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Record: 14

Title: The origin of AIDS.
Subject(s): AIDS (Disease)
Source: Rolling Stone, 3/19/92 Issue 626, p54, 9p, 5bw
Author(s): Curtis, T.
Abstract: Attempts to find the origin of the AIDS virus. The search for a polio vaccine by Dr. Jonas Salk, which may have inadvertently infected its recipients with the virus that causes acquired immune deficiency syndrome (AIDS); Medical sciences unintentional role in introducing AIDS to the human population; AIDS first appearance in equatorial Africa; Connection with monkeys and other primates; Viruses and vaccines; More. INSET: Man, monkeys and disease, by T.C.

Full Text Word Count: 9712

AN: 9203090054
ISSN: 0035-791X
Database: Academic Search Elite

THE ORIGIN OF AIDS

Contents

AFRICAN GENESIS

“IT’S NOT GOOD TO KNOW TOO MUCH”

THE FORTIETH MONKEY VIRUS

THE MARBURG MONKEY VIRUS

THE CONGO VACCINE

MONKEY AIDS

CONTAMINATION?

A TALE OF TWO MAPS

THE ZAIRE CONNECTION

TESTING SEED STOCKS?

A STARTLING NEW THEORY ATTEMPTS TO ANSWER THE QUESTION 'WAS IT AN ACT OF GOD OR AN ACT OF MAN?'

It was almost thirty years ago, but I clearly remember one event on that hot and humid day early in August 1962. Like communicants in some universal mass, my two brothers, my parents and I slowly moved to the head of a very long, snaking line composed of thousands of people - a significant part of the population of Galveston, Texas. All were awaiting admittance into the central hallway of Ball High School so we could approach a simple wooden table - a kind of altar of science - where a volunteer nurse handed each individual a tiny paper cup containing a sugar cube. I gazed intently at mine. One side had a faint yellow tinge and dark specks where the half-cubic-centimeter or so drop of liquid vaccine had landed. Though I was surprised that my cube was so dirty looking, I popped it in my mouth, chewed and swallowed. The rest of my family followed suit. Over the next two years, the same ritual was played out in towns and cities across America. These other patient

MONKEY VIRUS = HUMAN VIRUS

A THEORETICAL POSSIBILITY

“IT COULD HAPPEN”

EPILOGUE: AVOIDING FUTURE CATASTROPHES

braces and crutches or imprisoned in iron lungs - huge cylinders covering all but their heads. I had an even more terrifying image of the ravages of polio: A close friend of my parents', a vital young physician named Martin Schneider, had contracted the disease in 1948 and had spent the last two decades of his life paralyzed from the waist down and confined to a wheelchair.

In one of the greatest triumphs of twentieth-century medicine, the promise to deliver us from that crippling contagion was kept. The one-two punch of the “polio shots” developed by Dr. Jonas Salk and the oral vaccine developed later by Dr. Albert Sabin effectively eradicated polio in developed countries and later in much of the Third World.

But there was a shadow over the conquest of polio. It's estimated that early on, at least, the polio vaccines administered to many millions of people in the U.S. and around the world were inadvertently contaminated. “We took all the precautions that we knew of at the time,” Dr. Salk says today. “Sometimes you find out things after the fact.”

What Salk and the other pioneers of the polio vaccine found out was that accidents did happen. In the preparation of massive amounts of various polio vaccines - either weakened or killed virus that causes recipients to form protective antibodies - things occasionally went horribly wrong. Hundreds of people actually contracted polio by the very means they sought to protect themselves - and some died. Researchers who cultured the virus using the tissues of animals were stricken and sometimes killed by other viruses infecting the animals. And finally, the medium that scientists used to produce the vaccine - the kidneys of monkeys caught in the wild - was found to be sometimes contaminated by simian viruses that were later passed on to millions of unsuspecting people.

There is the prospect that we may find out something else after the fact: that another polio vaccine may have inadvertently infected its recipients with an even more fearsome and insidious virus, the one that causes acquired immune deficiency syndrome - AIDS.

In August 1991, Blaine Elswood, an articulate AIDS-treatment activist and diligent sleuth of medical literature who works at the University of California at San Francisco, mailed me a terse note paper-clipped to several Xeroxed items from medical and scientific journals raising the issue. “Here's a bombshell story just waiting for an investigative reporter,” he'd said.

We'd had a casual, two-year telephone-and-mail acquaintance ever since Elswood had been recommended to me as a source by a West Coast dermatology professor working on new treatments for AIDS. Clearly a maverick, Elswood was proudest of having cofounded “guerrilla clinics,” which research and provide alternative drugs for those with AIDS, in San Francisco and elsewhere. Elswood is neither a physician nor a Ph.D., and he has one clear bias: He does not think American doctors will easily acknowledge that medical science itself may have played an unintentional role in introducing AIDS to the human population.

As I soon find out, Elswood is right. When I broach this idea to Salk, who is once again working to develop a vaccine, this time for AIDS, he flatly refuses to discuss the subject. “I don't think I can be helpful to you,” he says, “other than to try to dissuade you from pursuing that kind of a hypothesis, because what value is it? What value is it to anyone to try to imply such a cause and effect relationship?” He also makes it clear that he strongly subscribes to another plausible theory: that the AIDS virus has lingered for eons in African jungle tribes and erupted to cause epidemics in recent decades only when those rural peoples migrated to the cities.

AFRICAN GENESIS

AIDS first appeared in equatorial Africa, many scientists now believe. The earliest evidence of its presence on the African continent dates from a plasma sample drawn in 1959 in what was then Leopoldville, the Belgian Congo, and is now Kinshasa, Zaire. Dr. Mirko D. Grmek's definitive book *History of AIDS*, published in 1990 by Princeton University Press, describes the primary African epidemic's radiating outward from a region located in Zaire and

believers, like me and my family, were seeking not life eternal but science's more secular but no less miraculous promise: everlasting immunity from the most dreaded scourge of the Forties and Fifties - paralytic poliomyelitis. Before the polio vaccines were introduced in the Fifties, the disease had struck about 22,000 people a year in the United States alone - often young children. The new, vibrant medium of television showed kids like us shackled by leg

Rwanda. There's also a tantalizing connection with monkeys and other primates: Several African species carry a virus related to the human immunodeficiency virus (HIV), which causes AIDS in human beings. Although HIV has yet to be found in monkeys, a "missing link" simian virus much closer to the human virus has been identified in two wild chimpanzees from Gabon. This has led to speculation that a chimp or a monkey with an AIDS virus identical to the human virus will eventually turn up.

