The River Runs Through It

Contaminated polio vaccines started AIDS in Africa in the '50s. A National Enquirer *headline? No. It's the premise of a big new book fueling an old controversy among researchers.*

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Could a human error in 1950s medical research be the cause of the massive global catastrophe of AIDS?

A highly controversial book positing just such a theory has been kicking up dust in the AIDS research world since its release last September. *The River: A Journey to the Source of HIV and AIDS* (Little, Brown and Company/Boston), written by British medical researcher and former BBC correspondent Edward Hooper, proposes that HIV emerged from a contaminated batch of experimental oral polio vaccine (OPV) administered to Africans in the late 1950s. After largely favorable coverage in the British media, the book's recent U.S. reception has been mixed, with AIDS researchers lining up on both sides of the debate. (One surprise was an in-depth, sympathetic article by *The New York Times*' conservative medical reporter Lawrence Altman, MD.) The institute that first produced the vaccine responded by promising to test its old vaccine stocks. But Hooper says that since other labs manufactured almost two-thirds of the supply used in Africa, there must be a more thorough search for vaccine samples -- and for research records, especially because key documents have strangely disappeared.

The stakes for the AIDS community are high. If the theory pans out, it could offer key clues to HIV's genetic evolution that may prove valuable in designing a preventive vaccine. Plus, the lessons learned about possible pitfalls of vaccine manufacture could enrich medical science as a whole. Perhaps most important, a clear resolution could satisfy our profound need to know the origins of a devastation so vast as to seem beyond human meaning.

Most AIDS researchers agree that HIV evolved from a closely related simian immunodeficiency virus (SIV) that somehow jumped the species barrier from primate -- specifically, an African chimpanzee -- to human. Yet the question of how that happened has fueled a heated debate. The predominant view is that a "natural transfer" of some sort occurred, most likely by the transmission of SIV through the butchering or eating of "bush meat." But in *The River*'s 850 pages of text and 174 pages of footnotes, Hooper lays out the case that from 1957 to 1960 an unknown proportion of the OPVs administered to more than one million residents of three then-Belgian colonies -- now Congo (formerly Zaire), Rwanda and Burundi -- may have been accidentally contaminated with SIV from the primate kidneys in which the vaccines were prepared. "I am 97 percent persuaded that this hypothesis has merit," says Hooper, who conducted hundreds of

interviews and inspected thousands of documents over a nine-year period. (His earlier book, *Slim*, explored the East African AIDS crisis.)

Not surprisingly, the researcher whose mistake is alleged to be responsible for the 33 million HIV infections worldwide leads the chorus of those who dismiss the theory. “This is an untenable hypothesis,” argues Hilary Koprowski, MD, PhD, who developed the vaccine while directing the Wistar Institute, a medical research center in Philadelphia, “and there is absolutely no way to prove or even consider the possibility that it took place.”

Koprowski was a pioneer -- along with the more famous Jonas Salk and Albert Sabin -- of vaccines designed to quash the polio epidemics that panicked the world in the 1940s and ’50s. While Salk pursued an inactivated (killed) polio virus vaccine, Sabin and Koprowski each chose to pursue the live, attenuated (weakened) virus approach. Each raced to gain U.S. government acceptance of his design. In 1956, Koprowski came up with an OPV he named “CHAT.” Even the name reflects the current controversy: The vaccine developer says it was an abbreviation of the name of the patient from whom he extracted the polio virus used, but Hooper believes -- partly based on Sabin’s use of “ch” in the title of one of his vaccines to indicate that the virus had been passed through a chimp’s gut -- that it may also stand for “chimpanzee-attenuated” or “chimp adapted and tested.”

Koprowski initially tested the vaccine in children of inmates at a women’s prison in New Jersey. When those children showed no ill effects after two months, Koprowski sought larger testing grounds. He found them in the Belgian Congo, where in 1957 -- with the colonial authorities’ permission and both U.S. government and private funding -- he oversaw the administration of 2,500 doses of CHAT to local residents. Far quicker than was customary, he proceeded to give vaccines to 215,000 more people in East Africa’s Ruzizi Valley, and ultimately -- before ending the program in 1960 -- to more than a million citizens of Congo, Rwanda and Burundi. But Sabin won out: After vaccinating 55 million people in worldwide trials, his OPV was licensed in 1961 by the U.S. Public Health Service and made standard, thus replacing the already approved Salk inactivated vaccine.

