

Experimental oral polio vaccines and acquired immune deficiency syndrome

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The simian immunodeficiency virus (SIV) of the common chimpanzee is widely acknowledged as the direct ancestor of HIV-1. There is increasing historical evidence that during the late 1950s, kidneys were routinely excised from central African chimpanzees by scientists who were collaborating with the polio vaccine research of Dr Hilary Koprowski, and sent—inter alia—to vaccine-making laboratories in the USA and Africa, and to unspecified destinations in Belgium. While there is no direct evidence that cells from these kidneys were used as a substrate for growing Dr Koprowski's oral polio vaccines, there is a startling coincidence between places in Africa where his CHAT vaccine was fed, and the first appearances in the world of HIV-1 group M and group-M-related AIDS. Because of the enormous implications of the hypothesis that AIDS may be an unintended iatrogenic (physician-caused) disease, it is almost inevitable that this theory will engender heated opposition from many of those in the scientific establishment, and those with vested interests.

Keywords: chimpanzees; kidneys; oral polio vaccine; HIV-1 group M; origins; iatrogenic

1. INTRODUCTION

The following exchange is an extract from the late Bill Hamilton's last interview, given on 1 December 1999, just four weeks before he set off on his final expedition—to the Democratic Republic of Congo. It was World AIDS Day, and he was speaking to Jim Clancy of the CNN 'Insight' programme about the oral polio vaccine (OPV) theory of the origin of HIV and AIDS.

B.H. 'I've been very concerned about this hypothesis since I first came across it in 1990, and realized that it was not being taken as seriously as I thought it deserved to be by the scientific community. That's my interest. Since then I've read a lot about it, and feel I now know the facts pretty well.'

J.C. 'Other scientists say: "It's all circumstantial; there's absolutely no evidence". Do you agree with that?'

B.H. 'Well, circumstantial evidence is still evidence, and eventually it can build into a convincing theory, as happens sometimes in courts of law. I would say that the circumstantial evidence is now standing very strongly indeed. To my mind, it's by far the most probable theory of how the disease got started.'

The large gathering at this Discussion Meeting showed that others too are now acknowledging that the OPV theory is worthy of examination. Significantly, in the two years since *The river* (Hooper 1999) was published, no evidence has emerged to refute the theory, even if some have claimed otherwise. What have emerged, by contrast, are several theoretical counter-arguments, which are impressive in range, if not always in substance.

In this paper, I shall provide some of the latest evidence in favour of the OPV theory, and also review the major arguments that have been offered to counter the hypothesis. I shall concentrate on the major HIV variant, HIV-1

group M, the strain that has caused the AIDS pandemic, and some 60 million infections to date worldwide. It is now generally accepted that group M came into being after the simian immunodeficiency virus (SIV) of the common chimpanzee crossed into *Homo sapiens* (Peeters *et al.* 1989; Huet *et al.* 1990). Broadly speaking, there are just two viable, though contrasting, theories about how that may have happened.¹

2. 'NATURAL' OR IATROGENIC ORIGIN?

Doctors Hahn, Sharp, Korber, and many other scientists favour the prevailing theory of origin of HIV—the 'natural transfer' or 'cut-hunter' theory. The aforementioned doctors postulate that a chimpanzee SIV was transferred casually to a human, perhaps when a hunter or bushmeat seller, with cuts on his or her hands, butchered a chimp for the pot, or perhaps when a chimpanzee pet scratched its owner. This one transfer, they maintain, sparked the pandemic.

The alternative theory is one of iatrogenic transfer, which proposes that HIV-1 group M was inadvertently caused by the medical profession. The most plausible iatrogenic hypothesis, the so-called OPV theory, proposes that certain batches of an experimental OPV, CHAT, which was fed to about a million persons in Central Africa between 1957 and 1960, were produced in chimpanzee cells that were infected with SIV. It further proposes that CHAT vaccine trials staged in at least 27 different venues in the Belgian colonies, now known as the Democratic Republic of Congo (DRC), Rwanda and Burundi, allowed different variants of chimpanzee SIV to become seeded in humans, thus giving birth to most of the group M subtypes that are recognized today.

There is a great deal of documentary and anecdotal evidence to support the OPV hypothesis—evidence that is related in some detail in *The river*. I shall not attempt to include all that evidence here, but I shall report what others, as well as myself, have found: that a far greater percentage of those (both scientists and non-scientists) who have read *The river* in its entirety find the theory persuasive than those who have skimmed the book, or those who rely on hearsay. By contrast, there has thus far been no published attempt to provide a step-by-step scenario to explain the specific mechanics of group M natural transfer, especially its more problematical aspects, such as why HIV and AIDS emerged first where they did (in the former Belgian territories), and just how the subtypes of M came into being. And of course, because the natural transfer theory is innately nebulous, it is impossible to prove or disprove.

3. ORAL POLIO VACCINES AND THE RISK OF CONTAMINATION

Now for some brief background on OPVs. An OPV, as distinct from a killed polio vaccine (like the shot in the arm developed by Jonas Salk), consists of live, but attenuated (or weakened) poliovirus. The vaccine developer produces a seed pool of his chosen strain of weakened poliovirus, and he tests this for safety in a variety of animals, such as rodents and primates. Portions of the seed pool are then grown or amplified in a tissue culture (usually consisting of monkey kidney cells) to produce batches of vaccine. This vaccine is filtered to exclude bacteria, but cannot be denatured further, lest that process affect the attenuated poliovirus that will render the vaccinee immune to polio. If the primate kidney cells in that final substrate are themselves contaminated with any hidden or unknown simian viruses, then these, as well as the attenuated poliovirus, will be swallowed by the vaccinee.

The scientists who developed and tested CHAT—Hilary Koprowski, Tom Norton and Stanley Plotkin, all from the Wistar Institute in Philadelphia, together with Ghislain Courtois and his team from the Medical Laboratory of Stanleyville (nowadays Kisangani)—had a research station, Camp Lindi, in the heart of the Congo forest where, they told others, they were ‘perfecting’, or putting the finishing touches to, CHAT vaccine. However, they never reported any but the most basic details of that research. From those basic details, we know that they carried out safety tests, by injecting the vaccine into the chimpanzees’ spines. They also carried out efficacy tests, by vaccinating the chimps, and then challenging them with wild, virulent, polioviruses. Dr Plotkin admitted to me during an interview that, in retrospect, these tests may not have told them very much of value. The important question here, however, is what other polio-related experimentation may have occurred at Camp Lindi?

If some of these researchers experimented, as I believe they did, by growing the vaccine in different substrates—different types of primate cells—then was not this exactly the sort of research which it was sensible and responsible to carry out? Nobody was doing anything illegal, or anything that ran counter to the scientific recommenda-

tions of the day. Even as late as 1960, the World Health Organization’s third expert committee on poliomyelitis stated that although the monkey kidney tissue culture in which polio vaccine was made would normally come from the rhesus macaque, the cynomolgus macaque (both Asian monkeys), or the African green monkey, ‘[o]ther species may also be found to be suitable’ (Expert Committee on Poliomyelitis 1960). In other words, the final substrate was a detail left to the discretion of the vaccine-maker.

