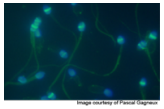
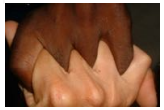


Image courtesy of Pascal Gagneux

This Domain lists topics dealing with biological traits related to reproductive organs and systems, their function and diseases.



This Domain lists topics dealing with biological traits related to the integument (skin).

Image courtesy of Pascal Gagneux

This Domain lists topics dealing with social groups, their sizes, composition, spatial distribution and relative stability.

# Matrix of Comparative Anthropogeny MOCA Graphic Tools

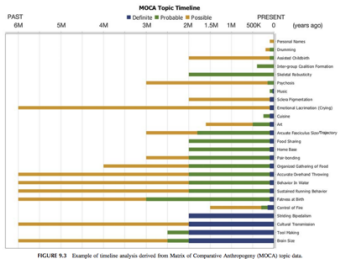



FIGURE 9.3 Example of timeline analysis derived from Matrix of Comparative Anthropogeny (MOCA) topic data.

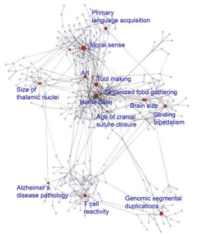



FIGURE 9.4 Example of a relational Matrix of Comparative Anthropogeny (MOCA) topics.

Varki and Gagneux 2017 in On Human Nature