

# Natural and iatrogenic factors in human immunodeficiency virus transmission

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In the light of the evidence and discussion presented during The Royal Society Discussion Meeting it seems to me that the oral polio vaccine (OPV) hypothesis for the origins of human immunodeficiency virus (HIV) and the acquired immune deficiency syndrome epidemic is less tenable now than one year earlier. The OPV hypothesis does not accord with HIV phylogenetic studies: the geographical correlation has been challenged; the testimony of those directly involved with OPV trial vaccines denies the use of chimpanzees, corroborating tests on the still-available vials of the CHAT vaccines, which contain neither simian immunodeficiency virus nor chimpanzee DNA. Yet one lesson to be learned from considering OPV as a source of HIV is how plausibly it might have happened and how cautious we need to be over introducing medical treatments derived from animal tissues, such as live, attenuated vaccines or xenotransplantation. To cast doubt on the OPV hypothesis is not to dismiss entirely the role of iatrogenic factors in HIV transmission from chimpanzees in the first instance, in HIV adaptation to onward transmission during its early phase in humans, or in the later spread of HIV to patients, for example, with haemophilia. To reduce the argument over the origins of HIV to the 'OPV hypothesis' versus the 'cut-hunter hypothesis' is an oversimplistic and false antithesis. Both natural and iatrogenic transmission of many retroviruses, including HIV, have been thoroughly documented and are not mutually exclusive. Exactly how, when and where the first human(s) became infected with the progenitor of HIV-1 group M, which gave rise to the pandemic strain, is likely, however, to remain a matter of conjecture.

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## 1. INTRODUCTION

Doubt is the first step along the path to knowledge and truth: he who doubts nothing discovers nothing  
(Diderot 1765).

In my review of *The river* (Hooper 1999) I wrote concerning the oral polio vaccine (OPV) hypothesis on the source of human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS): 'Hooper builds up layer upon layer of circumstantial evidence and plausible conjecture, until he declares: "The reader must make up his mind or her mind. I have made up mine". Yet after having read his 858 pages of text and 175 pages of notes and references, I remain undecided on the origins of HIV' (Weiss 1999). One year later, having listened to all the evidence and the arguments during this Royal Society Discussion Meeting, I am prepared to do as Hooper urges, to make up my mind.

It seems clear to me that the evidence for a chimpanzee-to-human cross-infection by HIV-1 group M taking place earlier than the first OPV trials is stronger, whereas the circumstantial evidence that one or more of the CHAT batches of OPV may have been prepared in chimpanzee kidney culture is much weaker. I am not saying that the OPV hypothesis is conclusively disproved; but there is such a burgeoning burden of doubt that the

arguments needed to sustain the hypothesis become increasingly contorted.

This view is a personal one, a view that has shifted in the light of this Discussion Meeting. Although my opinion has veered towards the mainstream, I do not imagine that everyone present shared it. However, it was not an aim of the meeting to reach a consensus acceptable to all; rather, to lay open all the arguments and counter-arguments for participants to draw their own conclusions. In my concluding remarks, I have not attempted an overall summary of the meeting, but I draw together some relevant points from most of the speakers.

## 2. HAMILTON'S LEGACY

Bill Hamilton, whom we honoured *in memoriam* at the beginning of this meeting, was much taken up with the notion that OPV was the cause of the AIDS epidemic, and in the medical world's blindness to the potential consequences of its practices in general. He and I shared a concern about possible zoonoses, animal-to-human infections, arising from xenotransplantation and the need to extend an aspect of the Hippocratic oath (at least do no harm) from the individual patient to the community at large (Hamilton 1999; Weiss 1998, 2000). Regarding the investigation of the origins of HIV, Hamilton made three important and practical proposals: to hold this meeting, to conduct tests on the host species used in the

surviving vials of OPV CHAT stocks, and to elucidate the natural history of lentivirus infection in wild chimpanzees.

