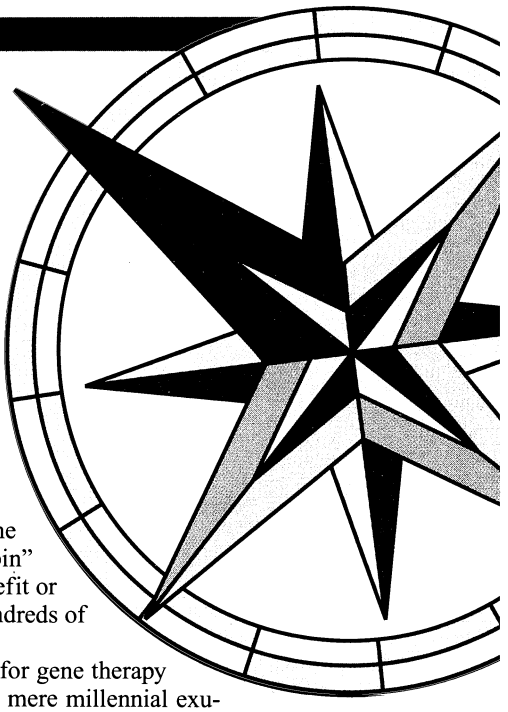

Gene Therapist, Heal Thyself

Leon E. Rosenberg and Alan N. Schechter

The late Dr. Robert Loeb of Columbia University's College of Physicians and Surgeons, one of the great clinicians and bedside teachers of the 20th century, often reminded medical students and residents of one of his cardinal clinical rules: "If what you're doing isn't working, do something else." At present, the ethos of the new field of gene therapy is clearly not working. Since the inception of its clinical trials a decade ago, gene therapy's leading proponents have given the field a continuous positive "spin" that is unusual for most medical research. Yet, despite repeated claims of benefit or even cure, no single unequivocal instance of clinical efficacy exists in the hundreds of gene therapy trials.

Perhaps of even greater concern are repeated predictions of a golden age for gene therapy in the near future. Do these claims deserve serious consideration or are they mere millennial exuberance? In the harsh light of the contemporaneously unfolding Gelsinger tragedy, which has already cast long shadows on the clinical, scientific, and ethical judgment of the investigators, on the state of the science dealing with viral vectors, and on the adequacy and coordination of the regulatory and oversight functions of the National Institutes of Health (NIH) and Food and Drug Administration, this kind of hype sounds bizarre. Yet such expressions of enthusiasm continue to be heard from major figures in the field. They have, much like a virus, integrated themselves into the culture and discourse of the field. Why is this a problem? We believe that unrealistic promises can affect the judgments of all concerned and lead to decisions that are not in the best interests of science, individual patients, or society.

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In our professional lifetimes, we have witnessed the slow, painstaking development of beneficial chemotherapy for many cancers and of effective organ and bone marrow transplantation. These advances came at the price of many deaths, both related and unrelated to the therapies, and much suffering early on. The leaders of these fields, however, sustained the confidence and support of the public by promising little and delivering much. Thus far, gene therapy has done just the opposite.

If the genuine promise of human gene therapy—to benefit patients with many inherited and acquired disorders—is to be achieved, we urgently need self-critical evaluations of the problems as well as the prospects. This can happen if investigators planning clinical trials using gene therapy ask themselves if they or their families in similar circumstances would volunteer for the proposed investigation. This can happen if those responsible for every current gene therapy trial (almost 400 in number) pause to assess the ratio of benefits to the risks, the care they are taking in communicating with trial participants, the timeliness and safety of their approach, the accuracy of their claims, and the responsibility they have to report untoward events, regardless of their effect on grant funding or investor confidence. This can happen if all members of the burgeoning American Society for Gene Therapy (now numbering more than 2000) pledge themselves to sound, disciplined science in the public interest and eschew uncritical winner-take-all gambles.

We also believe that more stringent guidelines should govern potential or real conflicts of interest. When individual investigators in academic institutions who are engaged in gene therapy trials have equity interests in gene therapy companies funding those same trials, as happens frequently today, the objectivity required for dispassionate clinical judgments is severely tested. Just as disturbing, such conflicts of interest may involve institutions as well as individuals.

At the dawn of the 21st century, Loeb's admonition is appropriate to the entire field of gene therapy, where neither the rhetoric nor the results are "working" now. We hope Loeb's advice will be heeded for the sake of the many children and adults whose lives and health might be improved or saved by this technology. Perhaps an old clinical dictum can help rescue a new clinical discipline.

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