And indeed, different vaccine-makers did use different substrates. James Gear from South Africa used the African green monkey (AGM) from the time of his first research in 1954—long before others adopted that substrate in the 1960s (Hooper 1999, p. 388). Pierre Lépine of the Pasteur in Paris used the Guinea baboon from West Africa, and other African primates too (Lépine & Paccaud 1957). Alexandre Jezierski, who was running a small veterinary laboratory in north-eastern Congo was, amazingly, growing polioviruses and making experimental polio vaccines in the kidneys of 15 different African primates, including chimpanzees (Hooper 1999, pp. 606–607). The Von Magnuses from Denmark used a cocktail of different primate cells for their 1955 killed vaccine, which derived from rhesus and cynomolgus macaques from Asia, together with the AGM, two different baboons and a mangabey from Africa (Von Magnus *et al.* 1955). That latter detail is intriguing, because the SIV of one type of mangabey (the sooty mangabey) is the direct ancestor of HIV-2, and we still do not know which species of mangabey the Von Magnuses used.

4. COUNTER-ARGUMENTS TO THE OPV THEORY EXAMINED

At this point, I would like to examine the scientific objections that have been raised against the OPV theory. These can be summarized as follows: (i) there is no evidence that chimpanzee kidneys were ever used to make CHAT vaccine; (ii) CHAT vaccine samples from the Wistar Institute and other Western laboratories have now been tested, and found to be negative for HIV and SIV, and not to contain chimpanzee DNA; (iii) purported epidemiological links between CHAT and AIDS can be explained by other factors; (iv) ‘wrong subspecies’; (v) ‘wrong time’; (vi) chimpanzee cells would have been an ‘absurd’ substrate to use for a polio vaccine; (vii) even if chimps had been used, not enough of them would have been involved to have sparked the group M subtypes; (viii) even if SIV-infected chimps had been used, SIV from their kidneys could not have survived through to the final vaccine preparation; (ix) HIV and SIV cannot (or can only with difficulty) be transmitted orally; and (x) that *The river*, to quote Stanley Plotkin, ‘does not withstand critical analysis’ (Plotkin, this issue (p. 822)).

I believe that there are counter-arguments to each of these objections, as follows.

(i) Were chimp kidneys ever used to make CHAT vaccine? According to the four doctors who were most actively involved in the development and testing of CHAT, they were not. Hilary Koprowski, the director of the Wistar Institute from 1957 to 1991, has vehemently

denied that chimp kidneys were ever used to make CHAT, but has also given conflicting versions of which primate kidneys were used (Curtis 1992). Furthermore, Dr Koprowski has not always been precise about his use of tissue culture. On more than one occasion in 1956 and 1957 he reported in the medical literature that he was using one type of tissue culture (chicken embryo) to grow his first type 1 polio vaccine (SM) when he was in fact using another (primate kidney) (Hooper 1999, pp. 384–387). Stanley Plotkin (also from the Wistar Institute) has said chimp kidneys would have been a ‘totally absurd’ substrate to use (S. A. Plotkin, personal communication 1994). Paul Osterrieth, of the Stanleyville medical laboratory, has denied that chimp kidneys were ever sent abroad, except for six pairs that were sent to the Children’s Hospital of Philadelphia (CHOP) not for polio work, but for hepatitis. In a second interview he contradicted this, claiming that chimp kidneys had never been sent from Lindi to the USA for any reason (Hooper 1999, pp. 351–352, 566). Gaston Ninane (also of the Stanleyville laboratory) originally said chimp kidneys were used to make the vaccine. A few minutes later (after consulting letters in *The Lancet* about the OPV theory of origin), he said he had meant to say *monkey* kidneys. Dr Ninane denied any knowledge of chimp kidneys being sent to the USA or Belgium, though he did add that it was possible, since—as he stressed—he (Ninane) had been ‘just the sergeant’ to Courtois’s general (Hooper 1999, pp. 271–280, 568–570).²

However, and this is crucial, none of the aforementioned doctors has ever revealed what eventually happened to the chimps, how they met their deaths.

We know from the few documentary records that still exist that Camp Lindi opened in June 1956. And we know from Fritz Deinhardt’s hepatitis data book (Deinhardt 1959) that by February 1958, 20 months later, the total number of chimps that had been present at Lindi had reached 416. This data book shows that 54 of them were still alive in February 1958, at the end of the polio research. Unless some of these chimps were sent to *other* research centres, in Africa or overseas (and there is, to date, no evidence to suggest that this happened), this means that 362 of them died. According to contemporary accounts, up to a quarter of the chimps died naturally during that time. This leaves us with approximately 270 chimps that must have died from causes other than natural causes.

The fate of these latter chimps, as I eventually learned from several different sources, including the widows of two of the other leading protagonists (the Wistar Institute laboratory chief and a ‘principal sanitary agent’ who participated in many of the vaccinations), was that they were sacrificed as part of the experimentation (P. Norton, personal communication 1995; J. Brakel, personal communication 1997). This is the crucial detail that is not mentioned by the four witnesses quoted above. And there is a dichotomy here, for in 1959 Dr Koprowski stated that he had used just 39 of the chimps for intraspinal safety tests—the only part of the research that would have required sacrifice (Koprowski 1959).

So let us turn to what others have to say about those chimpanzees. In July 1999, Bill Hamilton and I visited Kisangani, he to gather chimpanzee stools for SIV

testing, and I to try to find out more about what had happened in the old Stanleyville medical laboratory, and at Lindi. We met ‘Antoine’, one of the former caretakers of Camp Lindi, who had very precise memories of what had occurred there. I asked Antoine about the research conducted on the chimps. He recalled the safety tests. He recalled the vaccination and challenge experiments. He recalled the autopsies, in which small pieces of tissue from different organs were extracted after an animal died. And lastly, crucially, he recalled that routinely, from 1956 to 1959, chimpanzees (sometimes in groups of five or six) would first be bled and then a day or two later anaesthetized, after which they would be opened up down the centre, so that entire organs could be removed and put in large screw-top jars. Among the organs Antoine specified were the heart, liver and kidneys. The animals would still be alive when these operations took place, he said, but would be sacrificed immediately afterwards. The description he gave was exactly that of how kidneys were often extracted from primates for tissue culture work back in the 1950s. In those days, to minimize possible contamination, the kidneys were frequently extracted after the anaesthetic had taken hold, but before death (M. Briggs, personal communication 2000; D. Denham, personal communication 2000).

In July 2000, I called once more on Louis Bugyaki, the vet who had worked in Stanleyville from 1956 to 1959, and who had helped look after the Lindi chimps when they became sick. He gave an even more precise interview than those he had given in 1994 and 1996—and, at the end, he agreed to sign a statement encapsulating some of the major points in that interview.

Here is part of the final paragraph of that statement.

I was told by two of the Belgian doctors working at Lindi (Gaston Ninane and Paul Osterrieth) that chimp organs—mostly kidneys—were being sent from Stanleyville to the United States, at the request of Dr Koprowski. It is possible that the main purpose of sending the kidneys was to provide cells in which the Koprowski polio vaccines could be grown. I was told by the aforesaid doctors that the sending of chimp kidneys abroad was to be kept a secret.³

With this statement, Dr Bugyaki called into question the evidence of each of the three doctors, Ninane, Osterrieth and Koprowski, who are known to have been directly involved with the CHAT research at Lindi, and who insist that chimp kidneys were not sent abroad (except to the CHOP), and not used to make vaccine. It is interesting that the statements made by the fourth scientist mentioned previously, Stanley Plotkin, appear to be based on deduction, rather than personal memory. (When he first arrived at the Wistar Institute, Plotkin was apparently working on anthrax, and one wonders to what extent he was involved with the early CHAT research.)