Hamilton feared that the OPV hypothesis on the introduction of HIV in humans was not receiving sufficient attention from virologists. He also found difficulty (as we all experience with leading scientific journals) in persuading editors to print letters from himself and others concerning this hypothesis. Posthumously he has been vindicated in that *The Lancet*, *Science*, *Nature*, *Nature Medicine* and *New Scientist* sent representatives to this meeting and have reported the debate (Birmingham 2000; Cohen 2000; Day 2000; Dickson 2000; Horton 2000). Hamilton also thought that the OPV hypothesis needed to be openly and rigorously debated at a scientific forum, rather than be confined to the general media and Internet Web sites. He therefore strongly advocated this Discussion Meeting at The Royal Society where the OPV hypothesis could be examined fairly alongside other models of cross-species virus transmission and the current data on HIV phylogeny. Thus the meeting's topics were essentially the same as he agreed with his co-organizers before his untimely death.

It was also Hamilton (1999) who proposed that the available stored OPV batches at the Wistar Institute be tested by modern forensic DNA methodology, not only for the presence of viral RNA related to HIV or simian immunodeficiency virus (SIV), but also for host DNA, in order to identify the species used as cell substrate for the vaccine. Hamilton's useful suggestion was most persuasively advocated in *The river*, and it is a tribute both to Hamilton and to Hooper that these tests have now been performed, thanks to their exhortation. The results were first presented at this meeting by Basilico on behalf of the AIDS/Poliovirus Advisory Committee to the Wistar Institute and the independent laboratories performing the tests, and has recently been published (Blancou *et al.* 2001; Poinar *et al.* 2001). Moreover, the Wistar CHAT 10A-11 stock, most implicated in the OPV hypothesis, was also tested shortly after the meeting (Berry *et al.* 2001). No trace of primate lentivirus sequences was found in any of the OPV samples, no chimpanzee DNA was detected, and where host DNA was detected it clearly belonged to the macaque genus of Asian monkeys.

Many species of African primates harbour lentiviruses related to HIV, known as SIVs. The OPV hypothesis first gained notoriety in Curtis's article (Curtis 1992), which proposed that HIV came from SIV<sub>agm</sub> of the African green monkey, since the kidneys of this species were undoubtedly used routinely for polio vaccine manufacture (although not until after 1960). However, the HIVs are phylogenetically distant from SIV<sub>agm</sub>. HIV-1 is closely related to SIV<sub>cpz</sub> of chimpanzees (something of a misnomer, as Short pointed out in discussion, since apes are not strictly simians), and HIV-2 is closely related to SIV<sub>sm</sub> of sooty mangabey monkeys (Gao *et al.* 1992, 1999).

As a supporter of the OPV hypothesis, Hamilton agreed with Hahn, an outspoken opponent, that we do not know enough about the natural history of SIV<sub>cpz</sub> infection. The gaps in our knowledge are how endemic and widespread SIV<sub>cpz</sub> is among wild chimpanzees, and to what extent SIV varies geographically (Weiss &

Wrangham 1999). This was the spur to study chimpanzees in the Congo, where Hamilton became ill. The samples of faeces he brought back are being analysed, with negative results to date for SIV<sub>cpz</sub>, as we heard from Wain-Hobson. Hahn spoke at the meeting of a similar approach, in her case sampling chimpanzee urine for antibodies to SIV<sub>cpz</sub> and for viral genomes; only one wild animal examined so far was SIV<sub>cpz</sub> positive. At the moment, it appears that of the four SIV<sub>cpz</sub> genomes from captive chimpanzees, the three characterized from *Pan troglodytes troglodytes* are most closely related to HIV-1 groups M, N and O, whereas a single viral genome from *P. t. schweinfurthii* is far more distant (Gao *et al.* 1999).

