MEDICAL RESEARCH INSTITUTES

# Dana-Farber Death Sends a Warning to Research Hospitals

BOSTON—Its seamless combination of cutting-edge cancer research and compassionate care for patients has made the Dana-Farber Cancer Institute a standout in a city of world-class research hospitals. But last November, a seam ripped wide open, and Dana-Farber has been struggling to close it ever since. That month a dosage mix-up in an experimental chemotherapy regimen killed *Boston Globe* health columnist Betsy Lehman and crippled another Dana-Farber patient. Subsequent revelations by the *Globe* and various official inquiries pointed to a glaring institutional failure: The hospital's system for monitoring experimental drug doses did not work.

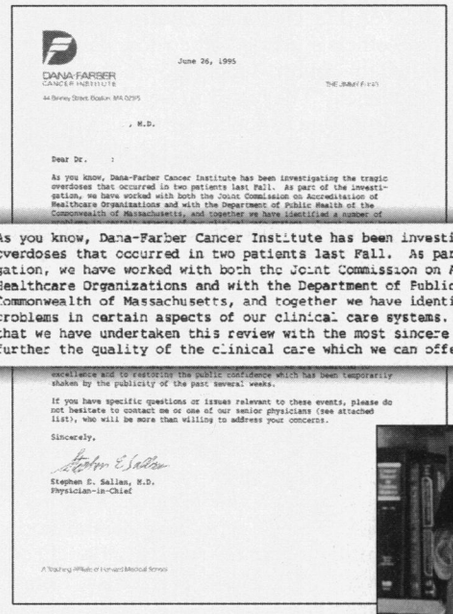
"Our inattention to detail was lethal," says Stephen E. Sallan, the hospital's new physician-in-chief. "It was hard for us to accept that." Sallan's appointment, however, is one sign of that acceptance. He replaces David Livingston, who resigned his post in the wake of the accidents, as did Dana-Farber's chief pharmacist. (Livingston continues as institute director and chief of a research division.)

Today the repercussions of that lethal inattention continue, both at Dana-Farber and at medical research institutions around the country. Lehman's death was "a very strong wake-up call" for a lot of institutions, says Martin Raber, physician-in-chief at the M. D. Anderson Cancer Center in Houston. Former National Cancer Institute (NCI) Director Vincent DeVita, who is chairing a committee investigating the incident, notes that research hospitals like Dana-Farber that are experimenting with dose intensification face a common problem: Dangerously high drug doses can be difficult to spot in such an environment. Adds Raber: "Cancer centers everywhere are at significant risk if they are not reviewing how they oversee clinical trials and assure quality in the delivery of drugs."

The need for such reviews was reinforced 2 weeks ago, when the *Journal of the American Medical Association* (*JAMA*) published the results of a study that found that major research and teaching hospitals did not have adequate systems in place to prevent such medication catastrophes. Dana-Farber has made changes—one of them being Sallan's appointment—to ensure such errors don't happen again; other institutions are following suit.

The events at Dana-Farber have sparked soul-searching in part because of the center's prominence as a leader in the cancer research community. The hospital received $82 million in research grants from the National Institutes of Health and other sources in 1994, and ranked seventh in total research funding from NCI. It also operates 57 beds for patients with advanced or rare forms of cancer.

Lehman, 39, and another patient, a 52-year-old woman whose name has not been released, were in two of those beds last fall. They were both taking part in an experimental, 4-day chemotherapy protocol for advanced breast cancer. The protocol was designed to test whether cimetidine, a common anti-



June 26, 1995

DANA-FARBER CANCER INSTITUTE

44 Binney Street, Boston, MA 02115

, M.D.

Dear Dr. :

As you know, Dana-Farber Cancer Institute has been investigating the tragic overdoses that occurred in two patients last Fall. As part of the investigation, we have worked with both the Joint Commission on Accreditation of Healthcare Organizations and with the Department of Public Health of the Commonwealth of Massachusetts, and together we have identified a number of

As you know, Dana-Farber Cancer Institute has been investigating the tragic overdoses that occurred in two patients last Fall. As part of the investigation, we have worked with both the Joint Commission on Accreditation of Healthcare Organizations and with the Department of Public Health of the Commonwealth of Massachusetts, and together we have identified a number of problems in certain aspects of our clinical care systems. I want you to know that we have undertaken this review with the most sincere desire to improve further the quality of the clinical care which we can offer to our patients.