Antoine’s eyewitness account, supported by Dr Bugyaki’s written statement, constituted the first really substantial evidence that a sizeable number of chimp organs, including kidneys, were being sent from the Congo to the United States during the late 1950s. But there is even more powerful evidence from a different part of Africa suggesting that chimp kidneys may have been used for vaccine manufacture.

We recently interviewed a man called Juma, who during the 1950s had been working as a microscopist at the medical laboratory in Bujumbura, Burundi, the same place where the CHAT vaccine used in the 1958 Ruzizi Valley trial was once stored in the deep-freeze. Juma told me that between 1955 and 1957, when a Dr Dierckx had been in charge of the laboratory, three large cages had been located on the waste ground just behind. One of these had contained between 10 and 15 chimpanzees. The second had contained about 30 other monkeys—he did not know of which species—while the third had contained snakes. He told us that the primates had been supplied by a parastatal organization called IRSAC (l'Institut pour la Recherche Scientifique en Afrique Centrale), from a camp at Kabunambo, just over the border in the Congo.

He added that operations had been carried out on a regular basis to remove a single kidney from each of the chimps. Afterwards, they would be sewn up again, and every four or five months they would be sent back to the Congo, to be replaced by 15 new ones. This meant that an average of three chimps per month had a single kidney removed. Juma further told us that a woman—he thought from the Stanleyville (Kisangani) laboratory—had come to instruct the doctors how to carry out the surgical procedures, and that the process stopped soon after Dr Dierckx left the laboratory, which documents show to have been in June 1957. He also remembered that a man called Cordier had been catching the chimps.

Now, IRSAC was set up in 1948 under the auspices of the Belgian American Educational Foundation, and Charles Cordier was indeed the man who caught chimps and other primates (both for IRSAC and for other organizations) from the mid-1950s onwards. And although Kabunambo was not an official IRSAC station, it was the headquarters of the Mission Medicale de Ruzizi, with which IRSAC scientists collaborated closely. Besides this, Kabunambo was the place used by the CHAT vaccinators as their field headquarters during the Ruzizi Valley trial (Courtois *et al.* 1958).

We asked Juma what had happened to the chimp kidneys, and he told us that they had been sent to a medical laboratory at what is now Butare in Rwanda, as well as to a laboratory in Belgium. He added that kidneys from the other Bujumbura monkeys had also been sent to these two places, but did not specify whether the monkeys, also, had only had single kidneys extracted. He did not know what the chimp and monkey kidneys had been used for.

So, intrigued, we began to investigate the history of the Butare laboratories. IRSAC had a major field centre in Butare. Throughout the 1950s there had also been a medical laboratory, and in 1955 a large and impressive veterinary laboratory was constructed. Its staff apparently worked in close collaboration with their medical colleagues (J. Mortelmans, personal communication 2000). Between them, the medical and veterinary laboratories had produced many of the human and animal vaccines that were used in the Belgian colonies. The only other government-run vaccine laboratories in those colonies were in the southern Congo at Elisabethville, now Lubumbashi. The human vaccines recorded as having come from Butare included those against

smallpox, tuberculosis and meningitis, but there was no official mention of polio vaccines.

However, the man in charge of the Butare veterinary laboratory from 1954 until 1957 was Tadeusz Wiktor, whom Dr Koprowski credits with playing a key role in helping to set up his chimpanzee research in Central Africa. The two men first met in July 1955, at a two-week rabies workshop in Kenya, and Wiktor then introduced Koprowski to Ghislain Courtois, who set up Camp Lindi. Another Belgian colonial vet, Joseph Mortelmans, had previously told me that Wiktor had helped organize 'a lot of experimental trials for the first vaccine [of] Koprowski' in chimpanzees. This was an intriguing comment, for there was no record of any chimpanzees being held in Butare. However, Juma's account indicated that there might have been chimpanzee kidneys.

Within this context, and in the light of the parallel evidence from Camp Lindi, it seems to me that the likeliest reason for going to such lengths to obtain the kidneys of chimps and other primates was to produce tissue culture for making experimental batches of CHAT polio vaccine.

And so it is that an entirely new factor enters the equation. Before Juma, it had seemed that all the CHAT vaccine fed in Africa had been made either in the United States, or in Belgium. But now, for the first time, there was evidence to suggest that small batches of CHAT vaccine may have been made *in Africa itself*.

I had previously been told by one of the sanitary agents who had worked in Rwanda and Burundi in the 1950s that he had vaccinated with CHAT around Butare, and in the next *territoire*, Nyanza, in 1959. But, significantly, he also mentioned some even earlier trials in Butare, he thought in 1957, and added: 'I think the whole thing started [t]here'. Accordingly, we investigated eight villages around Butare—in one of which two old men independently told us that they recalled oral vaccinations against *mbasa*, or polio, and that these had happened before independence.

A quarter of a century after the Butare vaccinations, in 1984, the prostitutes of Butare were tested for HIV-1. Twenty-nine out of 33 (88%) were found to be HIV-1-positive, an extraordinary percentage for so early in the AIDS epidemic (Van de Perre 1985). Two years later, 16% of the general population of Butare was HIV-positive (Busingo *et al.* 1988).

And what happened after 1957, when Tad Wiktor left Butare? An article from a Léopoldville newspaper, dated August 1958, suggests that further vaccine may have been produced locally, for it states that: 'The [CHAT] vaccine has been prepared at Elisabethville by the Wistar Institute' (Anonymous 1958). It turns out that the senior vets working in Elisabethville from late 1957 until 1960 were Tad Wiktor, newly arrived from Butare, as well as Alexandre Jezierski, the Polish vet who, at his small laboratory at Gabu in the north-eastern Congo, had been growing polioviruses and experimental polio vaccines in the kidneys of 15 different African primates (including the chimpanzee) for the preceding five years. During these years, Jezierski collaborated closely with Pierre Lépine of the Pasteur Institute (Barski *et al.* 1954), and he also spent three days with Hilary Koprowski in February 1957 (H. Koprowski, personal communication 1993).

There may have been another reason why only single kidneys from IRSAC chimps were used—a financial one. For even in the 1950s, before the CITES treaty, the great apes were among the species in Belgium's African colonies that were protected by an edict from the Belgian king: a special permit had to be obtained before any were killed. For Schedule 1 and 2 animals (like pygmy chimps and common chimps), scientific hunting licences had to be obtained, and a 'capitation fee' (of US\$120 for a pygmy chimp, and US\$60 for a common chimp) paid. For 'well-known foreign institutions', the Governor General could waive the latter fees, provided that such institutions had 'entered into an agreement with a Belgian scientific institution to be represented by the Museum of Tervuren, in terms of which the animals or the remains of such animals will be shared' (Anonymous 1956). This is intriguing, because there are records of 79 skulls from common chimps and pygmy chimps that were sent by Dr Ghislain Courtois of the Stanleyville Medical Laboratory to the Museum of Tervuren, apparently in 1956–1957. It seems that by entering into this agreement with Tervuren, and sharing the 'remains' of the chimps with the museum, the Stanleyville doctors saved nearly US\$8000 (in those days, a tidy sum) in capitation fees. Such fees would not, of course, have been payable by the Bujumbura doctors, who avoided sacrificing their chimpanzees.