Gagneux *et al.* (this issue) described the importance of employing molecular genetic techniques to clarify chimpanzee phylogenetics; the classical subspeciation based on morphology may not tally precisely with DNA sequence relationships. *P. t. troglodytes* live in western Central Africa (Gabon and Cameroon) and *P. t. schweinfurthii* in eastern Central Africa, where AIDS first flowered epidemically and where Camp Lindi was situated. If the geography and taxonomy of these subspecies and their SIV<sub>cpz</sub> genotypes is upheld, it would not appear to fit the OPV hypothesis. But this reasoning relies on data from the single SIV<sub>cpz</sub>Ant isolate from *P. t. schweinfurthii* being so distinct. Hence the importance of Hahn's investigation and the similar approach by Hamilton to attempt to gather more accurate information on the distribution and variation of SIV<sub>cpz</sub> in chimpanzees. As I have commented before with the primatologist, Richard Wrangham (Weiss & Wrangham 1999), one can challenge the argument advanced by Hahn and colleagues (Gao *et al.* 1999) that SIV<sub>cpz</sub> represents an ancient chimpanzee infection that has coevolved with its host during subspeciation. Indeed, we cannot be sure that chimpanzees represent a natural reservoir for SIV<sub>cpz</sub>; perhaps they are susceptible to sporadic infection from another animal reservoir in their habitat. Although that may seem unlikely, further samples from the wild are needed to gain a better knowledge of the prevalence, geographical distribution and genotype of SIV<sub>cpz</sub> in chimpanzees.

### 3. A QUESTION OF TIME AND PACE

Some of the most fascinating data and discussion at this meeting concerned the timing of the radiation of HIV-1 group M from a common progenitor virus into its many subtypes or clades. While Burr *et al.* (this issue) queried the evolutionary force driving the symmetrical 'sunburst' of this radiation, one can interpret the contrast between feline immunodeficiency virus and HIV-1 group M to be due to interclade recombination in the former, and recent cross-species transfer of the latter. There appears to be remarkable consensus about the recent common origin of HIV-1 group M, with a best estimate of 1931 with 95% confidence limits between 1915 and 1941 (Yusim *et al.*, this issue; Salemi *et al.* 2001). The question, then, is whether this point source represents the chimpanzee-to-human crossover event, as the founder effect for human colonization by HIV-1 group M. Hooper (this issue) argues not so, that multiple subtypes have been introduced by OPV, but I found the arguments against this reasoning by Sharp *et al.* (this issue) and Holmes's

points in discussion to be compelling (Rambaut *et al.* 2001). The lack of genetic recombination in the early phases of group M evolution in contrast to the frequent emergence of recombinant HIV-1 strains in Africa today suggests a point source without significant co-infection or superinfection during the early years of HIV's spread in humans. Yusim *et al.* (this issue) suggested that the early spread of HIV-1 group M was very slow, and if it was also less pathogenic, it may have gone unnoticed for decades.

On the principle of Occam's razor, it seems unnecessarily complicated to suggest that HIV-1 group M began its diversification in chimpanzees as recently as around 1931, but only spread to humans in 1957–1959. Transfer by OPV would have required some dozens or more separate transmissions for the origin of each non-recombinant subtype, and by different vaccine batches to effect such diversity, in which case, surely, at least one or two of the OPV batches tested would be expected to have been positive? Could this mean that all the chimpanzees supposedly used for OPV manufacture would be derived from a single troupe harbouring group M? It appears much more likely that HIV-1 groups M, N and O represent separate zoonotic events arising from a single infected human in each case.

The timing of the origin of group N and group O cannot be calculated with as much precision as for group M because of the paucity of isolates and sequence data. Hence we do not know whether these strains are relatively recent zoonoses, dated from around the time of the OPV trials, or perhaps earlier, even prior to the 20th century. One early case of AIDS, in 1966, was due to HIV-1 group O infection. However, had there been a really widespread epidemic of AIDS before 1960, it would have been noted, just as Ugandans recognized 'slim' disease as something new in the early 1980s (Serwadda *et al.* 1985; Hooper 1990).

Similar reasoning applies to HIV-2. Some human infections may represent primary zoonoses from sooty mangabeys: others clearly result from human-to-human spread. The timing is not clear, and the records of OPV trials in French and Portuguese colonies in western Africa are poor. At least six mangabey-to-human transfers are thought to have occurred (Gao *et al.* 1992). There is no evidence, direct or indirect, that sooty mangabeys were used to propagate OPV by Pierre Lépine or others with links to western Africa. Of course, we should bear in mind that lack of evidence is not synonymous with evidence that mangabey or chimpanzee were not used; the tests on stored OPV samples went some way to satisfy the latter point.

