

# The Trials of Gene Therapy: Ethical Issues in the Death of Jesse Gelsinger

## *Study Guide for the play "Eli's Gift"*

**By Nathaniel Binzen**

*The play "Eli's Gift" is a fictionalized story based very closely on the death of Jesse Gelsinger in 1999 at the University of Pennsylvania's Institute for Human Gene Therapy. All of the public events in the play mirror those of Gelsinger's death and its aftermath; some of the statements in the play are taken verbatim from the public record. However, all private dialogue, and the inner motivations imputed to characters, are entirely fictional, and are intended to dramatize some of the ethical and scientific issues of gene therapy today.*

*This study guide is intended to provide a basis for class discussion or further study. For that reason, it describes each concern and raises questions about it, without overlaying any forceful judgements.*

*The first section is a brief case history, outlining the short history of somatic cell gene therapy, the events of Jesse Gelsinger's life and death, and the consequences that followed. The second section is the heart of this study guide: a series of ethical issues, concerning medical protocols and procedures, the risks of cutting-edge technology, the regulatory environment, and commercial and financial influences on the practice of gene therapy in America. Each item includes discussion questions. The final section renders some judgements with an eye to the future.*

## **Case history**

On September 17, 1999, 18-year-old Jesse Gelsinger died, just four days after getting an experimental infusion of trillions of genetically engineered viruses from the University of Pennsylvania's Institute for Human Gene Therapy. Gelsinger, who had an inherited liver disorder, was the first person known to have died directly as a result of gene therapy. On November 3, 2000 the University of Pennsylvania announced an out-of-court settlement with Gelsinger's family, after disclosures of apparent wrongdoing, such as failures to notify the FDA of problems, overridden protocols, and questionable informed consent forms.

### ***Somatic cell gene therapy in the 1990s***

Somatic cell gene therapy tackles somatic cell genetic disease, i.e., diseases that arise from mutations in critical portions of important genes. The effects of somatic therapy are not

transmitted to descendants of the patient.<sup>1</sup> Nearly 375 somatic cell gene therapy trials have gotten underway in the United States since the first one was approved in 1990.

This study is not concerned with the ethical status of somatic cell gene therapy to cure serious disease *per se*. The practice is quite widely accepted by bioethicists, religious groups and government commissions as ethically acceptable in principle. The view has increasingly taken hold that somatic cell gene therapy “poses no new ethical problems”<sup>2</sup> and is a “natural and logical *extension* of current techniques.”<sup>3</sup> Ethicists have, however, been concerned about the uses to which somatic cell gene therapy is put, insisting that its use be restricted to human traits associated with disease – not, for example, cosmetic purposes.<sup>4</sup>

The introduction of gene therapy, starting in the 1990s, followed a more deliberate process of ethical discernment than the first use of virtually any other medical techniques that preceded it. Nonetheless, some critics have asked whether gene therapy was attempted in humans too soon. They note that available vectors are relatively primitive and that “many of the protocols...probably would not have been funded if the protocols had been reviewed according to the stringent standards of the usual NIH grant application process.”<sup>5</sup> And the results have been a disappointment. No reliable medical procedure or product has yet been produced from all these trials.

### ***The RAC and the regulatory environment***

Gene therapy has been monitored and governed by the Recombinant DNA Advisory Committee (RAC – pronounced “rack”), established in 1974 by National Institutes of Health (NIH) as a forum for public debate concerning genetic engineering. The scientific community had resolved from the early days of the gene therapy discussion that certain safety questions would have to be tackled before proceeding, and the RAC has been the body which has been responsible for that process. All information from approved trials is supposed to be made public through the RAC – but the committee’s effectiveness in that regard has come into question, as we shall see. Part of the problem may be that the lines of authority have at time been unclear: as the Food and Drug Administration (FDA) increasingly took on formal role of regulating gene therapy, some researchers seem to have increasingly regarded the RAC as merely an advisory body, and sidestepped it – especially when it comes to revealing commercially sensitive information.

