

review process is completed, deny Asgrow's petition to commercialize the product.

"The squash is the first engineered crop proposed for U.S. commercialization that has considerable numbers of wild relatives in the U.S.," says Jane Rissler of the Union of Concerned Scientists (Washington, D.C.). "APHIS' review of this engineered crop is important. Yet APHIS' environmental assessment is fundamentally flawed, as it relies primarily on an armchair analysis of risks rather than on experimental data." Rissler says that, since the U.S. and Mexico are so rich in wild squash,

special care is needed to preserve this diversity.

Several academic scientists also criticize APHIS' assessment of Asgrow's ZW-20 squash. Norman Ellstrand, a geneticist at the University of California at Riverside, says that widespread use of the engineered squash runs the risk that some of the squash's wild relatives may change from "being an occasional weed to one that is more of a problem. If enhanced weediness occurs by gene flow from transgenic squash, the cost would be tens of millions of dollars of additional weed control in the U.S. and Mexico."

G.A. de Zoeten of Michigan State University (E. Lansing, MI) urges that a specific safety claim about ZW-20 within the APHIS assessment be carefully tested by experiments. In the assessment, APHIS concludes that there is little or no likelihood that novel recombinant viruses could crop up from engineered ZW-20 plants that are infected by wild viruses. de Zoeten argues that researchers need to conduct experiments that explicitly address this question before Asgrow's engineered squash is approved for commercial-scale release.

—Jeffrey L. Fox

## NIH reconsiders nitrites' link to AIDS

A consensus is developing that the connection between nitrites and AIDS goes beyond their promoting of HIV transmission and that understanding nitrite toxicity should be a priority of AIDS research.

GAITHERSBURG, MD—A decade after being rejected by the Centers for Disease Control and Prevention (CDCP, Atlanta, GA), the role of nitrite inhalants in AIDS, particularly in its most visible expression, Kaposi's sarcoma (KS), has again become a subject of serious investigation, as evidenced by the papers and discussion at a recent two-day technical review held here under the auspices of the National Institute on Drug Abuse (NIDA, Rockville, MD).

The meeting opened with Hank Wilson, an activist who founded the Committee to Monitor Poppers (San Francisco, CA) in 1981, providing a history of the use of nitrite inhalants—amyl, butyl, and isobutyl nitrite—by gay men. Wilson noted that, when the first cases of AIDS were reported, attention initially turned to nitrite inhalants, or "poppers," because these powerful oxidizing agents, vasodilators, mutagens, and carcinogens were used heavily, and almost exclusively, by the people getting sick, gay men. In the 1960s, a few gay men began experimenting with nitrite inhalants, which produce a sense of euphoria and facilitate anal sex by relaxing smooth muscles. By 1970, a new industry was marketing bottles containing mixtures of butyl and isobutyl nitrite and was conducting a massive advertising campaign in the gay press. Within a few years, hundreds of thousands of men were persuaded that inhaling nitrite fumes was a necessary component of their gay identity.

By 1983, after AIDS was diag-

nosed in people who had never used nitrites, and limited pharmacological studies failed to show any apparent nitrite immunotoxicities, interest in pursuing the possible links between nitrite use and AIDS diseases diminished. And when a viral cause of AIDS was announced a year later, such interest all but disappeared. As demonstrated at the NIDA meeting, however, this dismissal may have been premature.

Meeting participants were divided into those whose primary interest is in studying nitrite inhalants as an important risk factor for AIDS, because their use encourages transmission of HIV via unsafe sex, and into those who think that the mutagenic and carcinogenic nitrites function more directly, either causing AIDS alone or acting as cofactors of HIV. Both sides were supported by strong epidemiological correlations between nitrite use by male homosexuals and AIDS. For example, according to Jay Paul of the University of California at San Francisco, the highest risk for AIDS involves the use of poppers and four other drugs. And Lisa Jacobson of Johns Hopkins University (Baltimore, MD) reported that 60-70 percent of the several thousand gay men at risk for AIDS who participate in the Multicenter AIDS Cohort Study (MACS) have used nitrites.

In addition, those favoring a more direct role of nitrites in AIDS pointed to data from the MACS showing that HIV-negatives had, on average, 25 months of nitrite use, HIV-positives had 60 months of nitrite use, and

AIDS patients had over 65 months of nitrite use—an apparent dose-response relation. When asked whether there was even one gay AIDS case in the cohort who had not used drugs, a somewhat-surprised Jacobson replied, "I have never looked at the data in this way."

Harry Haverkos, acting director for clinical research at NIDA and chairman of the meeting, extended his original observations on the role of poppers in gay AIDS and reported an essentially exclusive correlation between nitrite use and gay KS. The hypothesis of Harold Jaffe of the CDCP that an "unknown infectious agent" is the cause of KS could not be reconciled with Haverkos' evidence that there was not a single confirmed case of KS from blood transfusions, which often contain infectious agents.

Dan Lewis of the National Institute for Occupational Safety and Health (Atlanta, GA) and Lee Soderberg of the University of Arkansas (Fayetteville, AR) reported that short-term exposure of mice to alkyl nitrite inhalants for 2 to 14 weeks caused reversible immune suppression. Lewis acknowledged, however, that the doses were too low and the exposure times too short to exclude irreversible, AIDS-like immune suppression, and he concluded that nitrites "should be considered a hazardous substance."