How unique, then, was the 20th century regarding the initiation of more than one AIDS epidemic, and was OPV its only special feature? The enforced movement of peoples occurred over many centuries, as African writers have most movingly recorded (Achebe 1993; Equiano 1789). Environmental changes such as large-scale deforestation accelerated after the OPV trials period. Therefore the increase in hunter–chimpanzee encounters to provision logging camps and urban restaurants is probably too recent to pinpoint the 20th century as unique. It is more likely to my mind that chimpanzee-to-human zoonoses by SIVcpz have taken place rarely and sporadically throughout many centuries, as may be the case for

human T-cell leukaemia virus (HTLV-1) (Gessain & Mahieux 1999; Voevodin *et al.* 1997). If, however, the viral transmission rate was less than one (May *et al.*, this issue), and if it did not spread from village to village (Low-Beer, this issue), such infections would never have taken off in the community at large, and would eventually have petered out.

The uniqueness of the 20th century, therefore, may lie in the next-step transmission after the cross-species jump, namely, in the early adaptation of HIV to pass from person to person. The account of the growth of needle and syringe use and reuse in Africa, documented by Marx *et al.* (this issue), fits remarkably well with the origins of the HIV epidemic. The period during which inoculation was commonplace, but disposable equipment was not, should specially provoke our thoughts. Later, urbanization, trucking routes and sexual promiscuity (Hooper 1990) would have enhanced the spread of HIV. It thus seems plausible that iatrogenic events might well have aided the earliest spread of HIV in humans, in just the same way that it spelt disaster for persons with haemophilia between 1980 and 1985, and continues to be a risk for habituated injecting drug users today.

#### 4. A QUESTION OF PLACE

Why did both the HIV-1 and HIV-2 epidemics start in Africa? Why are HIV-1 group N (Simon *et al.* 1998) and group O (Gurtler *et al.* 1994; Mboudjeka *et al.* 1999) largely confined to that region of Africa where chimpanzees with related viruses live? Likewise, why did HIV-2 originate in western Africa close to the former habitat range of the sooty mangabey? According to the cut-hunter hypothesis, the answer seems obvious. According to the OPV hypothesis, answers look more contrived, unless the OPV was prepared locally (where facilities did not exist), in sooty mangabey kidney cultures in western Africa, and in chimpanzee cultures in Central Africa. If chimpanzee kidneys were used for OPV manufacture in Philadelphia (despite the declarations and affidavits to the contrary; see Plotkin *et al.*, this issue), what kind of fluke was it that an SIVcpz-contaminated batch found its way back to Central Africa, when all the other contemporaneous batches tested in North America and Eastern and Western Europe escaped contamination? For this reason alone, it is small wonder that OPV as a source of HIV has been more heavily criticized than the wounded-hunter interpretation.

There remains the issue of more local geography, and whether early AIDS cases really fit the areas of the OPV trials. In this issue, Hooper argues they do, while De Cock warns that co-incidence is not causality and Low-Beer is duly cautious. The earliest documented HIV<sup>+</sup> blood sample taken in 1959 (Zhu *et al.* 1998) came from a man in Léopoldville (now Kinshasa). This city is just across the River Congo from the natural habitat of *P. t. troglodytes* and is thus neutral regarding the cut-hunter versus the OPV hypothesis. We then have a gap of more than ten years before further group M infections (or AIDS-like disease) came to light, whereas the slim disease epidemic did not take off until the late 1970s. Nonetheless, the Democratic Republic of Congo (Zaire) does appear to contain the most complex and therefore probably the oldest human

Table 1. *Cross-species transmission of primate retroviruses*

(SRV, simian retrovirus; BaEV, baboon endogenous virus; SFV, simian foamy virus; SIV, simian immunodeficiency virus; STLV, simian T-cell lymphotropic virus.)

