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LETTERS

Possible Origins of AIDS

If *Science* has weighed in on "the origin of AIDS from polio vaccine" debate, it must be in the lightweight category. The principle of the debate is more complicated than is indicated in the recent article by Jon Cohen (News & Comment, 20 Mar., p. 1505). Many people in the field have known since the early 1980s that the "AIDS virus" is a lentivirus bearing biological and genetic similarities to other viruses in the group. We now have evidence—the characterization of the simian immunodeficiency viruses (SIVs) and the geographical distribution of AIDS—which indicates that the human immunodeficiency virus (HIV) resulted from an interaction between simians and humans. Two events could explain a species jump from simians to humans.

The first relates to the fact that rural Africans supplement their diet by hunting and eating small wild animals, often simians. Most markets in the cities and villages of equatorial Africa have "monkey meat" as an item of commerce. Those who hunt these animals occasionally injure themselves while preparing the animal carcasses, and animal blood has likely entered human tissues through accidental cuts (note that tularemia has long been a menace to rabbit hunters in America). If a hypothetical villager was infected with an aberrant (and hypothetical) virus in the years before the 1960s, others in the village could have eventually become infected. If the village remained isolated, gradually more members could have become infected and a portion of them would have died each year from a disease obscured by the background of all the medical problems of the Third World. In the late 1960s, however, there was a decided emigration of rural Africans to cities. The admixture of infected villagers with the mobile urban population could have resulted in the epidemic of HIV-1 (and HIV-2) that we now experience. This hypothesis is virtually untestable.

A second hypothesis involves the parenteral or mucosal exposure of as many as 400 million people to vaccines made from crude extracts of primary cultures of monkey tissues in the period from 1952 through 1982. These vaccines, responsible for the virtual elimination of paralytic poliomyelitis either through direct exposure or through the establishment of "herd immunity" from live virus vaccines, have been of unquestionable benefit to the entire family of man. However, the vaccines have had some serious biological problems. The first arose with the realization that formaldehyde kinetics are different from what was first assumed, and a number of cases of paralytic polio and some deaths resulted from the administration of "undercooked" Salk vaccine. A second problem was the unwitting exposure of at least 10 million people to the genome of simian virus 40 (SV40) (and presumably SVs1–68), which occurred before the discovery and characterization of that group of viruses, again in Salk vaccines. The foamy viruses (spumaviruses), a subfamily of retroviruses closely related to lentiviruses, are sometimes referred to as the "crabgrass" of polio-vaccine manufacture. While most cultures used in vaccine production have been free of cultivatable foamy viruses for many years, it is not known what retroviral proviral DNA was present in early and late poliovirus preparations.

Poliovirus is produced in primary cultures of monkey kidney epithelium for vaccine use. The numbers and species of wild caught monkeys used are not known but were impressive in scope. In some instances, minced bits of tissue were used rather than monolayer platings. In all cases, cells other than epithelial cells are likely to have been present as a complex function of the culture process. There is no good evidence that any lentivirus will infect kidney cell cultures, but there is abundant evidence that either HIV or SIV can grow in cultured lymphocytes or macrophages that may accompany industrial cultures of epithelium taken from wild caught monkeys.

The early days of poliovirus vaccine manufacture were not controlled by the U.S. Food and Drug Administration (FDA), when foreign vaccines were to be used by humanitarian groups in the Third World. Many lots of vaccine were produced by low-bid contractors, who were likely to have been cost conscious and to have rejected either screening for other viruses or good laboratory practice with their monkey kidney cell cultures. Nor was there much in the way of ethical debate about the testing of vaccines on rural Africans (as was done in the Congo).

Determining whether HIV-1 and HIV-2 could have entered the population through vaccines is problematic when one considers the variety of animals used and the 40 years of vaccine administration. The only way to test the hypothesis is to test serum samples and vaccines from the period between 1952

and 1982 for the presence of proviral DNA, reverse transcribable RNA, and whatever antigens are identifiable on Western blots and enzyme-linked immunosorbent assays (ELISAs), if such material still exists at the FDA or elsewhere. Any polymerase chain reactions should include at least four primers each for HIV-1, HIV-2, SIV, and spumaviruses. Positive results would result in some remorse and a number of lawsuits.