### ***James Wilson and the Institute for Human Gene Therapy***

With a staff of 250, the Institute for Human Gene Therapy (IHGT) at the University of Pennsylvania is one of the largest gene therapy institutions in the United States. Dr. James

---

<sup>1</sup> Le Roy Walters and Julie Gage Palmer, *The Ethics of Human Gene Therapy* (New York: Oxford University Press, 1997), 14-15. Alternatively, “germ line gene therapy” would pass genetic modifications on to subsequent generations through reproductive cells. Germ line therapy is widely considered to be ethically off-limits at this time.

<sup>2</sup> Michael J. Reiss and Roger Straughan, *Improving Nature? The Science and Ethics of Genetic Engineering* (Cambridge: Cambridge University Press, 1996), 213.

<sup>3</sup> Walters and Palmer, 36.

<sup>4</sup> The question of what conditions are considered “disease” is, however, itself problematic, and if future gene therapy could “correct” other traits such as behavior, it could potentially raise genuinely new ethical problems.

<sup>5</sup> Walters and Palmer, 50-51.

Wilson, head of IHGT, was a “high-flying” pioneer of gene therapy in the 1990s.<sup>6</sup> In Wilson’s first human gene experiments, in 1992, treating a rare liver disorder called *familial hypercholesterolemia* (FH), he was looking for a way to introduce the desired gene into the liver cells of FH patients as an alternative to highly invasive and supply-limited liver transplants. He removed liver cells from the patient’s body and then, in the lab, infused those cells with retroviral vectors. Then he returned those cells, with their new genes, to the patient’s liver, demonstrating that gene therapy conducted *ex vivo* – outside of the body – could work in humans.

But Wilson believed that gene therapy would not have any medical relevance “until genes can be bottled, distributed, and then administered in vivo by ordinary medical practitioners” – what he calls *injectable genes*.<sup>7</sup> In the marketplace of medicine, the “medical relevance” of a procedure is closely related to its financial viability – not only in the sense that it is economic for society to support such a therapy, but that it has the commercial potential to make of a profit for the companies which invest in its research. Wilson also runs a private biotech firm, Genovo, of Chestnut Hill, PA (which holds patent rights, along with the University of Pennsylvania, to the treatment in which Jesse Gelsinger participated. He understood that his own research would eventually need to meet the requirements of the market.

### ***The OTC trial and the death of Jesse Gelsinger***

In 1999, Wilson and IHGT gained approval for a new human gene therapy trial, for *orthinine transcarbamylase* deficiency, known as OTC deficiency, or OTCD. OTCD is a rare hereditary metabolic disorder in which the liver is unable to process ammonia, a toxic breakdown product of protein. When ammonia builds up in the blood, it can travel to the brain, causing coma, brain damage and death. OTCD is most often fatal in infancy. The trial was intended to produce a life-saving cure for infants with OTCD, but the judgement was made that it was unethical to conduct the trial on infants, so adults with a milder form of the disorder were chosen instead.

Jesse Gelsinger was the 18th subject enrolled in the study in 1999. Gelsinger had the gene for OTC, but he had survived to adulthood managing his condition well through diet and drugs. Four days after receiving the experimental treatment in September 1999, Gelsinger was dead. His immune system evidently reacted fiercely in attacking the adenovirus carrier, though the precise reason why is still not entirely resolved. Following an adenovirus-induced fever, he suffered jaundice, and was comatose by the second evening after receiving treatment. Then a cascade of organ failures ensued: a blood clotting disorder, a catastrophic rise in ammonia levels, kidney failure, lung failure, and ultimately brain death.

### ***FDA Findings***

In January, 2000, in advance of hearing by the U.S. Senate’s Subcommittee on Public Health, the FDA released its comprehensive “Inspectional Observations,” finding serious deficiencies in the way the Penn trial was conducted:

---

<sup>6</sup> For dramatic purpose, the play melds the characters of Dr. Wilson and Mark Batshaw, the Principal Investigator of the OTC trial.

<sup>7</sup> Walters and Palmer, 28-29.

- Gelsinger's high ammonia levels at the time of the treatment should have excluded him from the study. He was approved on the basis of ammonia levels recorded when he *enrolled* in the study, two months prior to the actual treatment.
- The university had failed to immediately report to regulators that two prior OTC patients had experienced serious side effects from the gene therapy – information required in the study design.
- The deaths of monkeys given a similar treatment (in considerably higher doses) were never included in the informed consent discussion with the Gelsingers; indeed, they were removed from the forms, without the knowledge or approval of the regulating agencies.