Scientists have proposed a grab bag of ideas to explain how the disease may have leaped the vast chasm from monkey to man. There is, for instance, the kinky-African-sex theory. It involves a bizarre sexual practice in which, to heighten sexual arousal, male and female members of tribes bordering the large lakes of Central Africa introduce monkey blood into their pubic areas, thighs and backs. Then there's the cut-hunter theory, recently described to me by the premier American AIDS researcher, Dr. Robert Gallo. Gallo suggests that since monkeys in Africa are killed for food, a hunter might have nicked himself while skinning an infected monkey and thus might have mixed virus-laden monkey blood with his own; repeated such incidents over time, he argues, could have infected enough people to spark an epidemic. Last Thanksgiving, an Oxford clinician writing in the prestigious British scientific magazine *Nature* presented another startling hypothesis: that the disease may have sprung from scientific experiments that lasted into the Fifties in which chimpanzee and monkey blood was directly injected into human beings to see if people could carry the form of the malaria parasite that infests those primates.

There are problems with each theory. The first couple are basically speculations that can't easily be confirmed or tested scientifically. Anyhow, those African sexual and hunting practices presumably have been going on for thousands of years; the AIDS epidemic is new. The idea involving the malaria experiments is extremely provocative. It may prove to be more than that if material from the original experiments still exists and can be scientifically checked. But the number of people involved in the tests was tiny: As discussed in *Nature*, a total of about seventy people received primate blood or primate-tainted human blood during the entire range of the malaria experiments, which ran from 1922 to 1955. Still, AIDS had to start somewhere, so like the other theories, this one has to be considered.

SPRINKLED THROUGH THE MEDICAL LITERATURE OF THE last thirty-five years are facts that buttress the unnerving prospect that HIV, the AIDS virus, may have crossed the species barrier as an unintended byproduct of a live-polio-virus vaccine. There was, in fact, an almost forgotten mass-vaccination campaign in which an oral polio vaccine was administered to at least 325,000 people, and perhaps more than half a million people, in equatorial Africa from 1957 to 1960. One of the two vaccines used in that experimental effort was subsequently reported to have been contaminated with an unknown monkey virus.

The timing seems right. A process called genetic sequencing, which tracks the evolution of a virus by measuring genetic changes, can read the molecular history of a disease. According to Gerald Myers, the federal government's chief expert in genetic sequencing, HIV dates from about 1960, assuming it arose from a single, common ancestor.

There are natural obstacles preventing a virus from crossing the barrier to become established and thrive in a new species. But it happens. And when it does, the virus frequently becomes much deadlier in the new species than it was in the original hosts.

In recent decades, some scientists believe, live-virus vaccines may have actually helped transfer viruses across species lines. Perhaps the classic example is canine parvovirus, or CPV, which abruptly appeared in dogs in 1977 and within months had become a widespread animal epidemic - or epizootic - on virtually every continent, causing entirely new dog diseases of the intestines and heart muscle. CPV is intriguingly similar in its genetic structure to a cat disease called feline panleukopenia virus (FPLV), but it's even more similar to the vaccine for this disease. This has led several virologists to suggest that by accident or design, the cat virus most likely was introduced into dog cells in the laboratory, where the strain adapted itself to the new host.

A 1989 article in the *Journal of the Royal Society of Medicine* noted that case and a number of other cross-species transfers of viruses in the context of AIDS. "It would appear," the piece said, "that the AIDS epidemic may be just one of the latest of several mammalian cross-species viral transfers triggered by the techniques of virology developed in the 20th Century, which subsequently spread out of control in the new host species."

To grasp how this possibility relates to a polio vaccine used in Africa, it helps to know how polio came to be suppressed in most of the world.

“IT’S NOT GOOD TO KNOW TOO MUCH”

Jonas Salk, backed by a private philanthropy popularly known as the March of Dimes, introduced the first widely used polio vaccine in 1954. His vaccine was a virulent form of the polio virus that had been killed by formaldehyde. This dead, or “inactivated,” virus was injected into people to provoke the body’s immune system to manufacture disease-fighting antibodies that would repel the wild, paralyzing types of polio. But medical science ultimately rejected Salk’s shots as the vaccine of choice in favor of a weakened but still living virus administered by mouth - in Albert Sabin’s sugar cube. Unlike the Salk shots, which were believed to require periodic booster vaccinations, the oral polio vaccine conferred lifetime immunity. It could be taken by mouth and required no injections; and the live vaccine silently spread the weakened, non-paralyzing virus even to those who failed to take the oral vaccine. These “susceptibles” would simply catch the weakened virus and get the infection without noticeable symptoms. They also would become immune to paralytic polio.

Polio vaccines are produced by selecting weakened strains of polio virus and then placing them in tissue cultures - live cells from primates. (Either monkey or human cells will work, but researchers selected monkeys because their tissue was more available and there were fears that human cell lines might spread cancer. The unrecognized danger, though, was this: Because monkeys are genetically similar to human beings, some simian viruses can leap the species barrier with devastating effect.) The virus then enters the cell and reproduces itself. All the polio viruses grown to produce the mass vaccines in the Fifties were fed one particularly nourishing medium: fresh monkey kidneys. And throughout the Fifties - a period that was barely beyond the dawn of scientific knowledge regarding tissue culture - some of those monkey kidneys were infected with numerous monkey viruses. Scientists knew about some of these viruses and developed tests to identify and then eliminate the tissues that contained them.

One of the earliest and deadliest was the so-called monkey B virus - a herpes virus first identified and isolated in 1932 by Sabin after it killed a medical colleague at New York’s Bellevue Hospital. The unfortunate polio researcher had been bitten by a monkey. “He had developed paralysis after the monkey bite,” Sabin recalls almost sixty years later as I interview him in the office of his Washington, D.C., apartment. “He died after a short time.” Sabin, who with his full white beard and hair looks a little like Robert E. Lee, continues: “At the autopsy I collected specimens and isolated a virus. Because I was too green behind my ears in virology, I would not accept [it] as being an ordinary herpes virus with which human beings are infected - which a professor at Columbia University, who knew much more than I, did.” Chuckling at the memory, he adds, “Sometimes it’s not good to know too much.”

While working at the Lister Institute, in England, in 1934, Sabin was able to prove that what he had found was a distinct virus. And in 1949, when he was working in Cincinnati, Ohio, he again isolated the virus after another physician researcher was killed by it. “Then, as thousands of monkeys began to be used for the preparation of the Salk vaccine in the early Fifties,” Sabin says, ten or so caretakers working with the monkey kidneys or who were bitten while handling the monkeys also developed the same illness and died.

