

Book

Monkeys, viruses, and vaccines

On any list of medical triumphs of the 20th century, polio vaccination is sure to rate a mention. In the 1950s and early 1960s, the shot and sugar-cube vaccines of Jonas Salk, and later Albert Sabin, offered people the first opportunities to protect themselves from a scourge as feared in its day as AIDS is in our own.

Few back then grasped that these vaccines might also be a huge, inadvertent, uncontrolled experiment in interspecies viral transmission. But from 1955 to 1963, according to a 1976 US National Institutes of Health (NIH)-funded study, 98 million Americans alone probably were exposed to polio vaccines contaminated with SV40—a monkey virus that can cause cancers in animals. Now, a July 7 report in *New Scientist* has raised fears that hundreds of millions of eastern Europeans, Asians, and Africans also may have been exposed to SV40 in Soviet-made polio vaccines. Michele Carbone of Loyola University Medical Center, Chicago, USA, announced at the 2004 Vaccine Cell Substrates meeting (Rockville, MD) that the Soviet vaccine could have been contaminated until the 1980s. This is worrying since, despite 44 years of medical debate, epidemiological studies have yet to establish conclusively whether SV40 has or hasn't caused cancers in people.

When Salk developed his vaccine, instead of using human tissues, as did the scientists who won a Nobel Prize for first growing poliovirus in tissue culture, he used minced-up rhesus macaque monkey kidneys, which were remarkably efficient poliovirus factories. Those who sought to supplant Salk's formaldehyde-inactivated vaccine with live, attenuated oral vaccine also used monkey kidney cultures. Despite a manufacturing problem that, at best, left six children who received the vaccine paralysed in the arm, and despite concerns about wild simian viruses, Salk's shots were declared safe and effective after 1954 field trials. The next year, after grudging approval by sceptical government regulators, free Salk shots were made available throughout the USA.

By 1960, scientists and vaccine manufacturers knew that monkey kidneys were sewers of simian viruses. Such contamination often spoiled cultures, including those of an NIH researcher named Bernice Eddy, who worked on vaccine safety. In 1959, fresh from co-reporting that the mouse polyoma virus could cause cancer in other animals, Eddy tested the rhesus monkey kidney substrate used to make polio vaccine. She injected 154 newborn hamsters with extracts of the cell cultures: 109 developed tumours. Next, she ground up three of the tumours and injected the residue into other hamsters. The animals receiving injections from two of the three tumours developed cancers. But when Eddy put the substance back into the monkey cell culture, nothing happened, and she couldn't isolate the suspected virus.

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In *The Virus and the Vaccine: The True Story of a Cancer-Causing Monkey Virus, Contaminated Polio Vaccine, and the Millions of Americans Exposed*, Debbie Bookchin and Jim Schumacher report that in 1960, when Eddy presented her results to her boss, a polio vaccine champion named Joe Smadel, he was livid and disbelieving: "Its implications—that something in the polio vaccine could cause cancer—was an affront to his career." Her discovery also threatened one of the USA's most important public-health programmes. "By 1960, tens of millions of Americans had been vaccinated against polio, and it was federal health policy that everyone should be vaccinated and continue to receive Salk booster shots."

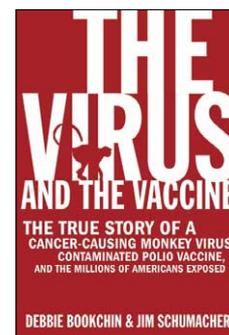
Eddy tried to get word out to colleagues but was muzzled and stripped of her vaccine regulatory duties and her lab-

oratory. However, two Merck researchers, Ben Sweet and Maurice Hilleman, soon identified the rhesus virus later named SV40—the carcinogenic agent that had eluded Eddy. In 1963, US authorities decided to switch to African green monkeys, which are not natural hosts of SV40, to produce polio vaccine. In the mid-1970s, after limited epidemiological studies, authorities concluded that although SV40 caused cancer in hamsters, it didn't seem to do so in people.

Fast forward to the 1990s: Michele Carbone, then at NIH, was working on how SV40 induces cancers in animals. One of these was mesothelioma, a rare cancer of the pleura thought in people to be caused mainly by asbestos. The orthodoxy held that SV40 didn't cause human cancers. Emboldened by a 1992 *NEJM* paper that found DNA "footprints" of SV40 in childhood brain tumours, Carbone tested human mesothelioma tumour biopsies at the National Cancer Institute: 60% contained SV40 DNA. In most, the monkey virus was active and producing proteins.

He published his results in *Oncogene* in May, 1994, but the NIH declined to publicise them. Doubters at NIH developed epidemiological evidence that showed no correlation between people who received potentially contaminated polio vaccines and increased cancer rates. Others suggested that the SV40 DNA was a laboratory contaminant. On the first point, the US Institute of Medicine reviewed all published epidemiological studies of SV40 and found them inconclusive. Meanwhile, Carbone had moved to Loyola University. There he discovered how SV40 disables tumour suppressor genes in human mesothelioma, and published his results in *Nature Medicine* in July, 1997. Studies in Italy, Germany, and the USA also showed associations between SV40 and human cancers.

Between 1997 and early 2003, say Bookchin and Schumacher, more than 25 published studies found SV40 in human mesotheliomas; 16 others found the virus in brain and bone cancers, lymphomas, and other cancers and in



The Virus and the Vaccine: The True Story of a Cancer-Causing Monkey Virus, Contaminated Polio Vaccine, and the Millions of Americans Exposed

Debbie Bookchin, Jim Schumacher. St Martin's Press, 2004. Pp 380. \$25.95. ISBN 0-31-227872-1.

kidneys and peripheral blood. As of 2003, SV40 had been found in human tumours in 18 developed countries. Bookchin and Schumacher claim that the rates of SV40-positive tumours seem highest in countries that used the greatest amount of contaminated Salk polio vaccine, including the UK, USA, and Italy.