Now, more briefly, let me address the other points on the list of objections to the OPV theory.

(ii) The testing of CHAT samples from the 1950s. The decision by the Wistar Institute to release CHAT vaccine samples for testing, albeit belatedly, should be applauded. However, it should also be placed in context. There is no evidence that any of the CHAT samples produced at the Wistar Institute and Wyeth Laboratories, which have recently been released for HIV/SIV testing and mitochondrial DNA analysis, have any relevance to the vaccinations conducted in Africa.⁴ Five of the samples were from pools never fed in Africa. The other two samples were from pool (or lot⁵) 13, which was indeed used both in Léopoldville, the capital of the Congo, and in Poland. However, a 1961 paper by Plotkin and colleagues described seven pools of CHAT, two of which were made at the Wistar Institute, and three at other laboratories (Plotkin *et al.* 1961); one can only conclude that the remaining two CHAT pools (almost certainly 13 and 10A-11) were each made in *more than one* laboratory. This suggestion was confirmed by Dr Henry Gelfand, the American virologist who, in August 1958, hand-carried bottles of concentrated CHAT pool 13 vaccine from Brussels to Léopoldville, and who told me he was '99.9% certain' that the vaccine fed in the Congolese capital had been made at a laboratory just outside Brussels, not at the Wistar Institute (H. M. Gelfand, personal communication 1996). By contrast, we know that the CHAT pool 13, which was supplied to a Polish group that vaccinated 2888 children at Wyszki, Poland, *was* made at the Wistar Institute, in that it was reported as having been 'prepared by Dr Koprowski' (Przesmycki *et al.* 1959). It seems this Wistar-made pool 13 was also used for small-scale tests on children at Clinton Farms prison in New Jersey (Plotkin, this issue).

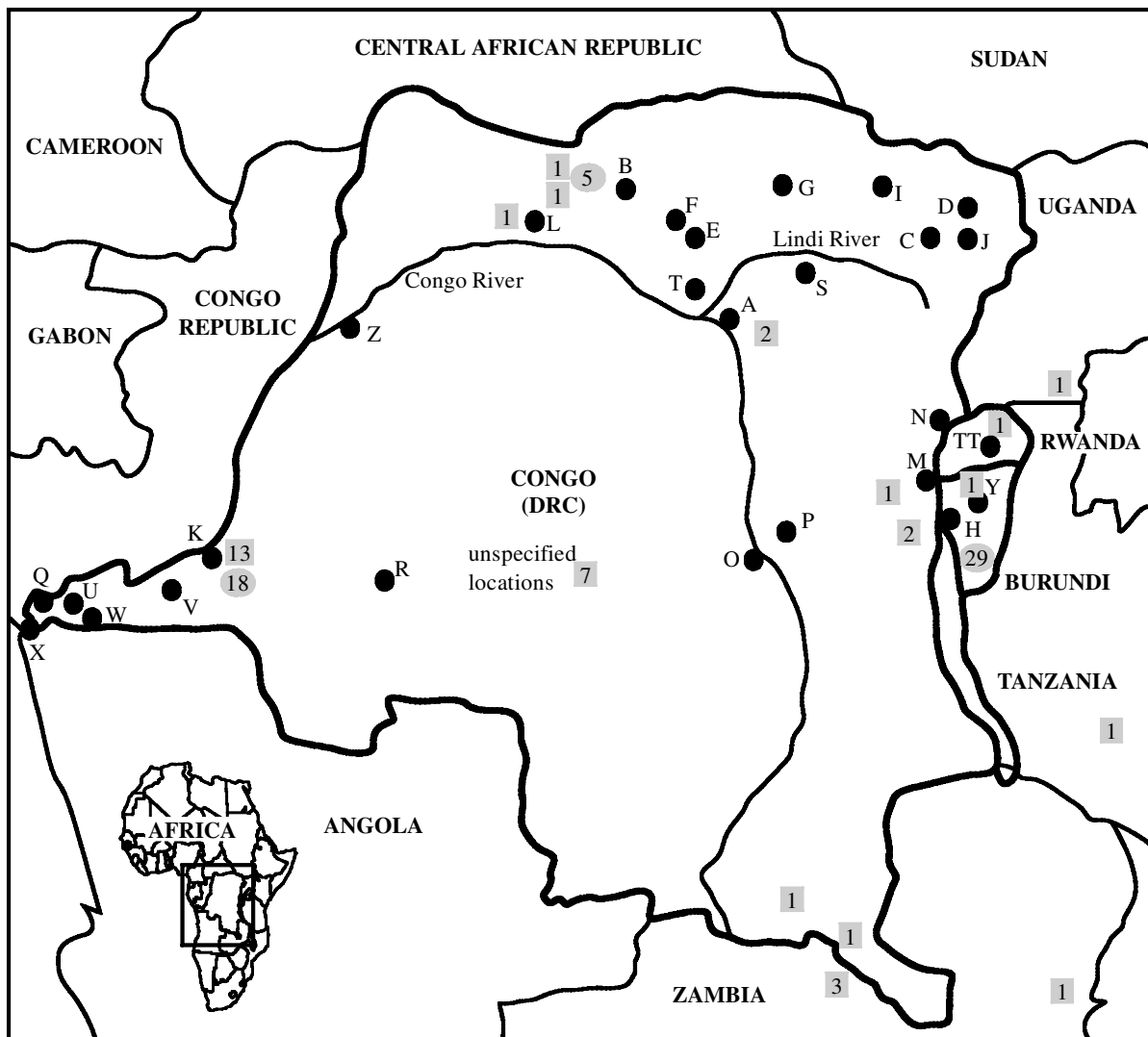
Dr Plotkin's own account of the shortfall of (CHAT pool 10A-11) vaccine for the Ruzizi Valley trial, and the

haphazard way in which additional capsules and small amounts of liquid vaccine were to be dispatched by Dr Koprowski (and perhaps others) to Burundi (Plotkin, this issue), is a further indication of how *ad hoc* the arrangements were for the early African field-tests. Furthermore, Dr Ninane was convinced that at least some of the vaccine used in Ruzizi had been prepared in Belgium (Hooper 1999, pp. 273, 358). Even the details of the region vaccinated are inaccurate in Dr Koprowski's official account of the trials. Dr Ninane and others have revealed that the 'Ruzizi Valley trial' actually included the eastern shore of Lake Tanganyika; in other words it covered almost twice the area detailed by Koprowski in his published report of the vaccination campaign (Courtois *et al.* 1958; Hooper 1999, p. 729). In short it is now apparent that the vaccine used in Ruzizi and along Lake Tanganyika did not comprise one homogeneous preparation of CHAT pool 10A-11, but rather several different CHAT preparations, made at different times and originating from different laboratories.

Even more importantly, different batches of the same CHAT pool were routinely prepared in different substrates (Hooper 1999, pp. 599–600, 732–733). Thus the Wistar-made pool 13 (used in the USA and Europe) may have been prepared in different primate cells from the pool 13 made in Belgium for use in Léopoldville (or, indeed, from a hypothetical pool 13 made in Africa). Since the pools or lots of CHAT vaccine are not homogeneous, the pool numbers become an irrelevance. What matters is to test the specific *batches* of CHAT that were prepared for use in Africa, none of which have so far been analysed. However, it may not be possible to do this, for Dr Koprowski is quoted in his recently published biography as saying, with respect to the material used for the African trials: 'The same lot of vaccine doesn't exist any more' (Vaughan 2000).