“In monkeys, it’s a disease which is as mild as ordinary fever blisters are in human beings,” Sabin says, but in humans it paralyzes and kills. “As a result of that, all the [research] monkeys had to be tested.” Special precautions were instituted. “But often precautions are not used,” Sabin says. Deaths from monkey B virus, though infrequent, have continued, the latest a veterinarian at a south Texas primate facility who died of monkey B virus last fall.

THE FORTIETH MONKEY VIRUS

So monkey B was kept out of the polio vaccines. But there was another monkey virus that polio researchers missed. Between 1954 and 1963, an estimated 10 million to 30 million Americans and scores of millions of people around the world were exposed to a virus that infected the kidneys of Asian rhesus monkeys imported mainly from India. The virus survived the formaldehyde that Salk used to kill his polio viruses. Since 1961 researchers have tested monkeys for SV40 - so called because it was the fortieth such simian virus identified - before using their kidneys for vaccine production.

SV40 was delivered straight into people’s bloodstreams along with their Salk shots and via sugar cubes in field trials of the weakened living virus developed by Sabin. Though it was later shown to cause cancer in hamsters and to “immortalize” human cells in test tubes - thus predisposing these cells to cancer - SV40 has not been proven to generate illness in human beings. Nevertheless, researchers at Johns Hopkins recently discovered that when they injected cells treated with SV40 into “nude” mice, which lack an immune system, the mice developed Kaposi’s sarcoma-like tumors, similar to those afflicting many AIDS victims. Remarkably, considering the large numbers of people who received the SV40-contaminated polio vaccines, no one has conducted a major epidemiological study in the U.S. to discover whether there is any pattern of illnesses caused by the virus.

Still, there are some troubling statistical associations. In 1968 a scientist in Australia described a correlation between polio immunization and cancers in children past one year of age. Much later, German scientists found evidence of SV40 in 30 out of 110 brain tumors, and later reports indicated a jump in the frequency of brain tumors among those who had received vaccine contaminated with SV40. And SV40 has been associated with other human cancers as well.

After news broke about the monkey virus SV40 contaminating some lots of Salk's and Sabin's polio vaccines, congressional hearings were called to examine the explosive issue. On April 14th, 1961, a rival polio researcher of Salk's and Sabin's sent a letter to the House Health and Safety Subcommittee taking issue with growing live-polio-virus vaccine in monkey kidneys.

Sounding like someone who had come to his understanding through hard experience, the researcher - Dr. Hilary Koprowski of Philadelphia's Wistar Institute - suggested that human cell lines be used instead. "As monkey kidney culture is host to innumerable simian viruses, the number found varying in relation to the amount of work expended to find them, the problem presented to the manufacturer is considerable, if not insuperable," Koprowski wrote the committee. "As our technical methods improve we may find fewer and fewer lots of vaccine which can be called free from simian virus."

But when Koprowski, Salk and Sabin were doing their initial vaccine development in the Fifties, little was known about the simian viruses, and there were no federal regulations stipulating that the viruses be grown in a specific type of tissue culture. No one knew then about retroviruses like HIV that might take years to develop, and so it was assumed that if no viruses had shown up in preparations after a couple of weeks, then those vaccines were clean.

In 1988, when researchers in the Washington, D.C., area reexamined an earlier study run between 1959 and 1965 on nearly 59,000 pregnant women, they found a startling connection: The incidence of brain tumors in children of mothers who'd been injected with the Salk vaccine was thirteen times greater than that of offspring of mothers who hadn't had those polio shots. Stored blood serum from these mothers still existed, and it was retested. The tests seemed to exclude SV40 as the cause. But if not SV40, what about the Salk vaccine might explain the increased risk of brain tumors in offspring of vaccinated women? The researchers asserted that some other infection was probably the culprit. After all, they noted, the Salk vaccine was known to have been contaminated with numerous monkey viruses.

THE MARBURG MONKEY VIRUS

In mid-August 1967, six years after the SV40 problem came to light, a mysterious, dangerous, infectious disease broke out simultaneously in German and Yugoslavian research institutes. Thirty-one people, including technicians making polio vaccines, suddenly became ill - and seven died. All those infected had direct contact with monkeys or their blood, organs or tissue cultures. Other people later got the disease, too, including hospital personnel who had contact with these patients. In one case, a woman contracted the disease from the semen of her husband, who had been infected three months earlier. Though millions of monkeys had been used as experimental animals and as raw material to provide kidneys to make vaccines, no such disease had ever been seen before. Eventually the "Marburg virus" was isolated, and its source was traced to monkeys shipped from Uganda.

But if HIV were one of those numerous anonymous monkey viruses contaminating the early Salk and Sabin vaccines, presumably there would have been an explosion of AIDS in the U.S. outside the currently defined high-risk groups: male homosexuals, intravenous-drug users, hemophiliacs and the sexual partners of those people. Of course, that sort of eruption hasn't happened in the U.S. But it did happen someplace else: in equatorial Africa.

THE CONGO VACCINE

As it happens, equatorial Africa was the site of the world's first mass trials of an oral polio vaccine - a vaccine cultured in monkey kidneys but different in at least one important respect from the Sabin vaccine ultimately adopted worldwide. This footnote in medical history took place from 1957 to 1960 right in the middle of what was then the Belgian Congo, Rwanda and Burundi - the epicenter of the future African AIDS epidemic. It was developed by a naturalized American polio researcher named Hilary Koprowski - the same Dr. Koprowski who four years later would warn congressmen of the dangers of an almost infinite number of monkey viruses contaminating polio vaccines.

Hilary Koprowski, the developer of the vaccines used in the Congo, is a charming, deep-voiced man of seventy-five. Born and educated in Poland, where he studied to be a concert pianist while going to medical school, Koprowski began

work for Lederle Laboratories in 1946. Like Salk and Sabin he took up the cause of saving the world from polio. He tested weakened strains of the virus in monkeys and chimps and in March 1951 surprised a meeting of polio researchers sponsored by the March of Dimes in Hershey, Pennsylvania. There he revealed that he had become the first physician in history to administer a polio vaccine to humans. The “volunteer” research subjects for Koprowski’s live, weakened polio vaccine included twenty children he later described as “mentally deficient” who lived in Letchworth Village, a facility operated by the New York State Department of Mental Health. Later he vaccinated other groups of children, among them the newborn babies of institutionalized women in New Jersey. But a larger test of the vaccine, planned for children of Belfast, Northern Ireland, in 1956, was scrapped amid reports that some of his tamed oral vaccine had reverted to its wild, paralytic form. While no one was paralyzed and Koprowski insists that no one ever would have been, authorities in Belfast feared that such a “reversion to neurovirulence,” to use the medical jargon, might spark a new polio epidemic.