### ***Consequences for University of Pennsylvania and IHGT***

At first, the University of Pennsylvania, the Institute for Human Gene Therapy, and James Wilson fought back vigorously against the FDA's charges, denying that the admitted "administrative lapses" uncovered by the FDA had anything to do with Gelsinger's death. But on May 24, 2000, after receiving the conclusions of an independent review panel, university president Judith Rodin announced that the IHGT would no longer conduct clinical trials on human subjects. Instead, its future work would be restricted to molecular and animal studies – permanently. In addition, the university took a number of actions applying to all its research programs. It made plans to:

- Assess necessary monitoring for strict compliance by all trials
- Review the ethical decision-making process for all human trials
- Create an Institutional Review Board (IRB) for gene therapy
- Review its IRB system generally
- Review its policies and procedures on conflict-of-interest

In November, 2000, the University of Pennsylvania settled a suit with the Gelsinger family out of court. Parties to the settlement included Penn, Genovo, Wilson and two of his co-researchers, including the study's Principal Investigator, and both of these colleagues' institutions.<sup>8</sup> The terms of the settlement were not disclosed.

### ***Consequences for the regulatory environment***

For the field of gene therapy, the year 2000 was dominated by the fallout of Gelsinger's death. In February, hearings by the Senate Subcommittee on Public Health raised questions about the wider regulatory environment. Senators were concerned about a regulatory environment in which the Penn researchers seemed to feel secure about taking dangerous shortcuts. Just prior to the hearings, the NIH acknowledged its failure to monitor gene therapy trials adequately, accepting that it should have recognized that the number of adverse reaction reports it had received from *all* trials was implausibly small. The committee chairman, Senator Bill Frist (D-St), called the problems of oversight "a multisystem failure."

---

<sup>8</sup> Rick Weiss and Deborah Nelson, "Penn Settles Gene Therapy Suit," *The Washington Post*, November 4, 2000 ([www.washingtonpost.com/wp-dyn/articles/A11512-2000Nov3.html](http://www.washingtonpost.com/wp-dyn/articles/A11512-2000Nov3.html)).

In March, the FDA and the NIH announced two new initiatives to shore up the safety of gene therapy trials. First, they would require new monitoring plans, to be conducted by the FDA directly, instead of by non-governmental Institutional Review Boards (IRBs) affiliated with the institutions sponsoring the trials. This tightening of regulation was based on the agencies' stated belief that "The UPenn program led to a death that might have been avoided if there had been a plan to monitor what they were doing." Future monitoring now also includes on-site inspections. Second, the agencies planned a series of meetings with gene therapy researchers to disseminate recent insights on safety.

In May, President Clinton announced, "a new legislative proposal to authorize civil monetary penalties for researchers and institutions found to be in violation of regulations governing human clinical trials." If the legislation passes, FDA will, for the first time for drugs and biologics, have the power to essentially fine researchers and their institutions, up to \$250,000 and \$1 million respectively. "This is a clear message," said Health and Human Services Secretary Donna Shalala, "that we intend to get serious."<sup>9</sup>

In December, the NIH proposed new guidelines for recombinant DNA research, which included:

- Expedited reporting of adverse reactions
- A reaffirmation that serious adverse event reports may not be kept confidential; trade secrets would have to be kept out of those reports
- Initiatives to protect individual patient information
- A new working group on safety.<sup>10</sup>

## Ethical issues and Discussion Questions

The Gelsinger case raises a number of bioethical issues in vivid relief. Important as they are, though, these issues are generally not *unique* to the field of gene therapy – they could just as well have happened in other areas of medical research.<sup>11</sup> Some of the ethical concerns involve general procedural features of research medicine, such as choices concerning appropriate research protocols for human studies, or informed consent. Some are especially characteristic of the present era of new high-technology medicine, and of the climate of investment and regulation in which it is emerging.