In the light of this, the fact that none of the ancient CHAT samples released for testing showed any traces of HIV, SIV, or chimpanzee DNA becomes less impressive as a scientific study than as a public relations exercise.

(iii) That the epidemiological links between CHAT vaccination and early AIDS are questionable. This claim, more than any of the others, is remarkable. There were 27 confirmed CHAT trials in Africa between 1957 and 1960, all of which occurred in the former Belgian colonies (the DRC, Rwanda and Burundi). On the accompanying map of vaccination sites there have been superimposed the first 39 cases of HIV-1 group-M-related AIDS in Africa (through 1980), 30 of which are identifiable by a specific town or village (figure 1).⁶ Note that all come from the former Belgian colonies, or places close to the borders of those colonies. The correlations are quite startling—70% of these earliest AIDS cases come from a town or village where CHAT had been vaccinated. If we analyse pre-1981 instances of confirmed HIV-1 infection in Africa, the correlation is even higher—over 84%. In fact, all 46 documented instances of HIV-1 infection from Africa through 1980 come from within 140 miles of CHAT vaccination sites. Because this represents the key scientific data supporting the OPV theory, it is also the area that has come under the most concerted fire from supporters of natural transfer. At this conference, Professor De Cock has separated the DRC data from the Rwanda/Burundi data,



Vaccination sites (in chronological order):

A	18 000	B	2 000	C	3 000	D	14 500	E	4 000	F	500	G	2 500	H	215 500	I	4 000	J	5 000
K	76 000	L	?	M	10 000	N	2 000	O	6 000	P	6 000	Q	10 000	R	?	S	2 500	T	?
TT	137 500	U	?	V	?	W	?	X	?	Y	321 000	Z	?						

Total vaccinees: 840 000 plus unknown number vaccinated in eight further trials

● vaccination sites
(1957–1960)

■ HIV-1-related AIDS
cases (through 1980)

● HIV-1-positive
blood samples
(through 1981)

Figure 1. Geographical correlations between CHAT vaccination sites in Africa (1957–1960) and the first appearances of HIV-1 and AIDS in Africa (through 1981 and 1980, respectively). Source: Hooper (1999).

thereby weakening the OPV/AIDS correlations (De Cock, this issue); it is his belief that because AIDS appeared first in towns like Kinshasa and Kisangani, the virus and disease were merely following a predictable route of spread up the Congo River. Even if this may be a tenable alternative explanation for the earliest AIDS cases, it fails to explain the remarkable distribution of the earliest confirmed instances of HIV-1 group M infection through 1981, over 42% of which relate to Rwanda and Burundi, countries that had no political association with the Congo after 1960. De Cock's analysis also fails to explain why a virus which, according to doctors Hahn and Sharp, first crossed from chimp to human in the range of the *Pan*

troglodytes troglodytes subspecies (Cameroon, Equatorial Guinea, Gabon and Congo Brazzaville), then began to infect persons only in the DRC, Rwanda and Burundi. Kinshasa is at least 150 miles from that range, whereas the other venues of early AIDS and HIV-1 group M in the DRC, Rwanda and Burundi are between 600 and 1000 miles distant as the crow flies. Why did the 'first HIV-1 group M infectee' not stay in Cameroon and Gabon, infecting people there, or travel west to Nigeria, north to Chad, or east to the Central African Republic? There is no evidence of group M virus in any of these countries before 1981. The presentation by Daniel Low-Ber includes further analysis of these issues (Low-Ber, this issue).

(iv) 'Wrong subspecies' is the claim made by the team of Beatrice Hahn. Since February 1999, when (at a press conference organized by *Nature*) Professor Hahn publicly concurred with what other virologists and geneticists had been saying for ten years—that HIV-1 came from the SIV of the common chimpanzee—she has maintained that there was host-dependent evolution of SIVs in chimpanzees, and that the chimps that carried the precursor virus to HIV-1 group M were exclusively *Pan troglodytes troglodytes*, from west Central Africa, and not *Pan troglodytes schweinfurthii* from the DRC and east Central Africa. However, as Pascal Gagneux demonstrated at this conference, mitochondrial DNA analysis does not allow scientists to make a clear distinction between the two alleged subspecies, *troglodytes* and *schweinfurthii* (Gagneux, this issue), which—on current evidence—might perhaps be better characterized as belonging to a single subspecies, namely *Pan troglodytes troglodytes*, the Central chimpanzee. There is an SIV sequence for one chimp, Noah, which is known to have come from somewhere in the DRC (almost certainly from the great rainforest on the north bank of the Congo River), and Professor Hahn has now announced evidence of a second SIV-positive chimp from the east of the range (perhaps from Tanzania or Uganda), although she only has a Western blot, not a sequence, for that one. Despite this fresh evidence that SIV is present in chimps from Central and eastern Africa, and despite the very limited number of samples, Hahn still proposes that chimp SIVs from the area she refers to as 'western equatorial Africa' are the only true ancestors of HIV-1 group M. I believe that it would be more appropriate to state that there is a wide variety of chimpanzee SIVs to be found in the range of the putative 'Central chimpanzee', which stretches from the western side of Cameroon right across the Congo and through to Tanzania—an area that embraces the zones marked 'PTT' and 'PTS' on the accompanying figure (figure 2)—and which includes all the sites where the pygmy hunters once captured chimps for Camp Lindi and where Charles Cordier captured chimps for IRSAC. It is encouraging that, despite the civil war in the DRC, field researchers are continuing the work of Bill Hamilton by sampling chimp stools and urine from the north and east of the country, and that Dr Hahn will be among those analysing the data. But at this stage we simply do not know where the closest ancestors to HIV-1 group M will be found, and it is unsafe to assume, on the basis of seven samples of chimpanzee SIV, that the source of the group M zoonosis lies in those parts of Gabon and Cameroon where most of the current sampling has been conducted.

(v) 'Wrong time', say Dr Bette Korber (Yusim *et al.*, this issue) and, more recently, Dr Ann-Mieke Vandamme. What Korber's super-computer proposes is that the most recent common ancestor (MRCA) of today's HIV-1 group M strains, the 'Eve virus' as she calls it, existed in 1931, with an outer range of 1915–1941. However, even if we accept this analysis, we still don't know if the MRCA was a human or a chimpanzee virus. Dr Korber's Eve virus is an abstraction created by theoretical analysis, which is itself based on a number of assumptions. As such, it does not carry the same weight as the earliest physical evidence of HIV-1 group M, which is the ZR59 Léopold-

ville/Kinshasa sample, which apparently dates from 1959. Dr Korber has produced some excellent phylogenetic analysis, but is unable to distinguish between the three scenarios proposed in the commentary by David Hillis that appeared in *Science*—that the first chimp-to-human transfer occurred *before* 1930, that it happened *in* 1930, or that *multiple* transfers occurred later (for instance, in the 1950s, as the OPV theory proposes), giving birth to the various HIV-1 group M subtypes (figure 3). Dr Korber has stated that her work renders the OPV hypothesis impossible or (in more recent statements) 'highly unlikely', but I would dispute this. A different perspective on dating the pandemic, one which concludes that there is evidence of 'synchrony', and that an unnatural 'punctuated event' may have sparked multiple and near-simultaneous introductions of chimp SIV to *Homo sapiens*, is to be found in the presentation by Tom Burr, Mac Hyman and the former head of the HIV/AIDS Sequence Database, Gerry Myers (Burr *et al.*, this issue). In addition, an even more drastic reappraisal of the dating may be required following recent publications about the impact of recombination on phylogenetic analysis. Dr Sharp confidently states 'It is clear that recombination would make the date of the common ancestor seem more recent', meaning that if recombination had occurred, it would push the Eve date even further back in time. But not all phylogeneticists agree. Some believe it could move the MRCA either forwards or backwards (Worobey 2001). Others warn that 'Dating the origin of the HIV-1 pandemic from an early (1959) sequence may yield misleading results' (Schierup & Hein 2000*a,b*). Some go further, and say that if recombination occurred early in the history of group M (as might be the case if different chimp SIVs combined in an OPV tissue culture), then this would in all likelihood be undetectable genetically, and would moreover invalidate any attempts at dating. Phylogenetic analysis is a useful tool, but it cannot prove, or disprove, a date of introduction. To claim otherwise is, quite simply, to over-extrapolate from the data.