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Cohen's account of my *Rolling Stone* article (*1*) about a hypothesis suggesting that the AIDS virus might have jumped the species barrier from monkeys to people via a contaminated polio vaccine was misleading in many respects. Cohen seems to burlesque my article as proposing the latest wild speculation or conspiracy theory. But I think any fair-minded reader will recognize that I took great pains not to demonize medical science in general or any individual researcher or scientist.

As for the assertion that there is not "a picogram of evidence" supporting the theory, that is flat-out wrong: there is a strong, if circumstantial, case. Moreover, at the time I wrote I expected that the hypothesis would be promptly and easily tested, since Hilary Koprowski assured me that samples of his original Congo vaccine were maintained in freezers at the Wistar Institute in Philadelphia. (I am now told he has recently said he was misquoted or misunderstood; the Wistar Institute has said so far it has been unable to find the vaccine material.)

Here is some of the evidence in favor of the theory. First, the vaccine in question was manufactured in a medium—primary monkey kidney tissue—known to be sometimes contaminated with monkey viruses, including simian immunodeficiency virus (SIV)—a member of the same lentivirus subfamily of retroviruses as the human immunodeficiency virus (HIV); Koprowski's recollection for Cohen that macaques from the Philippines and India were used to produce the Congo vaccine isn't quite what Koprowski told me several times in response to repeated inquiries: Koprowski said then that he did not know for sure what monkeys he used for the Congo vaccine and that, in any event, the kidneys had already been explanted from their hosts when they were received by the Wistar Institute. That circumstance might suggest that the donor monkeys' species and state of health would have been hard to determine.

On the question of the relationship between SIV and HIV, Gerald Myers of the Los Alamos National Laboratory and others have recently written (*2*) that as a "starting point for inquiry, we might ask whether human immunodeficiency viruses (HIVs) may simply be simian immunodeficiency viruses (SIVs) residing in and adapting to a human host. There is no clear answer to this question at this time; however, the notion is less far-fetched in 1992 than it was merely a few years ago. . . ." Myers *et al.* also note that lentiviruses "appear to have an enormous potential for diversification that is not witnessed in other retroviruses. As a consequence of this extraordinary plasticity, ecological and evolutionary dynamics become tightly intertwined with the lentiviruses."

Second, the vaccine was administered in the former Belgian Congo, Rwanda, and Burundi—a region of central equatorial Africa where seropositivity to HIV is among the highest in Africa, where some of the earliest AIDS cases were retrospectively identified by Western blot and enzyme-linked immunosorbent assay (ELISA), and where many scientists believe AIDS in humans originated. Third, the experimental vaccines were administered at a time, 1957 to 1960, that is consistent with genetic sequencing calculations by Myers and others for when the common ancestor of today's half-dozen major variants of the AIDS virus arose in humans.

Fourth, as Thomas Folks, chief of the Centers for Disease Control retrovirus branch, clearly explained to me, SIV may indeed infect lymphocytes, macrophages, and other blood products, contaminants ubiquitous in primary monkey kidney culture. The fact seems to negate the somewhat artificial experiment by Gerald Quinnan of the Food and Drug Administration attempting in vain to infect monkey kidney cells with SIV. One should consider how Quinnan's test compares with the much less pristine circumstances of vaccine manufacture.

Finally, readers of Cohen's article may have mistakenly concluded that I am the author of the theory. As I noted, the idea came to me from Blaine F. Elswood of the University of California–San Francisco. His paper, written with Raphael B. Stricker of the California Pacific Medical Center, has been accepted for publication by *Research in Virology*, a publication of the Pasteur Institute in Paris.

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1. T. Curtis, *Rolling Stone*, no. 626 (19 March 1992).
2. G. Meyers, K. MacInnes, B. Korber, *AIDS Res. Hum. Retroviruses* 8, 373 (1992).

