Dutch AIDS Researchers Feel Heat of Publicity

A paper describing a way to block HIV infectivity brought the authors a lot of attention, but their work was flawed

Amsterdam—LAST SPRING, HENK BUCK AND Jaap Goudsmit were the darlings of the Dutch media. Buck, an organic chemist at Eindhoven Technical University, and Goudsmit, a retrovirologist at the University of Amsterdam, had just published a paper indicating that they had devised a way to block the infectivity of human immunodeficiency virus (*Science*, 13 April 1990, p. 208). A year later, they are still attracting publicity, but of a less flattering kind: Four widely reported investigations of their work, the last of which was published earlier this month, have demolished all the claims made in their paper. The affair has resulted in Buck's early retirement and widespread criticism of the media hoopla initially generated by Buck and Goudsmit's findings.

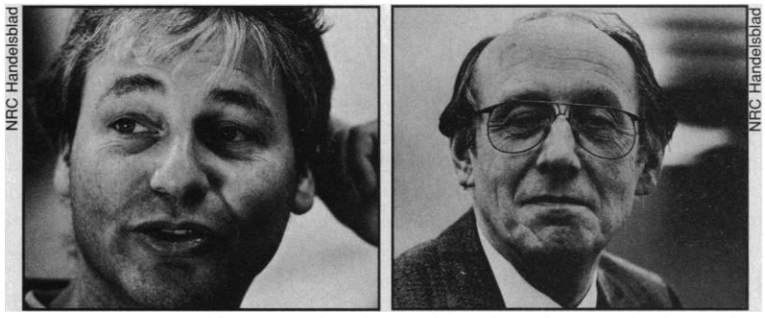
Their paper described a way to disable part of the AIDS virus's genetic machinery. Buck synthesized short stretches of DNA with sequences that would bind to specific portions of the HIV genome, and modified them by so-called phosphate methylation. The modified pieces of DNA were then hybridized to parts of the virus's DNA. The result, Goudsmit showed, was that the virus lost its ability to infect fresh cells.

When the paper was published, Buck, enjoying the limelight, appeared on Dutch TV news shows as well as radio talk shows and expressed confidence that his strategy would result in a treatment for AIDS "in a few years." However, his incautious statements angered fellow researchers and some AIDS patient organizations, who said the results were completely irrelevant to clinical practice. Even if the method proved effective outside the laboratory, it would take years of animal and human trials before any patient could be treated, they pointed out.

Overselling the implications of their work turned out to be the least of Buck and Goudsmit's problems, however. Their results encountered a firestorm of scientific criticism. Colleagues in Buck's department had been expressing doubts about the whole Buck-Goudsmit approach long before publication. In particular, Stan van Boeckel, an organic chemist and colleague of Buck's at Eindhoven, insisted that Buck's synthesis, as described, could never have yielded modified DNA of the purity Buck claimed. Buck ignored van Boeckel's critique, however, and van Boeckel resigned shortly after the *Science* paper was published.

Prompted in part by van Boeckel's departure, the administrative head of the faculty at Eindhoven commissioned three senior faculty professors to investigate Buck's methods and results. Their conclusion, published on 30 August 1990, more than confirmed van Boeckel's charges: Buck's samples were not merely impure, the panel reported, they contained no detectable modified DNA at all.

As a result, in September, the faculty of chemical technology, backed by the governing body of the university, relieved Buck of his administrative duties as dean of faculty and chairman of the department of organic chemistry. Buck and Goudsmit also prepared a letter for publication in *Science* retracting Buck's part of the work.



In the spotlight. *Chemistry done by Henk Buck (right) was the first to be faulted; now Jaap Goudsmit's virology has also been negated.*

But that wasn't the end of the matter. One staff member and four Ph.D. students quit Buck's lab, and former co-workers complained about his autocratic management of the department. The Dutch newspaper *Het Parool* aired these complaints and reported additional problems with Buck's data that had not been investigated by the Eindhoven panel.

Partly as a result of these allegations, the governing body of the Technical University then asked two former Eindhoven professors to investigate further. Their report, published last December, praised Buck's ability as a teacher but sharply criticized his research management. As for the *Science* paper, the panel was particularly critical of Buck's publication of a proton NMR spectrum of the alleged modified DNA, calling it highly atypical and anomalous, and selected from a large set of unusable measurements. Publication of this spectrum, said the panel, "certainly bordered on fraud." Before the committee reported, Buck took early retirement after acknowledging problems with his data but claiming he had made "an honest mistake."

Meanwhile, yet another Dutch newspaper became immersed in the affair. An early draft of the letter of retraction sent by Buck and Goudsmit to *Science* was given to the newspaper *NRC Handelsblad* and prompted the paper to launch its own inquiry. At issue: Why was only Buck's work being retracted and not Goudsmit's observations of antiviral activity? The newspaper commissioned a virologist, an immunologist, and two molecular biologists—all experienced in the techniques used but none working on AIDS—to scrutinize Goudsmit's virology. The panel focused on two specific questions: How could samples that contained no modified DNA still block HIV infectivity? And why had control experiments not detected the absence of the DNA? Their conclusions, published in September, were that the data were "fragmentary" and "misleading," and the claims "poorly substantiated," mainly because of a lack of essential controls, the panel reported.

In the original letter of retraction, Goudsmit had attributed the blocking of infectivity to an unknown DNA modification or to the "potentiating effect" of an equally unknown non-DNA by-product. The panel found these speculations particularly flimsy, and argued that Goudsmit should have retracted his own work too. Two days later, Goudsmit decided to remove his "virological speculation" from the letter, which was then already scheduled for publication. When it appeared (*Science*, 5 October, p. 125), the final sentence was retained: "There is no evidence to suggest that the observed antiviral effects should be ascribed to the phosphate methylation of natural DNA." In other words, the virus was inhibited, despite the lack of modified DNA.