After the Belfast debacle, Koprowski, who was racing Sabin for the distinction of producing the oral polio vaccine of choice, left Lederle Laboratories to direct Philadelphia’s Wistar Institute, then a modest research organization best known for developing a unique laboratory rat. But he held tightly to his goal of producing the winning polio vaccine.

ALMOST IMMEDIATELY, KOPROWSKI ARRANGED to have his weakened polio viruses tested in a colony of 150 chimpanzees in Camp Lindi at Stanleyville, in the Belgian Congo (now Kisangani, Zaire). To protect the animals’ caretakers, these humans, too, were fed the weakened virus. The successful immunization of the keepers then became the justification for mass vaccination trials in the Congo itself - the first mass trials in the history of an oral polio vaccine.

Called by drums, rural Africans traveled to village assembly points. There they lined up and had a liquid vaccine squirted into their mouths. Using this spray method, nearly a quarter million Africans were inoculated in six weeks. Later another 75,000 or so children in Leopoldville, now Kinshasa, got the vaccine, too - though European children living there apparently received their vaccine in capsule form, possibly a significant variation.

From the beginning, Koprowski’s campaign was marked by controversy. Trial by Fury, Aaron Klein’s 1972 account of the development of the polio vaccines, reports that Koprowski apparently claimed he had the backing of the World Health Organization, but WHO denied sanctioning the mass trial. Koprowski says today that although he was challenged by WHO, he needed only the approval of the Belgian authorities - and there’s no doubt he had that. Other preparations of Koprowski’s polio vaccines were later used in Poland, Yugoslavia and Switzerland, among other places.

Herald Cox, Koprowski’s superior at Lederle, had begun growing the polio virus in developing embryos in chicken eggs. Early on, Koprowski also used the brains of cotton rats to select his weakened strains and nurture the virus. But by 1956 and 1957, when he was readying his vaccine for use in the Congo, Koprowski and his associates had long since switched to minced-up monkey kidneys.

Monkey kidneys contained innumerable monkey viruses. Might the one that causes AIDS be one of them? And if it were, would Koprowski’s method of delivery - shooting the liquid into people’s mouths - be capable of transferring the virus from monkeys to humans?

“You can’t hang Koprowski with that,” Albert Sabin growls at me. He’s sitting at the desk in his study; the walls are covered with testimonial plaques, certificates of commendation and achievement, photos of him with several presidents. Sabin insists that the AIDS virus won’t survive swallowing. He’s certain of it.

But whether it does or doesn’t survive is really not so clear-cut, Dr. Robert Gallo and other retrovirus researchers acknowledged to me; no one knows for sure. Moreover, Gallo’s colleague, Dr. William Haseltine of Harvard and also of the Dana Farber Cancer Institute, in Boston, and others have reported that the AIDS virus infects mucous cells - which of course occur in the mouth as well as in the genitalia.

And Dr. Robert Bohannon of Baylor Medical School, in Houston - who in November 1991 reported finding a monkey retrovirus in the tumor of an AIDS patient with no known contact with monkeys - pointed out to me that the process of squirting the polio vaccine in people’s mouths would tend to send tiny drops into the air. It might go directly to the lungs or nose or eyes and thence to the blood cells it is known to infect.

Later I pose the same question - Could squirting an HIV-laden polio vaccine into people’s mouths cause AIDS? - to Dr. Tom Folks, the chief retrovirologist at the Centers for Disease Control, in Atlanta. “Sure it could,” he says. “Any time

a person has a lesion in his mouth, then there could be transmission if you put enough'' of the virus in.

MONKEY AIDS

But was there anything to transmit? The answer to that question hinges on the kind of monkeys used to make Koprowski's vaccine.

In 1957, when the Congo trials began, most researchers were using rhesus macaques from India. It would be another four years before scientists fully appreciated the danger that macaques, the natural hosts for SV40, were passing along the virus to humans. Once that troubling discovery was made, in 1961, vaccine producers shifted to kidneys from African green monkeys, which in the wild were free of SV40.

Unfortunately, green monkeys were infected with something else. More than two decades later, in 1982 and 1983, veterinarians at the California Primate Research Center and at Harvard's New England Primate Center observed that large numbers of their macaques were dying periodically of AIDS-like illnesses. These disorders had been killing animals since 1969, but suddenly, the researchers were struck by the similarity to the new disease afflicting American homosexual men. The monkeys' illnesses, the researchers discovered, were triggered by a previously unrecognized retrovirus called simian immunodeficiency virus (SIV).

Among the natural hosts for this virus were none other than African green monkeys, but in that species, typically, SIV didn't cause serious disease. SIV turned out to be related to HIV, though it was only about forty percent similar in genetic structure to the chief AIDS-causing human retrovirus, known as HIV-1. Robert Gallo says some versions of this monkey virus are virtually indistinguishable from some human variants of HIV-2, the second virus that causes AIDS in human beings and mainly afflicts western Africa.

No one who was involved with Koprowski's Congo project and is alive today remembers what kind of monkey kidneys were used in 1957-59. Today, Koprowski is still vigorous and remains at the Wistar Institute, in Philadelphia - now as the institute professor and until 1991 as the director of the facility, which is housed in a stolid Victorian structure on the campus of the University of Pennsylvania.

Koprowski insists that his associates used kidneys from African green monkeys to make the Congo vaccines. When I express surprise and mention that Salk and Sabin were using rhesus monkeys at that point, he agrees to check. When we speak next he admits he can't find a single paper describing which species was used to make his vaccine. "But I have a suspicion the virus was grown in the rhesus monkey at the original beginning," he tells me in his thick Polish accent. "Now when we switched to green monkeys, I have no idea." Thomas Norton, his associate who grew the virus for the vaccine, is now dead, Koprowski says - as are those who worked with Norton to prepare the vaccine. Significantly, the large lots of the vaccines used in the Congo apparently were prepared at the laboratories of the Wistar Institute, he says. Wyeth Laboratories made subsequent preparations, including those used in Poland.

CONTAMINATION?

The question of which monkeys were used to make the Congo vaccine may not be crucial. The virus that causes monkey AIDS occurs in several species, though the original hosts - African greens and others - remain healthy even when infected. Monkeys frequently were gang-caged in those days, facilitating the spread of viruses. If a green monkey turned out to have a virus quite similar to HIV-1, it could have infected the other monkeys.