(vi) That chimpanzees would have been an 'absurd' animal to utilize for a vaccine substrate: that they were too expensive, too rare, and improperly characterized. Superficially, this sounds like a good argument. Until one remembers that 400 chimps were collected in the space of 20 months for Camp Lindi, and that (according to one of the Stanleyville vets, Joseph Mortelmans) they could be procured in the 1950s in the Congo for about US\$5 each, and there was felt to be an unlimited supply. Or until one recalls that after they had been used for polio safety and efficacy trials, these animals were effectively useless for other polio research—unless they were sacrificed, and the blood and kidneys harvested (which, according to the Lindi caretaker and Dr Bugyaki, is exactly what happened). An important paper published in 1956 had found that after administering poliovirus to chimps by mouth, no detectable poliovirus persisted in the blood or kidneys, so it was apparently quite legitimate to make tissue culture from such materials (Bodian 1956). Both Doctors Plotkin and Koprowski insisted at this conference that they would never have used chimp kidneys to prepare polio vaccines, yet memories of such events inevitably fade at this remove, and it is notable that they can produce no first-hand documentation to support such

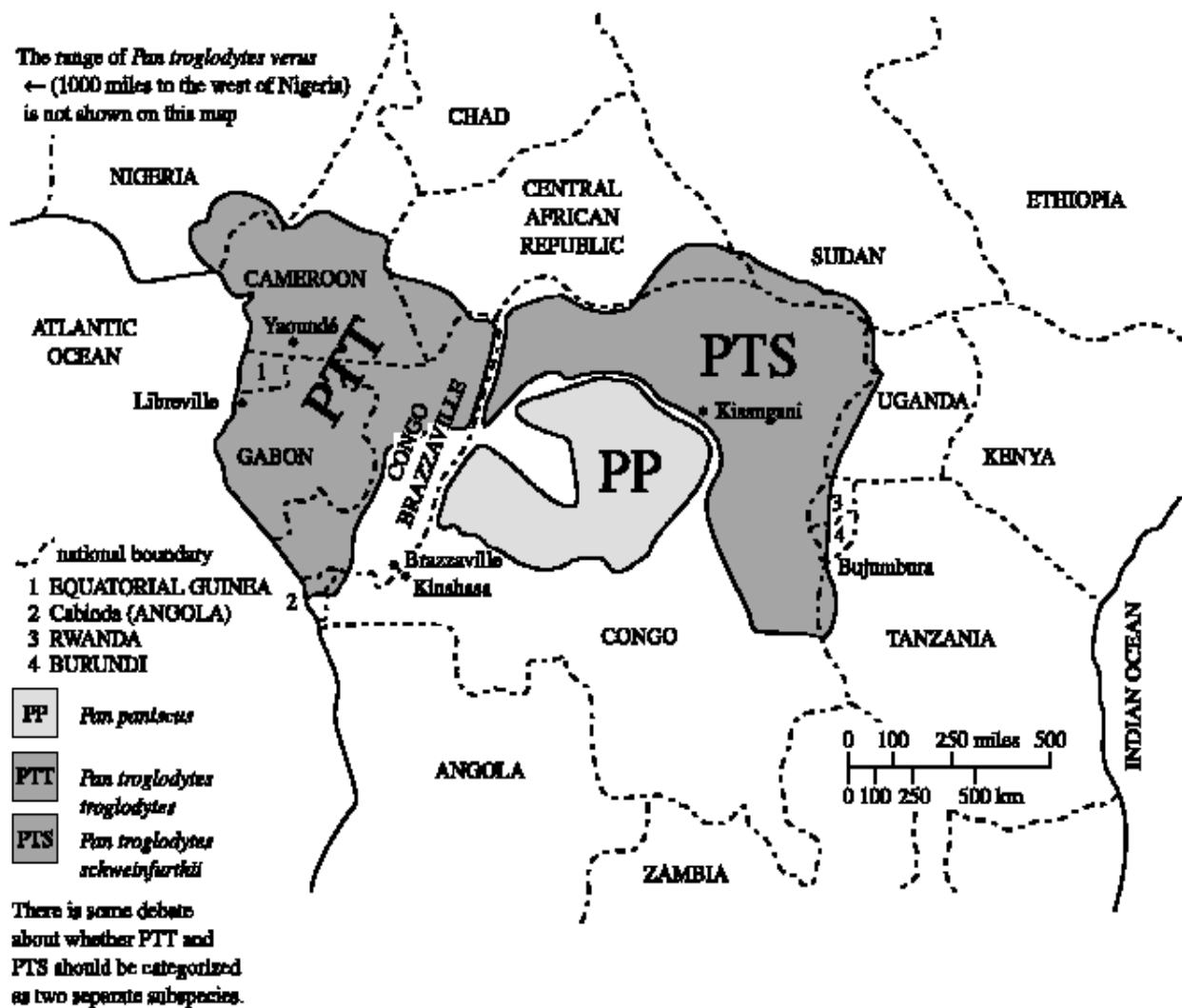


Figure 2. Distribution map of chimpanzees in Central Africa, *ca.* 1975. Source: Wolfheim (1983).

claims. Similarly, no records are available about the species of tissue culture used to make the further vaccine batches which, as Plotkin and Koprowski concede, other laboratories produced from the stocks provided by the Wistar Institute. (It should be borne in mind that kidneys were arriving in the laboratories concerned already excised—and nobody in the 1950s would have been able to distinguish between the kidneys of macaques and those of young chimpanzees by sight alone.) All of which brings us back to the key question: ‘*why not use chimp kidneys?*’. They were freely available; indeed, as observed above, they were otherwise going to waste—and they had already been tested for most of the serious pathogens, such as TB and simian B virus. Furthermore, papers published by Alexandre Jezierski, the vet with whom Koprowski spent three days in the Congo in February 1957, indicated that kidney tissue from chimps (and 14 other African primates) produced ‘very good’ cultures, in which poliovirus grew as vigorously as it did in cultures from rhesus and cynomolgus macaques (Barski 1954; Jezierski 1955). And such an approach hardly involved breaking new ground, for two other polio vaccines had already incorporated a passage through the gut of a chimpanzee. To conclude: the chimpanzee is the primate

closest to man, and several elements indicate that in 1957–58, scientists might have considered chimp cells a most appropriate substrate for a human vaccine (Hooper 1999, pp. 718–720).