Polio vaccines at the time (and, in many cases, today) were made in a tissue culture, or layer of cells, consisting of minced primate kidneys, in which the polio virus could be massively reproduced. The attenuation process weakened the virus so that it would not harm the vaccine recipient, but would still induce the formation of antibodies that would (it was hoped) prevent a future infection if the person was exposed. But by the late 1950s, researchers had found various primate viruses, thought to be harmless, that had made their way into various types of polio vaccines. SIV itself was not discovered until the 1980s, but another simian virus, SV-40 -- known to cause cancer in laboratory hamsters -- was found in 1960 to have contaminated millions of doses of Sabin’s and Salk’s vaccines. Many years later, researchers found SV-40 in human lung and brain tumors, and a study uncovered a staggering 13-fold greater rate of brain tumors in children of women who received the Salk vaccine.

Hooper’s thesis is that some batches of CHAT used in Africa were prepared from SIV-infected chimp kidneys, and that recipients of those vaccines -- many of them children -- swallowed a

cocktail of weakened polio virus and one or more strains of SIV. The virus then spread through sexual contact from the original recipients into the local populations, from which it fanned out across the continent and finally the globe.

Hooper freely acknowledges that this scenario remains unproven, and takes pains to include an appendix in *The River* listing 27 points of evidence for, and four against, the theory. Among the favorable points, Hooper lists these: that a remarkable 64 percent of the sites of the first (1962 to 1980) retrospectively diagnosed AIDS cases in Africa came from the same towns and villages where the CHAT vaccine had been administered; that the earliest known sample of HIV, found in frozen blood drawn from a Congolese man in 1959, coincides in place and time with a major CHAT campaign; that no sample of HIV-positive blood has been found anywhere dating from before 1959, two years after mass CHAT vaccinations began; and that Koprowski's Congolese scientific camp housed some 400 chimpanzees native to the region, which were used for unspecified polio vaccine experiments.

Countering this hypothesis, Hooper lists these facts: that no CHAT vaccine sample has yet been found to contain either SIV or HIV (he points out that the only such test run so far -- by the Swedish Institute for Infectious Disease Control in 1995, at his request -- came back negative, although he adds that the hypothesis does not contend that all vaccine batches were tainted); that theories involving reused hypodermic needles and tainted blood transfusions could theoretically also explain how a handful of hunters infected by chimps could have begun to spread the virus; and that "despite much circumstantial evidence," there is no "hard proof" that common chimps were ever used in CHAT's manufacture.

Koprowski, now 85, categorically denies that he used African chimp kidneys as a tissue culture. He insists that CHAT was made with kidneys of rhesus macaque primates from India and the Philippines. "There is no trace of anything like AIDS in kidneys from Asiatic monkeys," Koprowski says, adding that the chimps at his camps were only used to test the vaccines before human use.

But Hooper writes that in 1992, after an earlier version of the theory first hit the media, Koprowski was quoted as giving at least four different responses as to what type of simian species was used, before finally settling on the Asian variety with which he has stuck ever since.

Normally, such a simple scientific detail could be easily checked by reading the medical literature of that period. Researchers routinely list the species used for vaccine production. Yet Hooper's exhaustive search for all journal articles and conference presentations about CHAT by Koprowski found an unexplained absence of this information. Thus, the author had to rely on detective work, such as tracking down the fate of the camp's chimps (since the fate of most had never been documented), interviewing octogenarian CHAT researchers and their survivors, and searching their journals -- all of which added circumstantial evidence suggesting that some chimps' kidneys were used for vaccine production.

Also lending credence to suspicions of a cover-up is the mysterious disappearance of key relevant documents. Hooper writes that the Belgian state archives' "polio correspondence" for the crucial

period of 1956 to 1958 can no longer be found. And when interviewed by Hooper (and *POZ*), Koprowski said that all his files on CHAT had been “lost in a move” by Wistar.

Of course, critical evidence could come from the few CHAT samples still held in various labs’ freezers. Although Koprowski wrote in a 1992 letter to the journal *Science* that there was “no vaccine stored” at Wistar, the institute announced last November that it would allow two samples “that might be related to the Congo trials” to be tested by two labs of their choosing, asserting that the results should end the controversy. Wistar’s chief administrative officer, Clayton Buck, MD, acknowledges that the release of *The River* spurred the decision, but adds, “We agreed to that in 1992, so it’s not new.”

In March of that year, *Rolling Stone* had published a lengthy investigative feature by freelance writer Tom Curtis, which -- building on several medical journal articles -- first put forward the OPV/HIV theory in the popular media. The story quickly generated major media coverage. In response to the furor, Wistar convened a six-member panel (which included the soon-to-be AIDS star David Ho, MD) that acknowledged the theory’s plausibility, but deemed its likelihood “extremely low.” Koprowski sued *Rolling Stone* for libel. The case was finally settled out of court, with the magazine printing a short “clarification” in 1993 that simply restated the absence of definitive proof for the theory.