subfamily	virus	former host	new host	presence in new host
beta	SRV-2	macaque	human	case report
	GALV	gibbon	monkey	case report
gamma	BaEV	baboon	cat	endogenous
	STLV	chimpanzee	human	endemic
delta	STLV	baboon	human	endemic
		chimpanzee	human	case report
spuma	SFV	baboon	human	case report
		chimpanzee (SIVcpz)	human	epidemic or endemic HIV-1 N and O, pandemic HIV-1 M
lenti	SIV	mangabey (SIVsm)	human	epidemic or endemic HIV-2
			macaque	epidemic SIVmac
			human	case report

infestation with HIV-1 group M (Vidal *et al.* 2000). The anthropologist and historian of Africa, Vangroenweghe (this issue) documents the records of symptomatic or serological 'cases'. He poses the paradox that the chimpanzees in Gabon are far from the first epidemic of AIDS in eastern Congo, Rwanda and Burundi, but he also vividly described in his oral presentation the kind of floating society on the ferries and rafts plying upstream and downstream the River Congo that could so easily have spread HIV. By and large, HIV epidemics have blossomed far away from their origins. No one argues that HIV-1 group M subtype B actually had its origin among gay men in San Francisco, or subtype E in Thailand, while the explosion of subtype C infection in South Africa is a calamity of the 1990s, not earlier.

### 5. THE BURDEN OF PROOF

On 1 April 2000, Hooper wrote in *The Guardian* that this meeting would be a 'debate about how HIV and AIDS began, based on a comparison between the only two really viable theories of origin: viral transfer from butchered chimp to hunter; or transfer via contaminated polio vaccine'. Noting the date of his letter, I was inclined to take this statement with a pinch of salt, yet the stark alternative of 'cut-hunter versus OPV' has taken root in the minds of many commentators.

The cut-hunter versus OPV choice seems oversimplistic. Leaving aside non-hunters who become exposed to chimpanzees, it suggests that, if the OPV hypothesis is disproved or seriously weakened, we must fall back on natural transfer. Yet there are other postulated iatrogenic or behavioural routes for exposure to chimpanzee blood (Gilks, this issue; Karpas 1990) that might better fit the timing of the zoonotic event. Martin (this issue) queries why the cut-hunter hypothesis has not been as rigorously examined as the OPV hypothesis. By this reasoning, burdens of proof will need to be borne on the backs of several further, possible, although unlikely routes of transmission. Moreover, the OPV hypothesis is tight concerning the time and place and hence it can be more precisely put to the test than other theories; it is normal to test the testable (as Peter Medawar quipped 'science is

the art of the soluble'). So OPV was put to the test as Hamilton suggested.

If we pause to consider known routes of retrovirus transmission, the burden of proof becomes considerably lighter. Within its new host species, HIV-1 soon adapted to become naturally transmitted through sexual intercourse, but that did not preclude its unnatural, iatrogenic transmission to thousands of persons with haemophilia in the UK alone (Darby *et al.* 1995) through contaminated batches of pooled clotting factors. In Kyushu, Japan, before preventive measures were taken, approximately 10 000 new transmissions each year of HTLV-1 occurred naturally, mainly via mother's milk (Hino *et al.* 1985); a similar number of transmissions, however, occurred iatrogenically via blood transfusion (Okochi *et al.* 1984). An animal retrovirus closely related to HTLV-1, bovine leukaemia virus, was unwittingly spread among cattle by the practice of veterinarians wielding a single needle and syringe when inoculating an entire herd against other diseases, such as brucellosis (Burny *et al.* 1980).

The foregoing examples of both natural and iatrogenic transmission routes of retroviruses relate to transmission within a given host species. Let us therefore consider cross-species infection of retroviruses, and restrict the discussion to primate retroviruses. Table 1 lists ten or more known cross-species transmission events among five subfamilies of primate retrovirus. Although one instance, that of HIV-1 group M, has led to the worldwide pandemic of AIDS, others have been less catastrophic. Some of these are individual case reports with known dates of transmission: the natural transmission of gibbon ape leukaemia virus (GALV) to a woolly monkey in the unnatural circumstance of their sharing a Californian human household as pets (Teich 1982); infection of a laboratory worker with SIVmac (Khabbaz *et al.* 1994); infection by spumavirus of a human bitten by a chimpanzee (Heneine *et al.* 1998); and a macaque beta-retrovirus infecting two primate centre staff (Lerche *et al.* 2001). These cases exemplify the 'wounded-handler' hypothesis. Other cross-species transmissions led to community infection becoming endemic in the locality, such as HIV group O (Gurtler *et al.* 1994; Zekeng, this issue) and HTLV-1 related to chimpanzee simian T-cell

lymphotropic virus (STLV) in Central African pygmies and others (Gessain & Mahieux 1999; Voevodin *et al.* 1997). Infection in West Africans by the main group HTLV-I certainly pre-dates OPV by centuries because it is endemic among Afro-Caribbeans and Afro-Americans (Blattner *et al.* 1982).