If somatic cell gene therapy is not obviously *qualitatively different* from other interventions, what is *distinctive* about it? One *technical* aspect of genetic research that is unique is the way that it has married the information contained in biological material to high-powered computing. One of the upshots of this work is an unprecedented realization of the extreme complexity of the interactions between genes, proteins, the body, and the environment. Research medicine has always been a matter of acting in the face of uncertain understanding. Yet, perhaps never before have scientists, aware of their own limited grasp, been so acutely faced with a challenge of such extreme complexity. Importantly, though, knowledge of genetics is advancing

---

<sup>9</sup> Larry Thompson, "Human Gene Therapy: Harsh Lessons, High Hopes," *FDA Consumer Magazine*, Sept.-Oct. 2000 ([www.fda.gov/fdac/features/2000/500\\_gene.html](http://www.fda.gov/fdac/features/2000/500_gene.html)), 2.

<sup>10</sup> National Institutes of Health website ([www.asgt.org/broadcast/nih\\_guidelines.html](http://www.asgt.org/broadcast/nih_guidelines.html))

<sup>11</sup> By contrast, there are a number of realms of ethical concern in genetics that are truly unique to the field, for example, gene patenting, or the ethical and theological status of the various types of stem cells.

very rapidly – it is a very good bet that we *will*, in a few years, know new and important things that we do not know now.

How is ethical judgement affected by the need to act in the midst of a rapidly progressing research program? Perhaps this laudable progress in our knowledge is a good reason to reject riskier procedures on human subjects – after all, it is quite likely that a better procedure is just around the corner. For this reason, it could be argued that there is no place for non-terminal subjects in gene therapy trials at this time. Additional caution may be warranted when we consider what the reasons for rushing might be: is one of the causes for haste a highly competitive business climate that confers great benefits for being first past the post?

Perhaps it would be fair to say, then, that what the Gelsinger case especially highlights is the way in which genetic research, with its bold embrace of action in the face of unknowns, *raises the stakes* of ethical matters that are already found in other areas of high-tech medicine. Gene therapy seems to heighten the importance of judgements and decisions that might elsewhere be taken to be more routine, or at least less vexing. Certainly the field is being treated with kid gloves – is that because it is somehow intrinsically different, or because its proponents perceive a need to protect the field from the unpredictable sensitivities of the general public? Whatever the case is, we shall see a number of ways in which this heightening is evident in the following pages.

## 1. Informed consent

To be adequately informed to give consent, participants in gene therapy trials often must take a short course in the technologies and biochemical processes involved. Paul Gelsinger described his son's and his understanding:

[Jesse] believed after discussions with the representatives from Penn that the worst that could happen in the trial would be he would have flu-like symptoms for a week. With the knowledge I had at that time I was comfortable enough to send my son to Philadelphia alone to participate.... Jesse and I were told in late July 1999 that a prior patient had shown a clinical improvement of 50 percent in her ability to eliminate ammonia from her system following gene therapy. At the RAC meeting... I discovered that no efficacy was achieved at all in this patient. We were also unaware of the severity of liver injury incurred by several of the patients prior to Jesse. I learned, after Jesse's death, that Penn had removed from the information they gave Jesse and me any reference to deaths of monkeys, which had previously appeared in their documents.... I learned that at least one other monkey died in a related study using the same adenoviral vector used on Jesse.<sup>12</sup>

Some would argue that the fact that monkeys died is in itself sufficient reason not to go ahead with a similar trial in humans. But we should put the deaths of experimental monkeys in perspective. In fact, it is patients' rights groups who have opened the door to riskier human research. In the fight against AIDS, terminally ill patients argued that sometimes the process by which even unproven treatments should be administered to human subjects should be speeded up

---

<sup>12</sup> Paul Gelsinger, testimony to U.S. Senate Subcommittee on Public Health, Feb. 2, 2000 (<http://labor.senate.gov/Hearings/feb00hr/020200wt/frist0202/gelsing/gelsing.htm>), 1.

– because many patients can die before an experimental treatment that might save their lives becomes available.<sup>13</sup> However, the Penn OTC trial was arguably not a matter of the comparable urgency to the AIDS crisis.

In any case, the fact is that the deaths of monkeys given a similar treatment were never included in Penn’s informed consent discussion. Furthermore, the patient entered the trial unaware of the serious side effects that two prior patients had experienced (Nor was this adverse information from the forms was not reported to regulators as required).