As the SV40 story illustrates, until scientists know that a virus exists in cell cultures, they can't create a test to detect it and thus can't eliminate it from vaccines grown on those cultures. Might other potentially dangerous simian viruses lurk in primary monkey kidney cultures used for polio vaccines? Such concerns were relieved in January, 2000, when attenuated oral polio vaccine made since the 1950s by Lederle Laboratories on primary monkey kidney cultures was removed from the US market. Since wild-type polio cases had been eradicated in the USA in the mid-1970s, the eight to ten cases of paralysis caused yearly by return to neu-

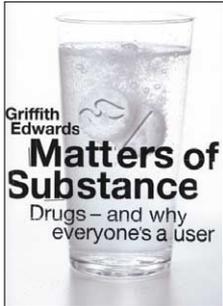
rovirulence of the live vaccine virus were finally deemed no longer acceptable. The vaccine was replaced with Aventis Pasteur's killed polio vaccine grown on a well characterised VERO monkey cell line. Thus the odds of further contamination by unrecognised viruses are thought to have been greatly reduced.

Bookchin and Schumacher complain that since the era of Bernice Eddy the NIH hierarchy has been consistently dismissive of evidence that SV40 from vaccines may have caused human cancers. Officials who had previously said SV40 was harmless were authorised to assess independent research that challenged that conclusion: "Not surprisingly, they reaffirmed their own previous wisdom." Accepting that SV40 is a human carcinogen, they continue, raises questions about what the government response should be: "A coordinated and extensive search for SV40 in other kinds of tumors, coupled with far greater efforts to study how the virus

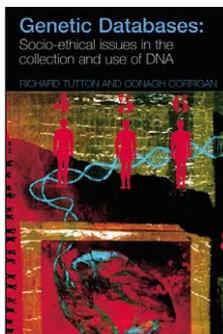
causes tumors? A crash SV40 screening program among populations most likely to have been infected? . . . An anti-SV40 vaccination campaign?" The problem, they continue, is that to undertake any of these options the government would have to admit that it should have acted sooner to protect public health.

In *The Structure of Scientific Revolutions* (University of Chicago Press, 1962) Thomas Kuhn suggests that paradigm shifts don't happen because opponents are converted by evidence, but rather because one generation of investigators and scientific leaders dies and is replaced by another. For credible epidemiological studies confirming whether SV40 from polio vaccines has caused human cancers, we may have to wait until a new generation is put in charge of the USA's health research bureaucracy.

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Matters of Substance: Drugs—and Why Everyone's a User
Griffith Edwards. Penguin Books, 2004. Pp 352. £18.99. ISBN 0-713-99689-7.



Genetic Databases: Socio-ethical Issues in the Collection and Use of DNA
Donagh Corrigan, Richard Tutton, eds. Routledge, 2004. Pp 224. £22.99. ISBN: 0-41531-680-4.

In brief

Book No drug is an island

"Posturing, fixed positions, monotonous repetition of untested assertions . . . too often that is the flavour of what passes for the debate on drugs." So opens Griffith Edwards, in his book on the pervasiveness of both legal and illicit drugs. Editor-in-chief of the journal *Addiction*, he argues persuasively that drug use is so embedded within social and historical contexts that prevention is maddeningly difficult. From the media-reinforced "glamour" of alcohol and tobacco, to the perversely "hip" status conferred on heroin or crack-cocaine users trapped in a deprived subculture, Edwards maintains that "drug use is a dimension of human activity which cannot be abstracted from the surrounding play". In other words, "No drug is a story unto itself".

In chapters baldly entitled Cannabis, Opiates, and so on, he surveys the historical appearance of these substances, and the ineffectual attempts to combat their influence. "When a drug arrives and is once taken up by a society, the likelihood is that it will not easily go away again." Drugs become symbols. "Champagne is a

symbol of good times . . . [giving a cigar] to a friend represents esteem and bonding." With illicit substances, the rituals of drug subculture reinforce their symbolic power, creating solidarity for users and giving mainstream society a convenient group to deplore.

Still, at the end, Edwards reluctantly plumps for keeping criminal law for drug control, but warns: "If the response to illicit drugs is to have credibility, far more attention must be paid to the problem set by licit drugs." No easy task, given the extent to which substance use, as cultural artifact or lifestyle adjunct, permeates society.

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Book DNA dilemmas

While the genetic therapies that the deciphering of the human genome was supposed to deliver have been slow to materialise, huge leaps have been made in disease aetiology. Undoubtedly, gene-based therapies and prophylactics will follow, but only after the construction of

large databases of genetic information. Much of this information is sensitive or stigmatising, and researchers are invariably unsure as to how it will be used in the future. We urgently need a broad, international public discourse on the social, ethical, and legal implications of these databases.

Genetic Databases could jumpstart this dialogue. For example, what is the best way to view the genetic sample? Is it a gift, whose donation severs ties with the giver and establishes property rights for the donee? Or is it an entrustment that the researcher holds for the participant? Is informed consent possible when future research directions and implications are unknown? Can we trust researchers not to abuse our genetic information—even after we have died? With deep insights and copious research *Genetic Databases* comes up with plausible (if not always practical) recommendations for ethics committees, scientists, policymakers, and concerned citizens everywhere.

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