Although most American researchers in this period apparently did use rhesus macaque monkeys from Asia, for a while around the time Koprowski was working with his vaccine, the monkey supply was interrupted. The Indian government - responding to popular alarm among its people about the widespread slaughter of Indian macaques for vaccine production and other research - barred export of rhesus monkeys to the U.S. For a time at least, that ban must have made suppliers scramble to find different markets and alternate monkey species, probably including African monkeys. Moreover, Koprowski says the kidneys used at Wistar were bought already removed from their hosts, meaning that researchers might not have been sure what kind of monkeys they came from, much less what viruses came with them.

According to no less an authority than Albert Sabin himself, at least one other virus did contaminate Koprowski's vaccine used in the Congo. In 1959, Sabin reported in the British Medical Journal that a special test he had devised revealed the presence of an "unidentified" cell-killing virus in "Koprowski's type 1 'Chat' vaccine used in the Belgian

Congo trials.” More than three decades later, Sabin says he never figured out exactly what the virus was.

Koprowski insists - as he did at the time in the *British Medical Journal* - that two other labs examined his vaccine and found nothing except the weakened polio virus. But one eminent polio researcher, Dr. Joseph Melnick, former chairman of the Department of Virology at Baylor College of Medicine, in Houston, who himself developed another oral polio vaccine while working at Yale Medical School, says Sabin probably was right. “Sabin was a very careful worker in the laboratory,” says Melnick, a tall, formal, distinguished-looking man. “And I have not known him ever to say that he has found a virus in some preparation that did not exist in that preparation.”

In any event, Melnick says, “Monkeys have a very high prevalence of lentiviruses,” one of the subfamilies of retroviruses. “You can isolate it from their tissues, particularly from their kidneys. That is one reason why we stopped using monkeys from the wild and just used home-grown monkeys.” Melnick pauses. “It’s of interest,” he says, “that HIV is a lentivirus.” So are the simian immunodeficiency virus and the so-called foamy virus, both of which widely infect monkeys, Melnick says. “In the early days of the vaccines, we didn’t know much about monkey viruses.” As for Koprowski’s contention that others looked and didn’t find the virus in his Congo vaccine that Sabin had noted, Melnick has a simple explanation: “It may not be in one batch and may be in another batch.”

A TALE OF TWO MAPS

Writing in the *British Medical Journal* on July 26th, 1958, Koprowski and his colleagues offered a preliminary report on their mass vaccination campaign. They included in the paper a detailed map showing where nearly a quarter million inoculations had taken place in the northeastern part of the Belgian Congo. The area outlined corresponds roughly to another map in a report published thirty years later in the *Reviews of Infectious Diseases* - this one identifying the regions of highest HIV infection in equatorial Africa.

Still another paper that appeared in the *British Medical Journal* in 1985 reviewed HIV infection in the Kivu District, a remote, rural population in eastern Zaire. There, somewhat puzzlingly, the researchers discovered “a high prevalence of antibodies” to the AIDS virus without symptoms of the disease. The Kivu District happens to be where Koprowski’s colleagues vaccinated the lion’s share of their reported sample - 215,504 children and adults. And there may have been many more vaccinations than initially reported. “Could have been 200,000 more, I really don’t know,” Koprowski says, because the subsequent mass trials were interrupted by tribal chaos and the civil war that followed independence. No one really knows how those individuals fared over time. No long-term follow-up was possible, Koprowski says.

The researchers who studied the Kivu District in 1985 offered several possible explanations for why the people they found with antibodies for the AIDS virus might not have the disease. The fact that there were more children than adults with antibodies to the virus suggested that the adults could have been exposed in childhood, and some of them might have died or departed from the area. Perhaps, the researchers ventured, if members of a rural population that was biologically adapted to the virus moved into an urban area, exposing a pool of more susceptible adults, this would create “new opportunities for the virus to cause illness in urban adults and the epidemic appearance of the disease in Africa.” Moreover, the researchers pointed out that they were looking at a region of “high mortality in childhood, particularly from infectious diseases.” Cases of AIDS in children a generation ago simply might have gone unrecognized.

Of course, many of the viruses contaminating the monkey kidneys went unrecognized in the Fifties and early Sixties. Koprowski and his colleagues in the mass-vaccine campaigns found some monkey viruses and eliminated them from their preparations. But many others weren’t known, and no test to identify their presence had been developed. “That’s the problem,” Koprowski says. “The viruses which you know, there’s a test - there’s no problem; the viruses which lurk, for which there is no test, obviously you can’t do anything about.”

So, might Koprowski’s Congo vaccine have been the vector that unwittingly first unleashed the AIDS virus among people in Africa? I ask the question and Koprowski dismisses the idea with a deep laugh: “Ho, ho, ho, ho, ho.”

I’m asking the question, I say.

He laughs again, this time longer and deeper. “By then you would have had plenty of opportunity to see AIDS in the vaccine,” Koprowski says. “You have started in 1960; now it’s thirty years. The latency period of AIDS is nine years.”

But according to Dr. Gallo, I point out, some retroviruses may take up to forty years to express themselves.

“There is no indication from any part of the world that any other virus occurring there [in the various polio vaccines] causes any problem,” Koprowski says.

There are reasons, however, why AIDS in the former Belgian Congo may have been invisible to medical science. In remote, rural eastern Zaire, where most of Koprowski’s vaccine was administered, or even in Kinshasa, the disease simply may have passed unnoticed or may not have been identified. “In the tropics, the wealth of lethal infectious pathology is matched by the poverty of diagnostic facilities, rendering undetectable sporadic appearances of AIDS,” notes Dr. Mirko D. Grmek, a medical historian, in his recent book *History of AIDS*. “It is entirely possible that localized or even moderately large epidemics have passed unnoticed.”

On the other hand, AIDS may have been slow to express itself when it was confined to rural areas where people had fewer sexual partners. A laboratory experiment with monkeys also showed how AIDS may have taken a bit longer to emerge as an epidemic in its present nasty form. When a researcher took a simian AIDS virus from a healthy mangabey, a monkey species in which it typically causes no symptoms, and injected it into a group of macaques, the disease became progressively more virulent each time it passed through the body of another macaque. Finally, this isolated virus even sickened a mangabey, although that species has natural resistance to the original virus. A similar process may have made African AIDS in humans increasingly deadly over time: It’s easy to envision a progression in which an original carrier infected by, let’s say, a Congo vaccine would have to infect several others before the disease became virulent. Such a process would take time and might explain the lull before the African epidemic appeared (just about the same time the epidemic surfaced in the United States and in western Europe).