If Buck and Goudsmit thought the revised letter of retraction would lay the affair to rest, they were mistaken. The *NRC Handelsblad* investigation led Jan van der Noordaa, head of the virology department of the

Amsterdam Medical Faculty and Goudsmit's superior, to acknowledge that an official university investigation of Goudsmit's work would be desirable. Goudsmit agreed in order to clear his reputation. Two months later, at the end of November, the faculty appointed a committee under Alex van der Eb, a professor of molecular biology from Leiden, to investigate further. The committee visited Goudsmit's lab, talked to researchers there, and scrutinized lab notebooks and other documents. Its report, published on 1 March, corroborated earlier criticisms and unearthed a number of other flaws.

The committee reported, for example, that some results were based on a single experiment, rendering the claim of reproducibility "not justified." It also concluded that Goudsmit and his virology team had selected favorable data—in one case they carried out two identical experiments but published only the one that supported their claims—and presented measurements of the DNA and proteins in a misleading way. Moreover, essential virological controls were missing, and controls for cytotoxicity were insufficient. Finally, the panel said Goudsmit omitted from the main table results from a control with random bits of modified DNA—as opposed to DNA targeted at HIV—that flatly contradicted the main claim of specific inhibition.

The Medical Faculty has accepted the report's conclusions and has asked for "guarantees to forestall future repetition." It has also acted on a suggestion in the report that Goudsmit's "heavy workload" prevented him from properly supervising his co-workers; new postdocs and senior staff have been asked to help with supervision. But because the faculty considers the episode a "lapse," it has decided to take no action against Goudsmit or his co-workers. Goudsmit has not commented on the report.

Van der Eb's report blames the great social importance of the fight against AIDS and the high publication pressure in the field for the errors of the Amsterdam virologists. But quite apart from its scientific aspects the Buck-Goudsmit affair has proved how dangerous it can be to base clinical claims on very early stages of basic research. Buck's speculation that his laboratory results would lead quickly to a treatment, AIDS patient groups and others have said, raised false hopes and, consequently, pointless suffering and disillusionment.

■ FELIX EIJGENRAAM

Felix Eijgenraam is a science writer with NRC Handelsblad *in Rotterdam who covered these events for the newspaper.*

Committee Treats Healy Gently

"We're not usually this nice," Senator Barbara Mikulski (D–MD) said last week at hearings on Bernadine Healy's nomination to be director of the National Institutes of Health. Mikulski had just tossed Healy an easy question—or as Mikulski called it, "a softball"—about her views on women's issues. Most other members of the Labor and Human Resources Committee, including chairman Edward Kennedy (D–MA), also gave Healy an easy time, and there now seems little doubt that the Senate will approve her for the nation's top biomedical research job.

A Harvard- and Johns Hopkins-trained MD, Healy currently heads the 400-staff Research Institute of the Cleveland Clinic Foundation and also works in the clinic's cardiology department. Well briefed on the political side of the NIH job, Healy herself introduced the one issue that might have brought her some right-wing opposition: She said she was aware that the Administration had imposed a moratorium on fetal tissue research and "I am prepared to support [it]."

Bernadine Healy

The only awkward moment in the hearing came when Senator David Durenberger (R–MN), himself recently censured for accepting free trips and gifts, probed Healy's views on conflict of interest rules. Durenberger read a news item that described Healy as being one of a group of scientists who had owned stock in the Genentech Corporation while involved in a review of its product, Tissue Plasminogen Activator. In response, Healy said: "I was not a TPA investigator while I owned stock...I have specifically avoided holding stock in a company for which I was testing a product." She said she had purchased the Genentech stock in this case "2 years after" her work for the TPA review panel was finished. However, she agreed that researchers sometimes get in trouble because they fail to realize that "perception is as important as reality when you're dealing with public trust." She is in favor of having clear "guidelines" to help NIH employees and grantees avoid conflicts.

In answering a related question, she said that it was an "outrage," if true, that universities like Stanford have been charging the government for parties, yachts, and antique furniture billed through the indirect cost allowance on research grants and contracts. She reminded the senators, however, that scientists themselves are not involved in deciding what is charged to the government

As for Mikulski's question on women and research, Healy said that, if confirmed, she would try to promote women to positions of leadership in biomedical research and focus on health problems that afflict women—such as cardiovascular failure after age 65. Women have been neglected in the past, she said, and it would be good for research and for the public interest if NIH could shift its emphasis a bit.

In her prepared remarks, Healy said that her chief goal as director would be to bring talented young scientists to NIH and retain those already there. To illustrate how tricky it can be to foster good science, she told a kind of parable involving the lead characters from the play *Amadeus*. Mozart, she said, came across as an inspired artist, but also, at times, as "difficult, childish, nasty, and unconventional." Salieri, on the other hand, was easygoing, "talented in a workman-like way," and popular at court. Salieri would probably have fared better than Mozart in the equivalent of today's peer review system, Healy said, but if medicine is to succeed, "the Mozarts must be allowed to flourish" as well. "Energetic and irreverent youth must thrive along with the older and wiser heads," she said.

Although Healy didn't say who she had in mind as the Mozarts of NIH, the committee members listened attentively. Several said they would ask Healy to give written answers to some detailed questions before casting a vote. But, by the end of the morning, the committee seemed to be unanimously behind Healy's nomination, and that will be good news for those unnamed Mozarts.

■ ELIOT MARSHALL