The Wistar committee report also called for tests of frozen CHAT samples to resolve the contamination dispute. Buck says Wistar sought help from the Centers for Disease Control and Prevention (CDC), which agreed to do the testing only if a second lab did so too, in order to buttress its credibility. Finding another lab proved unsuccessful, he says.

Hooper calls Wistar’s recent announcement “a most welcome development, even if testing really should have taken place back in 1992.” However, he argues for the critical importance of testing samples not only for SIV and HIV, but also for genetic evidence of the species from which the vaccine was derived. Hooper has proposed that to ensure fairness, a panel of independent scientists join Wistar in deciding which samples, labs and tests to use.

Hooper’s book actually proposes 17 specific investigations or experiments that could be conducted to test the hypothesis. For example, he says, Belgian laboratories -- which produced 70 percent of the CHAT doses administered in Africa -- could look for other samples of this vaccine, and a broad international search could be initiated for “any documents or protocols relating to the manufacture or testing of CHAT vaccine.” He also suggests that AIDS researchers search stored human blood and tissue samples from before 1956 to see if any contain HIV, a finding that “would clearly weaken -- though not destroy -- the OPV/AIDS hypothesis.” And he has separately invited lab technicians of the era to come forward with information.

But some AIDS researchers maintain that current evidence has already undermined this theory. “The hypothesis is a theoretically interesting possibility that needs to be checked out,” says Beatrice Hahn, a leading AIDS researcher and professor of medicine at the University of Alabama at Birmingham. “But I would also say, ’It did not happen this way.’” Last February, Hahn

coauthored a headline-grabbing article in the journal *Nature* that claimed HIV evolved from the SIV of a chimpanzee subspecies found only in West Central Africa -- 1,000 miles from the Congolese rainforest that was home to the different chimp subspecies used in Koprowski's camp. She also says that geneticists have dated the origin of HIV as prior to 1950. "I can only go by the weight of evidence," Hahn says, "and that on my plate would be a natural transfer of some sort."

Hooper replies that Hahn's research was based on comparing only a single SIV-positive chimp from Congo with three others from West Central Africa, and that further testing of Congolese chimps is needed. Research in this area is already underway, he adds. As for the genetic dating theory, he notes in the book that one of the experts who has proposed an earlier date for the introduction of SIV to humans, Paul Sharp, PhD, professor of genetics at England's University of Nottingham, has conceded that this date was calculated on the presumption of a single chimp-to-human crossover. A mass transfer by means such as a vaccine, he acknowledged, would allow for a later first appearance of the virus in humans.

Omar Bagasra, MD, a specialist in recombinant DNA and genetic engineering, lends support to Hooper's arguments. Bagasra, a professor of biology at Lincoln University, near Oxford, Pennsylvania, authored *HIV and Molecular Immunity*, a 1999 book on the origin of AIDS and prospects for an HIV vaccine. "The natural transfer theory is completely out of whack," he says. Noting that Africans have eaten primates for thousands of years, he asks, "How come we didn't start this epidemic many, many years ago?" He thinks the OPV/AIDS theory meshes well with the available knowledge of viral evolution.

And beyond offering an explanation of how the epidemic started, Bagasra argues that proof of the OPV/HIV theory could be very good news for a potential HIV vaccine. He postulates that some still-living CHAT recipients whose vaccines were contaminated with SIV might be carrying -- due to the attenuation process involved in producing the vaccine -- a weakened strain of SIV or HIV that has afforded them long-term immunity. Bagasra is planning an expedition to the Congo this summer, where -- using lists Hooper has compiled -- he hopes to locate and test the blood of CHAT recipients for such attenuated HIV, which might be a key component in the creation of an HIV vaccine. Bill Hamilton, a Royal Society professor at Oxford University and an acknowledged expert in evolutionary biology, concurs that such an expedition could spark a crucial breakthrough.

Hooper sees even greater benefits if the theory proves correct -- avoiding similar scientist-created accidental catastrophes. "In an age when new, potentially risky medical interventions are being proposed -- human cloning, the transplantation of animal organs and cells into humans, the testing of live HIV vaccines -- it is surely timely to think long and hard about the implications of this story," he says.

Meanwhile, the controversy rages on. This May, the Royal Society (a prestigious body of British researchers) will call the key players on all sides of this controversy to a London conference for a wide-ranging discussion of the theory. Perhaps they may agree on further testing, or even achieve some common ground.

So The River, while not resolving the question of how HIV originated, may push forward the search for its source. If the wellspring of the virus could be located, there’s no telling how that knowledge might alter the course of medical history.