Peter Duesberg of the University of California at Berkeley, a proponent of the controversial drug-AIDS hypothesis, who attended the meeting as an invited observer, proved to

be far less controversial than expected. In collaboration with Otto Raabe, an inhalation toxicologist at the University of California at Davis, Duesberg has designed experiments to examine the immunotoxic and K/Sarcomagenic effects of long-term, 6- to 12- months, exposure of mice to nitrite inhalants. Duesberg argued that long-term exposure is critical to imitate the 65 months, or more, of nitrite use that precedes human AIDS, a time usually regarded as the latency period of HIV infection. Duesberg's experiments also propose to investigate the possible role of retroviral cofactors in nitrite-inhaling mice. Curiously,

even with endorsements by Haverkos and Daniel Koshland, the editor of *Science*, a grant application for these experiments was denied, and deemed unworthy of further review, by the NIDA just last December.

Finally, Robert Gallo of the National Institutes of Health (NIH, Bethesda, MD) surprised some attendees and panelists by arguing that HIV is not the primary cause of KS, although it may aggravate the condition once KS is caused by "something else." As to what that something else might be, Gallo favored a microbe that has yet to be discovered, though he allowed that carcinogenic nitrites could well be a pri-

mary cause. In the true spirit of scientific inquiry, quite different from the rancor of prior discussions of alternative causes of AIDS, Gallo called for funding of Duesberg's nitrite experiments.

The meeting closed with a consensus—clearly meant for the ears of William Paul, the new AIDS czar at the NIH—that connections between nitrites and AIDS go beyond their promoting of HIV transmission and that understanding nitrite toxicity should be a priority of the AIDS research agenda.

—John Lauritsen

*John Lauritsen, who lives in New York, is author of The AIDS War.*

## COMMENTARY ON ETHICS

LES ROTHENBERG

# Is corporate and analyst hype unethical?

"Investing in biotech stocks isn't for the timid. But the potential payoff may be worth it," stated a recent headline in *The Wall Street Journal*. The writer, Anne Newman, pointed out that, because most biotech companies have no products or earnings, their stocks are "enormously volatile" and subject to hard falls if the companies receive bad news.<sup>1</sup>

Newman cited numerous historical examples. Genentech's (S. San Francisco, CA) stock plummeted 59 percent in 1988 after disappointing sales reports. Centocor's (Malvern, PA) stock experienced a 62 percent one-day drop in 1993 after reports of high numbers of deaths in a clinical trial of its septic-shock drug, Centoxin. And last year Synergen (Boulder, CO) saw its stock drop 68 percent in a single day after the efficacy of its septic-shock drug, Antril, was questioned.

A recent example of this phenomenon involves two companies—Alpha 1 Biomedical (Bethesda, MD) and SciClone Pharmaceuticals (San Mateo, CA)—and their hepatitis B drug, Zadaxin thymosin alpha 1. On April 28, following an announcement by Alpha 1 of disappointing phase III clinical trial results for Zadaxin, the stock of Alpha 1 fell 68 percent, while SciClone's stock plummeted 59 percent.

These two companies have a symbiotic relationship that links the fate of their stocks. Alpha 1 is the manu-

facturer of Zadaxin, having purchased rights to the drug in 1991 from Hoffmann-La Roche (Nutley, NJ) and the Regents of the University of Texas (Austin, TX), the university where the naturally occurring, 28-amino-acid peptide was discovered in 1972 by Allan Goldstein, who is now Alpha 1's chairman.

SciClone hopes to establish itself as a marketer of other companies' late-stage, proprietary therapeutics and has no manufacturing facilities of its own. The company, founded in 1989, entered into a license and supply agreement in September 1990 with Alpha 1 by which it acquired worldwide marketing rights to Zadaxin except in the U.S., Europe, Canada, Israel, and Korea. The agreement required SciClone, in most instances, to purchase the bulk drug from Alpha 1 and gave SciClone no control over U.S. clinical trials of the product. SciClone and Alpha 1 have a history of disputes concerning this agreement and are currently involved in legal proceedings that, when concluded, could alter it. In fact, on April 8, in the first phase of arbitration proceedings, SciClone was awarded royalty-free manufacturing rights for the bulk drug.<sup>2</sup>

What's intriguing about SciClone is that it was the subject of unusual media coverage that in effect predicted 10 months in advance the very calamity to its stock price that occurred in April. Columnist Gene Marcial, who writes "Inside Wall

Street" for *Business Week*, featured SciClone in his column at least three times in an 11-month period. Some three months after it went public in 1992, Marcial approvingly pointed to the company as one that "daring pros are now buying into" and quoted an analyst from the investment house of Josephthal, Lyon & Ross (JL&R, New York), which took SciClone public, who predicted that the company would be profitable by 1994 and that its stock would more than double in price.<sup>3</sup>

A year later, Marcial was quoting a negative report on SciClone by Evan Sturza, editor of *Sturza's Medical Investment Letter*, that predicted that SciClone's stock "could plummet on any disappointing news" because its "dependence on a single drug candidate leaves little room for error." Sturza was also quoted as saying that SciClone had made "misleading" claims about the results of a phase II trial, the number of hepatitis carriers worldwide, and the nature of the market for an expensive drug in China, India, and Africa.<sup>4</sup>

Yet, three weeks later, as if to make amends for his negativity, Marcial was again quoting SciClone officials and analysts favorable toward the company in a very optimistic piece about SciClone's future.<sup>5</sup>

Once SciClone's stock fell, however, Sturza's analysis was recalled in two newspaper accounts. Milt Freudenheim of *The New York Times* mentioned Sturza's negative views,

Hype by any corporation, or its friendly analysts, doesn't serve the long-term interests of company shareholders or the biotechnology industry as a whole.