THE ZAIRE CONNECTION

In 1987, Belgian researchers writing for a Scandinavian medical journal identified seven AIDS cases originating in Zaire and in nearby Burundi between 1962 and 1976 - well before the African epidemic exploded. Three of these were retrospectively identified as AIDS; the other four were cases in which patients had antibodies for the AIDS virus. Taken together, the authors said, this evidence indicated “that AIDS had already occurred in Central Africa several years prior to its emergence in the United States.”

There is yet another curious Zaire connection: its relation to the secondary AIDS hot spot, Haiti. No one knows for sure whether AIDS migrated from Africa to Haiti or from the U.S. to Haiti. But according to Grmek, in the early Sixties, after independence came to the former Belgian Congo, many Haitians worked in Zaire, especially in Kinshasa. The Haitians - who were French speaking, black and had no ties to Belgium - filled the void previously occupied by Belgian colonialists. Their arrival, of course, came only a couple of years after Koprowski’s vaccine had been tested in Kinshasa and in remote eastern Zaire.

As for the idea that the Congo vaccine started the African epidemic, Koprowski is skeptical. “Why do you choose Africa?” he asks. “Why don’t you compare the enormous number of other countries where exactly the same [vaccine] material was used? Why didn’t it start an HIV epidemic there?”

This answer seems to beg the question. Specific lots of a particular vaccine - not all polio vaccines everywhere - might have unintentionally spawned AIDS. For instance, specific batches of Salk’s killed-poliovirus vaccine prepared by Cutter Laboratories turned out to be insufficiently inactivated by formaldehyde, and those batches paralyzed 150 of the people who received them and killed 11. Later, specific lots of Salk’s and Sabin’s vaccines were found to have been contaminated by the monkey virus SV40, with as yet undetermined long-term consequences in people. Why is it unreasonable to ask whether a specific batch of Koprowski’s preparation - say, the unique lots prepared at the Wistar Institute solely for use in the Congo mass trials - likewise might have been made from monkey kidneys unknowingly contaminated, in this case by a retrovirus that causes AIDS?

“You’re beating a dead horse,” Koprowski says. “My opinion is that this is a highly theoretical situation, which . . . does not make sense.”

TESTING SEED STOCKS?

Koprowski told me that he maintains the seed stocks - samples of the original vaccines - from the Congo mass trials in freezers at the Wistar Institute. I venture that it would be easy enough to answer the question just by testing those seed stocks.

“Yes,” Koprowski begins uncertainly. “But I don’t really know how much HIV is really present in monkey kidney. . . . I have great doubt it would find its way to epithelial cells such as kidney. You are postulating that in the highly processed monkey kidney, you’ll get these viruses. I doubt that they are present there.”

Later, Koprowski describes for me how the kidneys used in tissue culture were minced up using “scissors or something like that.” He is quite correct that HIV and its monkey counterpart, SIV, do not appear to grow in the kidney cells. Instead, as he points out, these viruses are known to grow in lymphocytes and macrophages - cell forms found in the blood. But this doesn’t mean that under the right conditions a polio vaccine grown in monkey kidney cultures might not harbor an AIDS virus.

I raise this issue with Tom Folks, chief of the retrovirus laboratory at the Centers for Disease Control, in Atlanta. “You see, the problem with the kidney,” says Folks, is that “there’s blood and there are lymphocytes that would be contaminating the tissue. So, no matter how hard you try to mince it up - and I’ve made monkey kidney tissue cultures many a time - you haven’t gotten rid of contaminating lymphocytes. So, if the monkey that it’s derived from has a pretty fulminant SIV infection, and then they were placing polio [virus] on top of the monkey kidney, but there were contaminated lymphocytes, that is going to be part of the stock. Yeah, it would be there.

“That wouldn’t be surprising at all,” Folks continues. “And the fact that it’s a live vaccine would indicate that they had not gone through any inactivation procedures to denature the AIDS virus, because it would probably denature the polio virus. So, the polio virus is kept alive, and the SIV virus would just travel with it. The theory, the possibility is real. And I don’t think anybody would deny it.”

The ultimate way to test the idea, Folks agrees, would be to return to the original seed stocks of the vaccine and actually isolate the retrovirus, if any, from the polio vaccine.

Does Folks think there is value in figuring out where AIDS came from? “I think any time we can learn more about the natural history, it helps us understand the pathogenesis [how the disease process works], and it helps us understand the transmission.” Nonetheless, he says: “It’s a delicate issue. You’re going to put some people on the spot - the person who has the stocks.”

Some others in the AIDS establishment - like Dr. David Heymann, who heads the office of research for the World Health Organization’s Global Programme on AIDS, and Harvard pathology professor William Haseltine - are so hostile to the possibility that a vaccine could have introduced AIDS that they refuse to discuss it. “The origin of the AIDS virus is of no importance to science today,” Heymann says in a phone interview from Geneva. “Any speculation on how it arose is of no importance.”

Haseltine is even more adamant. “It’s distracting, it’s nonproductive, it’s confusing to the public, and I think it’s grossly misleading in terms of getting to the solution of the problem,” he says. “It’s over, it’s done with, it’s very, very, very unlikely it happened that way, and it’s another nonsense article. It’s the worst kind of reporting, as far as I’m concerned.”

But you haven’t even heard anything about it, I say.

“I know what that theory is,” Haseltine snaps.

You don’t think the origin of AIDS is a significant question?

“It’s not relevant,” Haseltine insists. “Who cares what the origin was? Who really cares? If you want to do something good, write about problems people experience. Who cares where it came from? It’s an unanswerable question.”

It may or may not be unanswerable, I say.

“I’m not interested in discussing it,” he says again, and we end the conversation.

MONKEY VIRUS = HUMAN VIRUS

In AIDS research, and in any inquiry about it, all roads lead to Dr. Robert Gallo, the federal government’s preeminent

AIDS researcher. Gallo, the embattled chief of the National Cancer Institute's Laboratory of Tumor Cell Biology, in Bethesda, Maryland, was more open-minded than Haseltine and Heymann.

Among the reasons Gallo cites supporting what he considers the settled question of the origin of AIDS in Africa was "the greater divergence in people of the virus." "The more divergent a microbe is in a population, the more time it's had to diverge, all things being equal," Gallo says. "The divergence in Zaire is far greater than the divergence in the United States or Europe or anywhere else."

