



Not everyone is gung ho about "a veritable tsunami of electronic information and electronic chores" that the Web and e-mail bring. Regarding the Food and Drug Administration's reaction to the death of Jesse Gelsinger from gene therapy, "[Gelsinger's death] need not have elicited heavy-handed overreaction by federal regulators." The historical message from five decades of research on sickle cell anemia is discussed: "What deserves our criticism is the overly optimistic promises, made by [Linus] Pauling and many after him, that knowledge of molecular processes alone would quickly and easily yield effective therapies at the molecular level." And to clarify misinterpretations of published research, authors explain their findings on room-temperature storage of hydrogen in carbon nanotubes.

E-Knowledge Hullabaloo—Or When Will the Glass Spill Over?

In his Editorial "*Science's* why not today problem" (*Science's* Compass, 7 Jan., p. 39), Floyd E. Bloom enumerates the changes that *Science* will institute in 2000, including electronic submission and review of papers. We, as scientists, are experiencing a veritable tsunami of electronic information and electronic chores. In the long run, this diversion from productive research and scholarly activities may have serious consequences for the scientific enterprise. With all academic institutions—universities, journals, professional societies, and granting agencies—transferring many functions to the Web, an assessment of this development seems in order.

I would classify our Web-based activities into three categories: (i) essential operations without which research could not go forward, for example, database searches; (ii) operations that save time and costs for both the institution and the scientist, for example, submitting reviews of articles and proposals electronically; and (iii) operations that save money and time for the institution but add to the work load of the scientist. An increasing amount of time seems to be spent with the third category. Some of these chores are inescapable. If a granting agency ordains electronic submission of proposals with programs that most of us are not familiar with, we shall have to comply. However, if an agency or journal asks me to review a proposal or manuscript on the Web, I request a mailed paper copy. I do not intend to read proposals and articles on the monitor, nor do I intend to invest time and resources to "download" them. We should, perhaps, paraphrase Karl Marx and declare: "Scientists unite! Let's break the shackles to our PC's and recover some of our time for creative activities." I guess that I also conform to those readers who, according to Bloom, "survey the literature the way they did last century" and who

have some reservations about the "e-knowledge hullabaloo." A paper copy of a journal may lead me astray from my narrowly focused personal key words, but I am bound to learn things that will widen my horizon.

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Gene Therapy on Trial

Eliot Marshall's News of the Week article on the aftermath of a gene therapy-related death last September at the Hospital of the University of Pennsylvania (17 Dec., p. 2244) does not provide some important context. The death of teenager Jesse Gelsinger, who was treated for ornithine-transcarbamylase (OTC) deficiency with an attenuated adenovirus vector into which a normal gene had been spliced, was tragic, but it need not have elicited heavy-handed overreaction by federal regulators.

In spite of intensive study during the past several months by researchers at the University of Pennsylvania and Children's National Medical Center in Washington, D.C., who carried out the trial, the exact cause of Gelsinger's multi-organ deterioration remains unknown. But that has not deterred the Food and Drug Administration (FDA), which oversees the clinical testing of all new medicines in the United States, from apportioning blame precipitously and prematurely. Before and during the 3-day conference convened by the FDA outside Washington, D.C.—and without knowing the cause of the problem—agency officials accused the researchers of various kinds of mistakes and misconduct: having admitted Gelsinger into the trial even though he did not meet eligibility requirements, having failed to immediately report information about two other patients who (long before the death) had experienced serious side effects, and having omitted information in the patient consent form about the

death of monkeys that had received a similar but much higher dose treatment. The first of these accusations is untrue. The second was misleading, in that although the toxicity in other patients had not been reported *immediately* after it occurred, the FDA had had that information long before Gelsinger's treatment. The third was well within the usual, acceptable standards of clinical research: the results of animal studies, especially those that use a much higher dose than would be administered to humans, are seldom mentioned in the patient consent form, and the fact that 17 human OTC-deficient patients had been treated in the Penn trials before Gelsinger without unexpected problems also argues against the importance of the monkey data. [Moreover, the consent form had received the required approval from the hospital's Institutional Review Board (IRB), whose sole responsibility is to protect the rights of human participants in clinical research.]

The FDA appears to be making an example of the Penn researchers to divert attention from its own culpability. If there was an identifiable mistake, it was in the choice of patients for these first attempts at gene therapy for OTC deficiency. Rather than stable adult patients, it would probably have been more prudent to treat OTC-deficient babies who were in coma and had a dire prognosis. That was the original intention of the Penn researchers, but their bioethicist, Arthur Caplan, said that parents of dying infants are "coerced by the disease of their child" and are, therefore, incapable of giving informed consent (1). In other words, the protocol treated and placed at risk a group that did *not* need the therapy, because the patients who might have benefited from it could not give genuine informed consent and were declared ineligible. The hospital's IRB or FDA officials could and should have reversed that decision.