(vii) It has been claimed that even if chimp kidneys were used as a vaccine substrate, not enough of the Lindi chimps (most of which were juveniles) would have been SIV infected to spark all the different group M subtypes. By contrast, some observers believe that introductions of different variants of SIV/HIV in different African vaccination sites in the late 1950s would have been a very effective way of introducing the different subtypes. At a conservative estimate, a minimum of 2% of juvenile chimps from the mooted new *troglodytes* range embracing west Central and east Central Africa are SIV-infected, and this percentage may be much higher in specific locales. Furthermore, the chimps at Lindi were regularly held two to a cage, and even two species to a cage, for pygmy chimps and common chimps were caged together as a matter of course. There was also one large cage at Lindi in which up to ten young chimps were placed at a time (Courtois 1967), just as there was, apparently, at Bujumbura. The possibilities for onward (and possibly cross-species) spread of viruses like SIV are obvious. Most

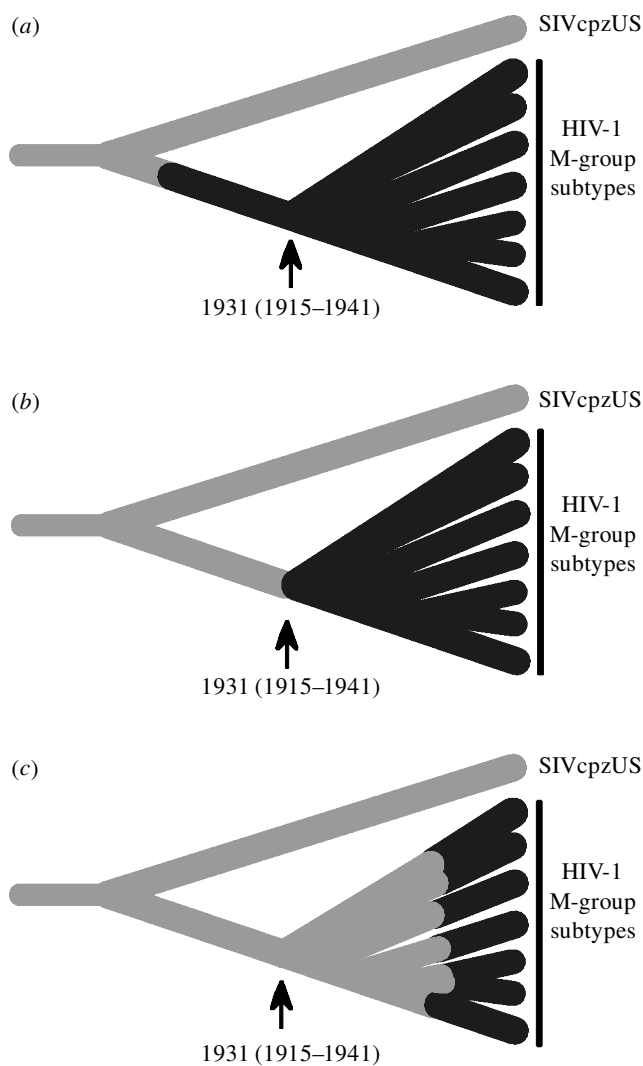


Figure 3. Three dating scenarios for HIV-1 group M, following Korber *et al.* (2000). Source: Hillis (2000). (a) Early transmission; (b) transmission causes an epidemic; (c) parallel late transmission.

importantly, some geneticists have recently questioned whether it would take 10 or 50 transfers of chimp SIV to humans to spark the different group M subtypes seen today, as Sharp and colleagues maintain. These geneticists propose that if two chimpanzee SIVs with sequences that differed from each other by at least 5% (as might be encountered in chimps infected either before capture or after arrival at Lindi through communal caging) were transferred into the same individual or tissue culture, 'a whole new diverse population' of SIV/HIV could be created through recombination. Such a population would embrace the 'high diversity and complexity of HIV-1 strains' recently reported from the DRC (Vidal *et al.* 2000), which includes all the recognized group M subtypes, as well as unique variants. This would be all the more likely if the two original strains were highly divergent, or if three strains rather than two were involved in the initial co-infection.

(viii) In any case, say natural transfer supporters, SIV cannot survive the vaccine-making process. This is a controversial issue and not one that can be resolved by multiplying odds until they reach the billions, as one

contributor has sought to do. Although one carefully controlled experiment along these lines has been conducted (Garrett 1993), the investigator conceded that his tissue cultures could have been prepared employing laboratory standards relevant to the 1990s, rather than the 1950s (Hooper 1999, pp. 659–662). Other data presented at this conference suggest that SIV from an SIV-infected macaque can survive, at least through to a tissue culture derived from that animal's kidneys (Lena & Luciw, this issue). The OPV hypothesis presumes that there was a very low level of SIV contamination in some of the polio vaccine batches administered in Africa, enough to infect just a tiny fraction of the one million or so Africans fed with those batches. Further tests need to be carried out, including tests on whether low levels of SIV in primary kidney culture still survive after inoculation of an attenuated poliovirus. (There is also, of course, the possibility that at some stage during CHAT vaccine production in the 1950s, there was a rogue event—a breakdown or failure in the system—which went unrecognized at the time, or an atypical occurrence that went unrecorded.)

(ix) That HIVs and SIVs cannot be transmitted orally. This is readily disprovable. In humans, we have cases of infants who are HIV-negative at birth, but who seroconvert after getting breast-milk from an HIV-positive mother or wet nurse. And of gay men who get HIV after having only oral sex. And in monkeys, Ruth Ruprecht has shown this even more dramatically, with five out of ten infant macaques getting simian AIDS after being fed with a candidate live attenuated AIDS vaccine, and four of the other five becoming immunosuppressed (Hooper 1999, pp. 649–657).

(x) That *The river*, to quote Stanley Plotkin's address to this conference, entitled 'Untruths and consequences', 'does not withstand critical analysis'. The speeches and press releases given by Doctors Koprowski and Plotkin at this conference contain very little in the way of hard data, but have rather been based on signed testimonies, argument and indignation. They attempt to counter the OPV argument largely by challenging *The river* on specific points of detail, yet have managed to identify only two or three minor errors, or potential errors, in a book of some 1100 pages. I believe that, by contrast, the majority of the claims made in their two press releases are provably incorrect, and that their two papers also contain a large number of inaccuracies and misrepresentations. Regrettably, misplaced claims such as these have encouraged the perception among many scientists and reporters that the OPV theory has been discredited. To illustrate the errors in these papers would require far more room than is available here, so I shall restrict myself to responding to Dr Plotkin's claims that I have misquoted or misrepresented witnesses. I have carefully checked these claims against my original recordings of the interviews in question, and in every instance I stand by what I have written in *The river*. The persons quoted have been quoted accurately and in context. A more detailed response to Plotkin's and Koprowski's presentations and press statements will be posted on a Web site dealing with the origin of AIDS.⁷ This response will also examine Koprowski's allegation that *The river* has damaged polio vaccination initiatives in Kenya.

5. SUMMARY

So, to close, let me reiterate the two major new points of information offering support to the OPV hypothesis that have come to light in the last few months.

1. There are eyewitness testimonies (recorded on either audio- or videotape) that organs, including kidneys, were extracted from a large number of chimpanzees from the Belgian colonies of Central Africa during the second half of the 1950s. Some chimps were sacrificed and had both kidneys removed; others had only a single kidney removed, and were sewn up again.