It seems odd that just one of these retrovirus subfamilies, the primate lentiviruses or SIVs, should be marked out for an OPV origin when there is no controversy at all in accepting natural transmission or wounded-handler events for the others. To be fair, an OPV origin of a D-type  $\beta$ -retrovirus infection has been postulated (Morozov *et al.* 1996), although it has not been possible to confirm the serological evidence for the purported human infections. Moreover, we accept a non-OPV origin of SIVmac in captive macaques having crossed host species from SIVsm of sooty mangabeys. Should we, then, feel obliged to invoke an OPV origin for each of the six groups of HIV-2 separately from SIVsm, and of the three HIV-1 groups (M, N and O) from SIVcpz? If, however, we were to allow that HIV-2 and HIV-1 groups N and O might originate from natural transfer in their respective localities, why should the subsequent, pandemic spread of HIV-1 group M single it out for a different route of its original zoonosis?

Thus there are numerous examples of retroviruses crossing host species (table 1; Martin *et al.* 1999). Osterhaus (this issue) reminded us of other viral epidemics emanating from foreign hosts, e.g. influenza. Indeed, most human infections probably had an animal origin within the last 10 000 years (Diamond 1997; Oldstone 1998; Weiss, this issue). It is for these reasons that I think a greater burden of proof is required for the OPV hypothesis than for natural cross-species transmission—we already have ample evidence of the latter.

By focusing exclusively on HIV, those who favour the OPV hypothesis tend to ignore our broader knowledge of virus transmission routes. Nevertheless, because natural transmission repeatedly occurs, albeit on rare occasions, does not mean that contamination of a vaccine could not have been the route on another occasion. As with other infections, e.g. hepatitis B virus, natural and iatrogenic transmissions of retroviruses are not mutually exclusive.

## 6. THE BURDEN OF BLAME

'Ex Africa semper aliquid novi' commented Rome's leading biologist, Pliny the Elder, 1932 years ago. This notion that 'something new always comes out of Africa' is not viewed kindly by most Africans still burdened by the consequences of their colonial heritage (Davidson 1992). Identifying Africa as the hearth on which AIDS was forged is widely seen as blame for it happening at all. A frequent response is why blame Africa, why blame Africans and why blame African fauna? Faced with the terrible burden of AIDS, stories that HIV was introduced into Africa from the West by an accident such as OPV or intentionally by the USA Central Intelligence Agency have gained widespread credence.

But science, like the microbes it studies, is not politically correct. It must follow lines of evidence that may be highly unpalatable to politicians whether that be HIV as the cause of AIDS in South Africa (Durban Declaration

2000) or 'mad cow disease' in the UK (Phillips *et al.* 2000). The practical health problem raised by the OPV hypothesis on the origin of AIDS as we move towards global eradication of polio, is to reassure governments and populace that today's OPV is not contaminated by HIV. While the proponents of the OPV hypothesis have never suggested this, there is a danger of modern vaccines being viewed with deep suspicion in this climate of fear where HIV and AIDS are daily taking a heavy toll.

The burden of blame also falls heavily on the pioneers of the OPV CHAT vaccines identified by proponents of the OPV hypothesis as the probable source of SIVcpz contamination. Although Hooper (this issue) is at pains to state that the postulated OPV origin of HIV was an entirely unwitting and unpredictable event, the strong denials by those active in the African OPV trials (e.g. Koprowski, this issue; Plotkin *et al.*, this issue) tend to be viewed by OPV proponents as 'cover ups' after a ghastly mistake (Hooper, this issue; Cribb, this issue; Hamilton 1999). Let us then accept the sincerity of both sides and leave motives aside in examining the weight of the actual evidence.