Concern by FDA officials about Gelsinger's death is warranted. But what action is appropriate? Before all the data are in, certainly not a rush to judgment. Certainly not a trial by press conference of one of the most eminent and reputable gene therapy teams in the world. Certainly not the FDA's impulsive tightening of manufacturing and quality control requirements for academic researchers, which are traditionally (and appropriately) more relaxed than in drug companies, or the FDA's sudden freeze on the remaining seven Penn gene therapy protocols (not all of which involve adenovirus). These actions will likely inhibit the pace and amount of research done in academia.

Worse still, the FDA halted two gene therapy experiments being conducted by drug company Schering-Plough that used adenovirus—one for the treatment of liver cancer, the other for colorectal cancer that



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has metastasized to the liver—although (as noted by Marshall) scores of patients at the University of California, San Francisco and Cornell University have received adenovirus-mediated gene therapy for other indications, with no fatalities and only two serious incidents of toxicity.

While a treatment is still unproven and unfamiliar—the stage at which gene therapy is now—therapeutic success may be elusive. In the 1970s, for example, bone marrow transplantation was highly experimental. It was being performed at only a handful of medical centers in the United States, and success rates were abysmal. But clinical research has refined the technique and identified diseases for which the technique is useful: in thalassemia major, for example, a genetically determined disease of red blood cells, more than 80% of the patients are now cured.

In the Gelsinger case, the FDA has thrown its weight around inappropriately and prematurely. The result has been the intimidation of gene therapy researchers throughout the country and, possibly, costs to future generations of Jesse Gelsingers.

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Sickle Cell Anemia Therapy: Progress Since Pauling

In his Perspective on the importance of the 1949 paper on sickle cell anemia by Linus Pauling and his associates ("Sickle cell anemia, a molecular disease," *Science's Compass*, 19 Nov., p. 1488), Bruno J. Strasser repeats a theme that we believe is outdated. Strasser says that "extremely detailed understanding of the molecular etiology of sickle cell anemia...has contributed only modestly to improvements in therapy." This view is perhaps also an implicit criticism of the reductionist approach of the current era of molecular medicine that resulted from Pauling's work.

Research during the last three decades on how deoxygenated sickle hemoglobin polymerizes inside the cell, and on the specific inhibition of this polymerization by fetal hemoglobin, has led to the discovery of ways to increase the production of fetal hemoglobin pharmacologically in patients (1). Among the useful agents that have been studied are 5-azacytidine, hydroxyurea, recombi-

nant erythropoietin, and butyrate analogs, all of which augment fetal hemoglobin production in patients, with minimal short-term toxicity (2). Indeed, hydroxyurea was found to afford significant clinical benefit to adult patients (3) and has been approved for this use by the U.S. Food and Drug Administration.

Obviously, cure of sickle cell anemia by gene replacement is the ultimate, yet still distant, goal for this "first" molecular disease. However, rapidly improving methods of hematopoietic stem cell transplantation have effectively done this for many patients by allowing the permanent replacement of the abnormal cell population with normal genotype cells.

The transition from identification of an abnormal gene to an effective therapy for patients with inherited diseases is rarely simple or rapid. We should not, however, lose sight of the fact that molecular medicine is advancing in small but significant incremental steps, on the basis of the continuous feedback between basic and clinical research, beyond diagnoses toward effective treatments. We suggest that this is another historical message that one should ponder on this 50th anniversary of Pauling's work, as we near the completion of the DNA sequence of the human genome and the "postgenome" era of medical research.

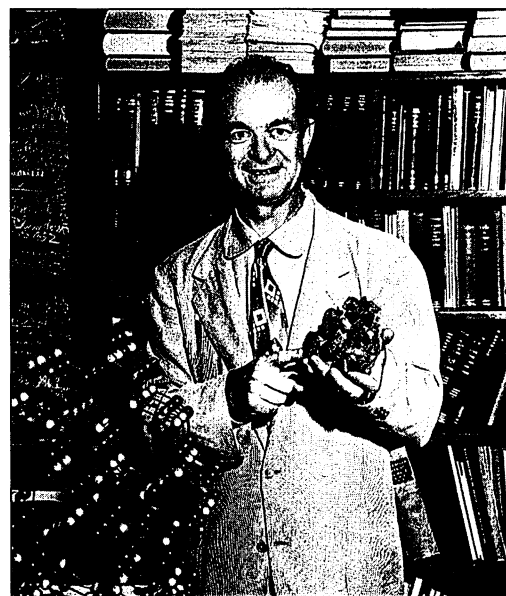
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Linus Pauling (1901–1994), one of the pioneers in the field of molecular medicine.

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