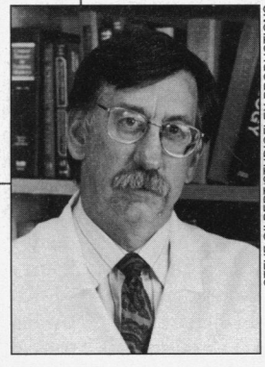
excellence and to restore the public confidence which has been temporarily shaken by the publicity of the past several weeks.

If you have specific questions or issues relevant to these events, please do not hesitate to contact me or one of our senior physicians (see attached list), who will be more than willing to address your concerns.

Sincerely,

Stephen E. Sallan, M.D.
Physician-in-Chief

A Teaching Affiliate of Harvard Medical School



STEVE GILBERT/STUDIOFLEX PRODUCTIONS

**Damage control.** Dana-Farber's new chief physician, Stephen Sallan, wrote to local doctors about clinical care concerns.

ulcer drug, would enhance the tumor-killing effects of a second drug, cyclophosphamide. But the summary of the plan used by the floor staff immediately responsible for patient care was ambiguous on a crucial point: whether the specified dose of cyclophosphamide—4000 milligrams times the patient's body surface area in square meters—was intended as the daily dose or as the cumulative, 4-day dose.

On the day the therapy was to begin, a physician employed as a research fellow followed the first interpretation and wrote orders prescribing the entire dose each day. Other doctors countersigned the orders. Although pharmacists were required to compare drug orders with a more specific written treatment plan on file, they prepared the drugs without detecting the error, and nurses administered them.

It was a ghastly mistake: The two women received 16 days' worth of cyclophosphamide in 4 days. Less than 3 weeks later, Lehman died from massive toxic injuries to her heart. The other patient survived but remains hospitalized with irreversible heart damage. (Three other women enrolled in the trial did not receive the overdoses.)

A data manager entering data from the trial into a computer discovered the errors on 13 February. Livingston informed the staff 3 days later and launched two internal reviews. Says Livingston, "Clearly, [the system for] drug-dose monitoring had failed." Livingston also ordered immediate steps such as the creation of a special oversight committee to screen all high-dose chemotherapy prescriptions and the "beefing up" of computer systems that flag unusual drug doses at the moment they are ordered.

But the hospital did not report the overdoses to the Massachusetts Department of Public Health (DPH) until 24 March, the day after a special report on Lehman's death appeared in the *Globe*. The article sparked a DPH reprimand for the reporting delay and led to investigations by DPH officials and the Chicago-based Joint Commission on the Accreditation of Health Care Organizations. In April, the Commission lowered Dana-Farber's accreditation status to "conditional," giving the hospital 6 months to implement a plan of correction. Also in April, DPH compiled a 33-page report detailing deficiencies in Dana-Farber's "quality assurance" plan, including poor analysis of trends in medication errors and the lack of a system to verify dose accuracy immediately prior to chemotherapy.

Dana-Farber matched changes in practice with changes in personnel. In May, the hospital's pharmacy director, Steven Steckel, resigned. Livingston ceded his post as physician-in-chief to Sallan, the former director of pediatric cancer treatment. While Livingston, in his multiple posts, had been required to divide his attention between research and clinical operations, Sallan will oversee patient care exclusively.

Sallan says the overdose cases will provoke both human and mechanical changes in the way experimental protocols are man-

aged. "Most important to us is to educate our staff at all levels, so that anyone who comes between the patient and the protocol—doctors, nurses, pharmacists, or anyone else—will understand the objectives and the expectations and what is beyond the realm of acceptability," he says. This means bringing the three groups together regularly to confer on the maximum daily chemotherapy dose for each patient. The institute will eventually purchase a fully computerized drug ordering system with the capability of "locking out" doses higher than protocols allow, Sallan adds, but it hasn't yet found a completely reliable system.

Changes like these will help protect against the opportunities for error created by Dana-Farber's research mission, say other medical researchers. "A high chemotherapy dose at a hospital where no dose-intensification programs are under way is more likely to be recognized as out of line. At a research institution, it's more likely to be missed," explains DeVita, now director of the Yale Comprehensive Cancer Center and head of a committee recruited by Dana-Farber to evaluate the institute's own review of the overdose cases.

DeVita says Dana-Farber is a "fine institution" that is "doing a lot of new things" to minimize such hazards. But while the new oversight committees and fail-safe checks are "appropriate," says M. D. Anderson's Raber, the crucial test will be whether future deviations "are reported quickly to the highest levels of the institution, so that they can be acted upon." At M. D. Anderson, Raber says, the Dana-Farber case has inspired administrators to "re-engineer" the oversight of clinical trials to include more staff involvement. "Physicians and nurses should never be giving care they're uncomfortable with just because the protocol says that's the way it should be done."