2. There is also further testimony that these chimp organs, including kidneys, were sent to laboratories in the United States, to at least one vaccine-making laboratory in Africa, and possibly also to laboratories in Belgium.

In the light of (i) the history of secrecy surrounding Camp Lindi; (ii) the fact that the 1950s papers from Dr Koprowski's group, uniquely, never described which primate species they employed as polio vaccine substrates; (iii) the missing vaccine records; (iv) the lost or destroyed vaccine samples; (v) the number of different laboratories where CHAT vaccine was produced; and (vi) the remarkable correlations between CHAT feeding in Africa and the first appearances not just in Africa, but in the world, of HIV-1 group M and group M-related AIDS, is anyone in a position to state with authority that no batches of CHAT vaccine were ever prepared in chimpanzee cells?

Finally, an important point. Despite claims to the contrary, this debate is not about blame or culpability; it is not about making scapegoats. Rather than apportioning blame (or, indeed, acting defensively in response to perceived blame), scientists, medical historians and journalists should surely be attempting to unearth the truth about how the pandemic got started, and then using that knowledge to help better focus efforts to combat AIDS. In that sense, the search for the origins of HIV and AIDS, though belated, is a justifiable and, indeed, necessary endeavour.

6. A FREE AND FAIR DEBATE?

As admirable as it is that this conference should have taken place at all, I do not believe that it provided the sort of free and fair debate into the origins of HIV and AIDS that Bill Hamilton envisaged when he first proposed the idea to The Royal Society at the end of 1999. There have been manoeuvrings behind the scenes, and the conference has provided evidence of a desire by many scientists to dismiss the OPV theory as 'discredited' or 'fatally weakened' on the basis of *a priori* assumptions.

One eminent virologist, a co-organizer of this conference, has even recently declared the matter closed, pronouncing in *Nature* that 'some beautiful facts have destroyed an ugly theory' (Weiss 2001). He is wrong. No relevant facts, beautiful or otherwise, have thus far been presented to destroy OPV/AIDS. Yet the hyperbole and the rush to premature judgement are a good indication of how hostile and defensive many scientists have become. Some, it seems, want at all costs to protect the good names of public health and vaccination; others seem more concerned about personal reputations.

Nonetheless, there have been certain new and significant data, statements and ideas presented at this conference that support both major theories of HIV origin, together with some for which the significance is not yet clear. For cut-hunter/natural transfer, there are additional theoretical phylogenetic studies proposing that HIV-1 may have existed before the polio vaccine trials in Africa. There is the renewed claim that chimp SIVs from eastern Africa may be less close to HIV-1 group M than those from west Central Africa, and doubts have been raised about whether an SIV contaminating a primate kidney could survive through to a vaccine made therefrom. On the other hand, for OPV, there are the eyewitness testimonies from Africa of chimp kidney and chimp organ extraction occurring at the very time and places that CHAT was being developed and tested on humans. (An attempt by one of the vaccine-makers to dismiss such testimonies on the grounds that they come from 'low technicians' was, to say the least, unconvincing.) There is the theory that the pattern of HIV-1 group M subtypes is suggestive of synchronized introductions, caused by an artificial event in the 1950s or 1960s. And almost unmentioned at the conference itself, there is fresh analysis of the impact of recombination on phylogenetic dating, suggesting that recombination early in the group M tree (as may have occurred in a chimpanzee cell culture) would be both hard to identify, and would invalidate attempts to date the branching nodes. Lastly, there are what may yet turn out to be the most important new data of all, data which indicate that diverse, as well as unique, group M variants are to be found in three different locations in the DRC, and that this country may well represent the epicentre of the pandemic (Yusim *et al.*, this issue; Vidal 2000). Despite the interpretation placed on this new information by Doctors Sharp and Hahn, it is my contention that it fits less well with their scenario of west Central African origin than with the Belgian colonial origin proposed by the OPV theory.

The question of how HIV-1 group M came into being is still far from settled, and it is hoped that the majority of scientists will recognize this, and will conclude that the potential benefits of discovering how this dreadful human virus emerged demand that open-minded investigation into its origins should continue.

I thank William D. Hamilton, Stephane Horel and Siddhartha Singh for their help with different aspects of the research detailed above, and Gerry Myers, Brian Martin, Pascal Gagneux, Simon Wain-Hobson, Walter Nelson-Rees and Julian Cribb for helpful discussions. Many other scientists, researchers and writers have also given generously of their time and intellectual energy, and I thank them too. They know who they are.

ENDNOTES

¹The 'reused needles' theory (Marx *et al.*, this issue) is actually a hypothesis that seeks to explain the origin of AIDS (not HIV) through the iatrogenic spread (and possibly increased virulence) of SIVs that have crossed to humans. Whichever theory of HIV origin proves to be correct, Marx's hypothesis about needle spread may or may not provide a useful adjunct. However, it should be noted that supporters of natural transfer increasingly rely on some version of the needles theory to explain how an

SIV may have adapted to humans and become virulent, whereas the OPV theory has no innate need of a supplementary hypothesis.

²A review of the transcripts of my tape-recorded interview with Dr Ninane in May 1994 confirms that he did indeed state that he had tried, and failed, to make tissue culture (including chimpanzee kidney tissue culture) in Stanleyville. This conflicts with the blanket denial on this point that Dr Ninane apparently gave to Dr Plotkin's team shortly before the former's death.

³As was revealed by Dr Plotkin in his speech (Plotkin, this issue), Dr Bugyaki had already, in February 2000, given a handwritten statement to Dr Plotkin's representatives in which he attested that he had no knowledge of chimpanzee kidneys ever being sent to Belgium, 'or to other countries' (p. 819). These last four words clearly conflicted with the detailed statements he had made to me (on audiotape) in 1994, 1996 and July 2000, the last of which he confirmed in writing. When asked to clarify this issue shortly after The Royal Society meeting, Dr Bugyaki said he did not exactly recall what he had written for the 'five or six doctors' who had visited him, and that he had no copy of this document. However, he once again affirmed that chimp kidneys had been sent to the USA during the 1956–1959 period.

⁴The items released comprised samples produced at the Wistar Institute (from CHAT pools 13, 16, 23, 24 and 25), a Wyeth-made sample from CHAT pool 4B, and a sample of pool 13 from Wyeth. A sample of pool 10A-11 has since been analysed in London, with similarly negative results.

⁵Both 'pool' and 'lot' are used interchangeably in 1950s' articles about Koprowski polio vaccines. Certain recent publications on this topic have confused the terms 'pool' and 'batch'. In terms of OPV, a batch is a small amount of vaccine made in a single production run from a specific pool of attenuated poliovirus or, in the case of CHAT, polio vaccine, as recently revealed by Dr Plotkin (Plotkin, this issue).

⁶One of the few points on which I agree with Dr Plotkin is that the proposed trial involving 64 000 persons 'in the regions of Kabare/Lubudi' has not been confirmed, and I have therefore deleted this trial from the map of CHAT/AIDS correlations that appears in this paper. However, the medical director of Katanga (the province in which Lubudi is situated) during the 1950s told me that this trial 'probably' did go ahead, under the aegis not of the government, but of one of the local companies (such as the cement company which had two of its three factories in the Kabare and Lubudi regions). Further investigations are underway.

⁷See www.uow.edu.au/arts/sts/bmartin/dissent/documents/AIDS.

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