Response: In my article, I noted the stir caused by Curtis's *Rolling Stone* article, and I looked at the scientific evidence supporting the hypothesis that polio vaccines were the origin of AIDS. It's beyond me why this would lead Fox to characterize *Science*'s contribution as "lightweight" and imply that I missed the principle of the debate. As the researchers I quoted agree, bridging the gap between the possible and the probable requires hard evidence. The existing evidence, including tests of poliovirus seed stocks, more than 20 vaccine lots, and serum samples from 250 vaccine recipients (*1*), makes it appear highly improbable. Although these tests did not include Hilary Koprowski's "Congo vaccine" highlighted by Curtis, they still support the null hypothesis.

When Fox recounts poliovirus vaccine history to buttress his argument, he clouds the point Curtis explored and oversimplifies complicated events. The vaccine Curtis wrote about was made at Philadelphia's Wistar Institute, not some backwater lab run by a low-bid contractor in a loosely regulated country. To say that deaths resulted from the "undercooked" Salk vaccine ignores the many other leading explanations for the so-called "Cutter incident," including sediment and filtration problems (*2*). And while it is likely that early polio vaccines would have been more rigorously evaluated before going into humans had the Food and Drug Administration existed, Fox leaves the incorrect impression that no government agency evaluated the safety of these preparations. The Laboratory of Biologics Control at the National Institutes of Health evaluated batches of the Salk vaccine as far back as the 1954 field trial.

Curtis takes me to task for asserting that there is no evidence backing the theory and then once again offers his speculations. There's no there there. Where is a vaccine lot supposedly made in macaque kidneys that contains lentivirus? Beyond the gross regional argument, where is the epidemiology showing a link between a group of polio-vaccine recipients and AIDS? Where is a monkey naturally infected with *any* strain of the human immunodeficiency virus–1 (HIV-1)?

I agree that the scenario is possible. But Curtis—especially by citing Myers and Folks, two researchers who are highly skeptical of the thesis—seems to be exploiting the fact that the nature of science is to never say never. Curtis uses Myers's contention that SIV might have been the parent to HIV in humans, but how does this support the polio-vaccine theory any more than the cut-hunter theory that Fox spells out? Also, as Myers wrote in the same paper Curtis cites, genetic sequencing data suggest that the HIV-1s known today may have diverged from a common ancestor (which may well have been an HIV-1 incapable of infecting monkeys) 30 to 50

years ago. "In the absence of more direct evidence about the emergence of HIV-1s," the paper continues, "this inference remains decidedly tentative." As far as the types of monkeys Koprowski used, I based what I wrote both on what he told me and on what he published at the time (*3*).

There *is* a real problem with undetected viruses contaminating primary cell cultures that are used to make vaccines. But, given the evidence to date, there also is a real problem linking that issue to the origin of AIDS.—**Jon Cohen**

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2. J. Salk, *Am. J. Publ. Health* **46** (no. 1), 1 (1956).
3. H. Koprowski, *J. Am. Med. Assoc.* **178**, 151 (1961).

■

Correction

I would like to correct a misattribution in the 10 April "This Week in *Science*" (p. 155) in the discussion of our report in the same issue (p. 243) (*1*). We (*1*) did not inject lithium into cells of the early frog embryo and show that it disrupts mesoderm development. Rather, this was first done by Kao, Masui, and Elinson (*2*), and in later work Gimlich and I (*3*) extended these studies and demonstrated that *myo*-inositol counteracted lithium's effect. In our study of lithium-sensitive polyphosphoinositide cycle activity during mesoderm induction (*1*), we added Li^+ to the bathing medium; no microinjections were performed.

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2. K. R. Kao, Y. Masui, R. P. Elinson, *Nature* **322**, 371 (1986).
3. W. B. Busa and R. L. Gimlich, *Dev. Biol.* **132**, 315 (1989).

Corrections and Clarifications

In Joseph Palca's article "The case of the Florida dentist" (News & Comment, 24 Jan., p. 392), it should have been made clear that when Barbara Mishkin was indirectly quoted as saying that data gathered by government scientists is fair game for Freedom of Information Act requests, she was speaking of data generated by scientists in the National Institutes of Science intramural research program, unless those data fall within one of the statutory exemptions.