But how did the virus come to infect Africans? Thanks to recent research by Gallo's protege, Beatrice Hahn of the University of Alabama, Gallo notes, we now know that there are genetic sequences of SIV that are extremely similar to HIV-2, the second identified AIDS virus that afflicts people and is found mostly in western Africa. "In other words," Gallo explains, "the monkey virus is the human virus - there are monkey viruses as close to isolates of HIV-2 as HIV-2 isolates are to each other."

The same is true, Gallo says, of HTLV-1, the human T-cell leukemia virus, a retrovirus he discovered that causes a form of leukemia in people. Genoveffa Franchini in Gallo's lab has found some monkey viruses, specifically simian T-cell leukemia viruses known as STLV-1, which are, Gallo says, as close to most of the human HTLV-1 viruses isolated from the Caribbean islands, southern United States, southern Japan and equatorial Africa as some STLV-1s are to one another.

What does this mean? Logically, it seems to suggest that there may well be a monkey with a virus that exactly matches the one that causes AIDS in humans. So far, however, nobody's found it. The closest counterpart - the so-called missing link - has been found in two chimps from Gabon. But Gallo says that it is nowhere near as close as the two other monkey viruses he described are to HIV-2 and HTLV-1. "Close enough to argue that it might have been a source of entry some decades ago," he says. "But it's not close enough to be called equivalent."

I ask if Gallo thinks a monkey with a virus resembling HIV-1 will ever be found. "I wouldn't be shocked if there was another species where [the virus] was even closer [to HIV than the variant found in the two chimps]," he says. "Nobody would be shocked. It would be interesting and in a sense exciting, but you wouldn't say, 'I can't believe it.' "

So I raise the question of whether Koprowski's polio vaccine, if contaminated with a simian AIDS virus, could have passed it on to man.

At first Gallo dismisses the idea. "Chimps have a virus like ours," he says. "The African green monkey doesn't. So, start with the basics, okay? You make an assumption that it's got to leapfrog and change dramatically. Well, that's ridiculous. . . . SIV from African green monkeys is not real close to HIV-1. So, stop right there. It ends your theory. Period."

But, I ask, if we know some monkeys have a virtual twin of HIV-2, and if some monkeys have a virtual twin of the human T-cell leukemia virus, why wouldn't some group of monkeys somewhere have a twin for HIV-1? Might this monkey virus exist somewhere?

"Your point is well taken," Gallo says. "In support of your contention is the fact that HTLV-1 is a far more ancient virus in man. A very ancient virus in man. You can say that conclusively. There are Melanesians who were never exposed to Europeans until the last fifty years who are widely infected with HTLV-1. . . . Yet . . . yet, there are HTLV-1s that are virtually identical to some monkey STLV-1s, even though it's had much longer to evolve [in man]. Similarly, HIV-2 is probably an older infection in man than HIV-1. Yet there are HIV-2s and SIVs that are almost identical - that are as identical as many HIV-2s are to each other.

"Therefore, you would suppose that in a newer infection of man, you would be far more likely to find an identical virus in a species of monkeys," says Gallo. "That's the support of your notion. Very much so. Against it is that a great number of species have been looked at without finding anything.

"Maybe I'll just say I would have expected somebody would have found it by now," Gallo says. "But maybe we just haven't looked at anywhere near enough monkeys. Because I guess you could argue that even a monkey species where we think we know the virus [exists], that it could have a second virus [equivalent to HIV]. And that not all monkeys are infected with that second virus, and that we haven't hit the monkey that is."

After pausing for thought, Gallo adds, "I don't think that we can easily come upon that data, though, because there's not a lot of experiments being done on monkeys in the wild in Africa."

A THEORETICAL POSSIBILITY

But even assuming that a monkey version of human immunodeficiency virus exists, Gallo, like Koprowski, initially questions whether it would grow in monkey kidney cells and whether enough virus would be in the preparation to infect people - perhaps through lesions in their mouths, through mucous membranes in the mouths or since the vaccine was sprayed into people's mouths and some of it may have become airborne, through the lungs into the blood system. After hearing how the polio vaccines were prepared and delivered in the Fifties, Gallo concedes that in some fashion this way of transmitting AIDS is "a theoretical possibility." One important issue is whether the virus can be absorbed through mucous membranes. Gallo has his doubts, but Haseltine and others think it can.

Earlier in our talk, before I broached the polio-vaccine theory, Gallo discussed the case of a Norwegian seaman who visited an east African coastal city in the mid-Sixties, became sick with an AIDS-like illness in 1966 and died in 1976 at age thirty after infecting his wife and a daughter, who died shortly thereafter. The family's blood-serum specimens were tested in the mid-Eighties and were positive for HIV.

Gallo reminds me of the Norwegian sailor's case. "That sort of goes against" the theory, he says, noting that the sailor was only known to have been in east Africa, some 700 miles away from the Kivu.

The virus "sure traveled," says Gallo sarcastically. He pauses, considering the large numbers of people inoculated with the oral polio vaccine. "It might travel," he says, "but if those are rural people, I wouldn't expect it to travel to east African prostitutes that fast."

"IT COULD HAPPEN"

But the vaccine wasn't administered only in rural areas. It was given to at least 75,000 people in Leopoldville, a port city on the Congo River that was on a major trade route and that was visited at the time by around a million people a year, according to a paper by Koprowski and his colleagues.

After hearing these facts, Gallo pauses and then says: "It could happen."

Well, I ask, based on the circumstantial case alone, wouldn't it be wise to check Koprowski's seed stocks?

"Sure, why not?" Gallo says. "Certainly it's not a hard thing to do. How can I argue against checking the seed stocks? I think clearly that would be interesting. You have to say what they [Koprowski and his colleagues] were doing was a good thing, trying to help people."

Absolutely, I agreed. If this happened, it would be as unintended an effect as --

Gallo cuts me off.

"It happens, sometimes, in medicine."

EPILOGUE: AVOIDING FUTURE CATASTROPHES

At my suggestion, Dr. Robert Bohannon of Baylor College of Medicine has already written to Koprowski in Philadelphia requesting samples of his Congo vaccine so that the material can be tested for the presence of extraneous viruses including HIV. Koprowski hasn't yet responded, but the pressure on him to do so may be building. The original source for this story, Blaine Elswood, has submitted a paper to a European medical journal, which has sent Elswood's paper to Koprowski for comment.

Bohannon has also written to the U.S. Food and Drug Administration requesting access to early seed stocks of the Salk and Sabin vaccines. The FDA has agreed to supply seed stocks dating from 1976 on. But Bohannon won't be getting any earlier samples - there isn't enough of this material left. Dr. Gerald Quinnan, acting director of the agency's Center

for Biologics Evaluation and Research, tells me that Sabin's original seed stocks from the early Sixties were not tested even by the World Health Organization in the middle Eighties when concern about simian AIDS was high. That was because there are "only a small number of vials" of the preparation, Quinnan says, and tests "might use it all up."