But the problems that lead to medical errors go beyond simple staff communication and are quite widespread, according to the *JAMA* reports, published on 5 July. Investigators from the Harvard School of Public Health and Boston's Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH) tracked mistakes in medication orders on 11 hospital floors at MGH and BWH, both affiliated with Harvard Medical School. The investigators detected 264 such errors over 6 months, only 83 of which were intercepted by attentive nurses or pharmacists. (Of the 181 nonintercepted errors, 39 resulted in injuries, although none were fatal.)

Physicians' written orders specifying the wrong dose, the wrong drug, or the wrong frequency of administration accounted for the largest slice of the errors, some 49%. But this form of human error isn't going to go away, says the study's lead investigator, Lucian Leape, a former surgeon now at Harvard School of Public Health, and hospitals must find effective ways of dealing with it. "What we have done from time immemorial is try to prevent medical error by making people ever more careful," says Leape. "We've got to get beyond that. Many errors are multifactorial and systemic rather than primarily individual." Because one of the hospitals lacked standardized forms, for example, drugs that provoked allergic reactions often slipped past as many as six separate checks of patients' allergies. Centralized and standardized records and computer systems that flag dose deviations are potential solutions, he says.

"These are not bad physicians and pharmacists. They are caught up in the same damn problems that are happening all over the country," says Michael Cohen, director of the Pennsylvania-based Institute for Safe Medication Practices, which tracks medication errors for several nursing and pharmacy journals. According to Yale's DeVita, even the most high-tech treatment centers are vulnerable to disaster unless checks against medication errors are "universally applied and unavoidable." In the wake of Lehman's death, that's a prescription research hospitals are very anxious to fill.

**–Wade Roush**

SUSTAINABLE DEVELOPMENT

# China Meeting Signals New Commitment

**BEIJING**—Environmentalism has never been a popular cause in China. Chairman Mao Zedong said environmental problems afflicted only capitalist countries, and Chinese officials bristled when foreigners suggested the country's rapid growth threatened the planet. "They used to say that if other countries were so concerned about acid rain and ozone depletion from coal, they should pay for the improvements," says one Western environmental specialist in Beijing.

But such hostility is fading. One clear sign emerged last week when the Chinese government, along with the Massachusetts Institute of Technology (MIT) and Beijing's Qinghua University—one of China's foremost science institutions—sponsored a 3-day international conference on sustainable development and the environment. Chinese officials took the occasion to demonstrate a high-level commitment to the cause. Deng Nan, physicist and vice minister of China's State Science and Technology Commission, said China is dedicated to international cooperation on environmental issues. Deng, the daughter of ailing Chinese senior leader Deng Xiaoping, also said that "the implementation of China's sustainable development will mainly depend on our own efforts."

The chief vehicle for China's efforts through the next century is Agenda 21, an initiative derived from the 1992 Rio meeting that moves away from a pattern of high input, high consumption, and high pollution. Its $4.1 billion budget assumes a 40% contribution from outside sources to pursue 62 research projects ranging from an experimental clean-technology paper mill in Shandong Province to a sustainable development computer network connecting Chinese universities to themselves and to sites in North America, Europe, and Japan.

The conference included reports by Chinese and foreign scientists that explored several pressing environmental problems. Chemical engineer Masayoshi Sadakata of Tokyo University cited findings that as much as 30% of the acid rain observed in western Japan can be traced to Chinese sources. But he noted that the use of existing wet-process coal scrubbing technology designed for industrial facilities will not solve the problem, because water is scarce in China and most coal is burned in small home stoves.

Instead, Sadakata is developing a coal briquette for home use that is formed under high pressure and contains added limestone. Although the briquettes are less effective than wet-processing technology in reducing sulfur dioxide emissions, he believes they are much more likely to have a significant impact on China's overall emissions.

In another presentation, MIT urban planner Alice Amsden said that the only way China can meet the projected cost of environmental recovery and protection is by tapping into the profits from continued economic growth. "A no-growth scenario holds no hope for the environment," she said. China's current 5-year plan to spend $4 billion on pollution controls falls far short of what is needed, she added, noting that it excludes the cost of developing new technologies and training people to use them and covers only a portion of the factories and work sites that need to be cleaned up.

Agenda 21 has also earmarked money for public awareness, in the hope that the interest shown by the central government will percolate down to the lower levels. The challenge is to show that the goals of the initiative are not incompatible with the country's hunger for prosperity. "Environmental protection is for many Chinese a big phobia," admits the program's coordinator, geologist Wang Qiming. "We are trying to teach people that they can conform with the needs of sustainable development and still make money."

**–Ted Plafker**

*Ted Plafker is a free-lance writer in Beijing.*