## 7. THE BURDEN OF TRUTH

At this meeting we have witnessed not only scientific controversy, but also accusations and counter-accusations: namely, that the events and records of the African OPV trials in the late 1950s have not been honestly presented. Hooper (this issue) asked what the fate was of the numerous chimpanzees and bonobos held captive at Camp Lindi, and claimed that witnesses observed the removal of internal organs at autopsy, which may have included kidneys. Plotkin *et al.* (this issue) have replied and we have heard the presentations of four of those involved in OPV research at the time: the account of the Wistar Institute OPV trials, and source material in Philadelphia by Plotkin (this issue), followed by the vehement declamation by Koprowski (this issue). We also heard the resonant statements by Prinzie (Plotkin *et al.*, this issue) and Osterrieth (this issue) that chimpanzee kidneys were not to their knowledge ever used to prepare OPV at the two laboratories capable of doing so in Belgium. In the Congo by all accounts, facilities for vaccine propagation, preparation, and dispensing into aliquots did not exist.

In his foreword to *The river*, Hamilton (1999) worried about the difficulty in laying open to objective investigation the unpalatable idea that one of mankind's greatest recent acts of public health, protective immunization against polio, may inadvertently have triggered the AIDS epidemic. Hamilton began: 'Every time two people put their heads together, Truth suffers; when many put their heads together, she suffers more. . . . When the heads are great ones with much to lose, Truth can be made so ill that we should all shiver.' His ensuing essay on 'evasions and untruth' perhaps inspired the title of Plotkin's riposte 'Untruths and consequences' (Plotkin, this issue).

So has there been a gigantic cover-up with a concerted 'closing of the ranks' of those involved, as Hamilton (1999) implied? There does not appear to have been any motive for it at the time. If chimpanzee kidneys had been considered a better cell substrate than those from macaques, and in plentiful enough supply, there would

have been no reason not to record it, indeed to promote it. As Desmyter told us at this meeting (Desmyter & Teuwen, this issue), Jezierski did test the propagation of polio virus in kidney cultures of chimpanzees as well as of several monkey species, but he did not suggest their use for vaccine production. Neither does the polio vaccine industry have a particularly bad record of cover-up. The Cutter incident was fully explored in 1955, when the Salk vaccine was incompletely inactivated resulting in paralysis of many recipients. The discovery of simian virus 40 (SV40) as a viral contaminant of OPV was immediately reported by Sweet & Hilleman (1960). Millions of vaccine recipients were potentially exposed to SV40 (Nathanson & Shah 1976), and recent studies claim harmful effects (Butel & Lednicky 1999); although these findings are as controversial as the origins of HIV, cover-up was absent. The presence of SV40 in kidney cultures from Asian macaques led to their replacement as an OPV substrate by African green monkeys. One could regard that as leaping out of the frying pan into the fire had SIVagm been the source of HIV, as Curtis (1992) proposed. While SIV was not demonstrated to survive OPV purification (Beale & Horaud, this issue), one cannot wholly preclude it slipping through on rare occasions considering the billions of doses administered during the last 40 years. But genetic sequence data revealed that SIVcpz is the only known animal virus closely related to HIV-1. Hence the suspected use of chimpanzee kidneys as a cellular substrate had to be invoked if the OPV-AIDS hypothesis was to remain plausible.

“What is Truth?” said jesting Pilate, and would not stay for an answer. Thus Francis Bacon began his essay on Truth (Bacon 1625 (in Vickers 1999)). In his deep concern that Truth should not suffer, Hamilton urged The Royal Society to hold this Discussion Meeting on the origins of HIV and the AIDS epidemic. Wain-Hobson and I helped him to assemble the multidisciplinary topics and speakers to address the source of AIDS. Those who ‘would stay for an answer’ have heard and have been able to discuss all the evidence available to us at this time. To investigate when, where, how and why a human health catastrophe started is an important and proper pursuit for a scientific academy such as The Royal Society. But it does nothing to alleviate the burden of the AIDS pandemic. That is the daunting challenge facing us now.

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