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# Man, monkeys and malaria

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Bizarre though it may now seem, in the last century a whole series of experiments was conducted that involved injecting fresh monkey blood into human volunteers or patients. The reasons, valid at the time, were either to treat neurosyphilis with a relatively benign simian malaria infection (so-called pyrogen therapy), or to establish which monkey malaria species were potential zoonotic reservoirs of infection that then may have interfered with malaria eradication campaigns. Although direct inoculation of fresh blood is the most effective way of retroviruses as well as malaria parasites crossing the species barrier, this hypothesis was never taken up or researched. Unlikely, but not disproved, it is important to remember some of the more hazardous experiments that were done in good faith, too long ago to be recorded on electronic databases.

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Person-to-person transmission of human-adapted simian retroviruses can take place in several distinct ways. Sexual transmission is the rule. The oral route, particularly with breast milk, is important in neonates. Human immunodeficiency virus (HIV) can pass through abrasions and wounds if they are contaminated with infected blood. Undoubtedly, the most efficient way to transmit the virus is to inject fresh infected blood directly into a susceptible host. This meeting has considered in several sessions oral transmission, the only way that oral polio vaccine (OPV) putatively infected with SIVcpz could have crossed the species barrier. The alternative and most widely accepted theory, hunters being infected as they killed and then butchered chimpanzees in the bush meat trade, needs to invoke contaminative transmission. Thankfully nobody these days dwells on discredited anecdotes of bizarre sexual practices of man with monkeys. But what of direct inoculation of monkey blood into humans—the most effective way for a simian retrovirus to cross the species barrier?

In 1991, I pointed out that there were several instances recorded in the literature of humans either inoculating themselves, volunteers or patients with chimpanzee blood; and even two instances when sooty mangabey blood was inoculated (Gilks 1991). These experiments were either to define the species boundaries of African primate malarias, particularly whether humans were susceptible, or to investigate the therapeutic value of primate malarias in 'pyrogen therapy'. Bizarre that this now seems, there were valid contemporary reasons for such experimentation. Whether the host range of primate malarias was restricted or not was initially a taxonomic nicety, but it assumed importance in the 1950s when there was a concerted effort to eradicate malaria. Primate malarias could have been a potential zoonotic reservoir to re-infect human populations. Before the discovery of penicillin, there was no specific therapy for neurosyphilis. However, it had been known since the early 1900s that a period of sustained high fever was capable of reversing

some of the symptoms, and even seemingly curing the infection in some patients. One of the most effective, and widely used, way of producing a controllable fever was with 'induced' malaria and many studies were done in mental asylums. Some institutions had their own insectaries and relied on mosquito passage, whilst others maintained infection by direct person-to-person inoculation of blood-stage parasites. Virulent infection, especially with the virulent human parasite *Plasmodium falciparum* could result in death from the therapy, and there was considerable interest in the use of other less virulent but adequately pyrogenic malaria species. Several institutes thus experimented with the chimpanzee species *Plasmodium richenowi*, *Plasmodium schwetzi* and *Plasmodium rodhaini*.

Given what we know today about the enormous risks posed by such procedures, these experiments seem foolhardy, unethical and extremely dangerous. It is important to put these events into their contemporary context; and to remember that syphilis was viewed before the antibiotic era in a similar way to HIV and acquired immune deficiency syndrome (AIDS) today. Desperate measures were invoked to treat the disease. Similarly, many human parasitic infections are zoonotic and the potential of malaria to lurk in animal reservoirs was an appropriate concern given the aim of global eradication.

A final part of my thesis was that the African primate malarias, including *Plasmodium gonderi*, the tertian parasite of the sooty and agile mangabeys, were often maintained in captive macaques because of the scarcity of African primate hosts in research laboratories. It is conceivable therefore that the outbreak of SIVmac in North American animal houses was related to primate malaria work as well, rather than co-housing valuable primates of different species, all with an inevitable propensity to interspecies fighting.

It was rather disappointing that this thesis was never properly evaluated and followed up after it was published by the institutions where the documented work was

carried out. One of its important aspects was that it was testable by going back to type material, patient records and perhaps to archived human specimens. The theory never attracted someone with the zeal and determination of Ed Hooper; and did draw attention to what were by today's standards relatively dubious clinical investigation in humans (probably without any informed consent) using primate material in reputable institutions that are still today active in medical research. I suspect there was understandable reluctance to take the hypothesis further.

Timing the ancestor of the HIV-1 pandemic strains to the 1930s coincides with some of the Belgian studies I uncovered that were carried out in that decade, albeit in Europe rather than the Belgian Congo. Given what we know now about multiple cross-species transfers of both SIVagm and SIVcpz to humans, the notion of malaria work being the sole mechanism of cross-species transmission is unlikely. It could still, however, account for the origin of the outbreak of SIVmac in North American

primate colonies, an issue to my mind never properly addressed or convincingly explained.

Unlikely but not disproved, it is important to keep the idea in the public domain if only to remind us today of some of the more hazardous experiments that were done on human subjects with monkey products. Others are documented, not just in tropical medicine, but all were reported far too long ago to be on any electronic database. To many nowadays, this renders such work almost invisible. Bizarre historical curiosities certainly, perhaps we have been remarkably lucky not to have encountered serious problems from such experimentation. Or perhaps we just have not yet recognized what else has been accidentally transferred from monkey to man?

#### REFERENCE

Gilks, C. 1991 AIDS, monkeys and malaria. *Nature* **354**, 262.