In his 1991 book *Virus Hunting*, Robert Gallo suggests that probing for the origins of AIDS and especially seeking to find out whether a monkey carries the virus that causes AIDS in people is an important quest. "We may never know for certain the answers to these questions," he writes, "but they are of more than academic interest because answering them may help avoid future zoonotic catastrophes - that is, transmission of disease from lower animals to humans."

Current methods of growing the Sabin poliovirus vaccine "eliminate most of the blood and lymphocytes" known to be susceptible to the AIDS viruses, Quinnan tells me. Preparations are monitored, and that "provides assurance that there is freedom from most agents," he says. As for being sure the stuff is free from all agents, like some new retrovirus we don't yet know about, Quinnan says: "No, you can never prove something absolutely. However, as far as we know, the system we use doesn't result in any extraneous viruses."

Like Salk and Sabin, Koprowski had the best intentions: He wanted to eradicate a debilitating and deadly scourge. But with what we know now, it's clear there was a certain hubris involved in the rough-and-ready campaigns to conquer polio. There is evidence that all three pioneers used vaccines inadvertently contaminated with viruses from a species dangerously close to our own. If the Congo vaccine turns out not to be the way AIDS got started in people, it will be because medicine was lucky, not because it was infallible.

Map: SITE OF MASS POLIO VACCINATION, 1957-1960: 325,000 KNOWN INOCULATIONS (RODICA PRATO)

Photo: AN AFRICAN CHILD RECEIVES THE POLIO VACCINE IN THE BELGIAN CONGO IN 1957. MOST OF THOSE VACCINATED WERE CHILDREN. (ROBERT PHILLIPS)

Photo: DR. JONAS SALK, PIONEER OF THE POLIO VACCINE, IN HIS LABORATORY IN 1954 (ALFRED EISENSTAEDT/LIFE MAGAZINE-COPYRIGHT TIME WARNER)

Photo: DR. ALBERT SABIN, WHOSE VACCINE HELPED ERADICATE POLIO, PICTURED IN 1962 (BILL EPPRIDGE/LIFE MAGAZINE--COPYRIGHT TIME WARNER)

Photo: THE KIVU DISTRICT, BELGIAN CONGO, 1957: SUMMONED BY DRUMS, RURAL AFRICANS GATHERED AT ASSEMBLY POINTS TO RECEIVE ORAL POLIO VACCINE. (ROBERT PHILLIPS)

Photo: DR. HILARY KOPROWSKI AND AN ASSISTANT MAKING POLIO VACCINE IN 1956 (YALE JOEL/LIFE MAGAZINE-COPYRIGHT TIME WARNER)

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By TOM CURTIS

## MAN, MONKEYS AND DISEASE

- **1932:** Young Albert B. Sabin identifies and isolates a monkey virus that has killed a polio researcher at Bellevue Hospital, in New York. It is later named monkey B virus.
- **1946:** Hilary Koprowski and his superior at Lederle Laboratories, in Pearl River, New York, begin work on live polio-virus vaccine.
- **1950:** Koprowski tests first polio vaccine on human beings - a live oral vaccine. The virus is grown in chicken eggs and passed through rat brains.
- **1954:** Jonas Salk introduces his killed polio vaccine, made from virus grown in monkey kidneys.
- **1955:** India, reacting to the widespread slaughter of monkeys to make vaccines, restricts exports of rhesus macaques.
- **1956:** Sabin begins testing a live polio vaccine on humans.
- **1957:** Koprowski's vaccine, now grown in monkey kidneys, becomes the first oral polio vaccine to be tested on a large population - in the Belgian Congo. More than 240,000 are vaccinated in the first six weeks, most in the

remote eastern part of the country.

- **1957:** Sabin begins field trials of his vaccine in the Soviet Union. Later, upward of 70 million get it there.
- **1958:** A three-year campaign to vaccinate African children in Leopoldville (now Kinshasa, Zaire) begins. Some 75,000 children will receive Koprowski's vaccine.
- **1959:** Nationalist riots erupt in Leopoldville.
- **1959:** The first detection of HIV in Leopoldville, according to two standard blot tests of stored blood conducted in 1986.
- **1959:** Sabin reports that an unidentified monkey virus contaminated Koprowski's Congo vaccine.
- **1960:** Independence and civil war come to the Congo; Belgian workers depart. At least 325,000 Congolese, maybe many more, have been inoculated. No long-term follow-up is done.
- **1960:** First case of HIV, according to a rough estimate based on genetic-sequencing calculations by Gerald Myers of Los Alamos National Laboratory, New Mexico.
- **1961:** Batches of Salk and Sabin vaccine given to millions worldwide are reported to have been contaminated with SV40, a monkey virus that causes cancer in hamsters.
- **1961:** French-speaking Haitians stream into the former Belgian Congo to take over jobs previously held by Belgian colonialists.
- **1961-62:** Sabin vaccine is licensed in the U.S. and becomes vaccine of choice. Koprowski's is frozen out.
- **1962:** Several more AIDS cases originate in Zaire in this year and later, according to subsequent testing. Some scientists believe that AIDS radiates outward in Africa from Zaire.
- **1967:** Marburg monkey virus kills polio researchers in Germany and Yugoslavia.
- **1980:** A new, fatal disease - later identified as AIDS - begins to appear among American homosexual men.
- **1982:** An AIDS-like disease is identified as killing monkeys at California and Massachusetts primate centers; a virus is later isolated as the culprit. The contagions, it turns out, have been wiping out captive monkeys since 1969.
- **1983:** AIDS virus isolated by Luc Montagnier in Paris.
- **1985:** Researchers report finding HIV among remote villagers in the Kivu District, in eastern Zaire.
- **1987:** "Missing link" chimps found with closest thing yet to the human AIDS virus.
- **1991:** Some strains of simian immunodeficiency virus (SIV) are found to be almost identical to HIV-2, the form of AIDS plaguing West Africa. This boosts speculation that a monkey with a virus quite close to HIV-1 eventually will be found.
- **1991 (December):** Researcher Robert C. Bohannon requests samples of Koprowski's, Salk's and Sabin's seed stocks to check for contaminating monkey viruses. No response to date from Koprowski; limited success with the Food and Drug Administration.

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**Source:** Rolling Stone, 3/19/92 Issue 626, p54, 9p

**Item:** 9203090054

Top of Page

◀ Back

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