It is hard to disagree with the FDA’s finding that the researchers were wrong to omit this information from its informed consent disclosures. One response to these problems came from President Clinton in his proposals in May, 2000. Clinton announced “new actions designed to ensure that individuals are adequately informed about the potential risks and benefits of participating in research ....”<sup>14</sup>

- Why do you think the researchers removed the information?
- Are informed consent procedures in danger of being more a way of protecting the institution than of protecting the patient?<sup>15</sup>
- Are the problems with informed consent the core of this entire affair? Or do the serious problems go further? Is this, or any other problem that you see in this case unique to somatic cell gene therapy?
- Jesse Gelsinger had just turned eighteen, and so was legally responsible for consenting to his treatment. Is there a special obligation with a person of his age?

## 2. Choosing a vector: a place for the precautionary principle?

A number of different *vectors* – the vehicles used to carry modified genes into the body – have been employed in gene therapy. Nearly 80 percent of the gene therapy trials so far have used *viral vectors*.<sup>16</sup> Viruses, of course, are highly adept at delivering genetic material into cells. In viral vectors, the natural genetic contents have been removed and the desired genes inserted. The most popular choice initially has been a type known as retroviruses, which have been employed in nearly half of all clinical trials. But retroviruses have certain drawbacks, and do not work for all applications. So researchers have turned to domesticated versions of the flu-like *adenovirus*, again replacing its genes with the desired genes. Adenovirus has the advantages of being able to introduce genes into non-dividing cells, and of its ability to be massively reproduced – up to 100 trillion virus particles can be conveniently generated. Adenovirus has been used in about a quarter of the gene therapy trials to date.<sup>17</sup>

---

<sup>13</sup> As described by Karen Lebacqz (in class, May, 2001).

<sup>14</sup> Thompson, 2.

<sup>15</sup> Again, thanks to Karen Lebacqz for posing the question.

<sup>16</sup> Inder Verma testimony to U.S. Senate Subcommittee on Public Health, Feb. 2, 2000, 1.

(<http://labor.senate.gov/Hearings/feb00hr/020200wt/frist0202/gelsing/kast/patter/fda-zoon/verma/verma.htm>)

<sup>17</sup> Verma, 2.

The University of Pennsylvania researchers isolated the OTC gene and packaged it in an adenovirus. To reach the target cells in the liver, the Philadelphia scientists proposed to inject trillions of copies of the adenovirus directly into the hepatic artery, which leads to the liver (remember that many previous trials, including Wilson's earlier work, had employed the gene vector on cells *outside* of the body, then put that modified *tissue* back into the body, not the vector itself). Some members of the RAC objected to this method, fearing that direct delivery to the liver was dangerous. Nonetheless, "after a vigorous public discussion with the University of Pennsylvania researchers, the RAC voted for approval of the study."<sup>18</sup>

In the course of investigations following Gelsinger's death, reports emerged of adverse symptoms among adenovirus gene therapy patients in a number of other trials. These included drops in platelet counts, fever, and flu-like symptoms. Based on these findings, Dr. Savio Woo, president of the American Society for Gene Therapy, concluded that it is probably safe to inject the current adenovirus directly into tumors or muscle, but that putting it into the bloodstream is a matter for extreme caution.<sup>19</sup> The fact is, though, that these risks were to some extent known and acknowledged before the OTC trial at Penn began – as reflected in the heated debate over the procedure that occurred within the RAC and its stipulation that the method be changed.

Within a month of Jesse Gelsinger's death, the FDA ordered the pharmaceutical company Schering-Plough to halt two similar studies, both liver-related and using high doses of adenovirus. Schering-Plough later revealed that three liver cancer patients who had been treated the same way as Gelsinger – using the intra-hepatic artery route – had experienced serious side effects that might have been related to their therapy.<sup>20</sup> Some other groups voluntarily suspended similar studies in order to assimilate the lessons learned.

- What kind of risk assessment should the RAC use in approving a procedure that some of its members see as dangerous?

It was noted earlier that, in gene therapy, if a given procedure appears at all risky, it is likely that a better alternative will appear within a few years. Given that fact, extra precaution may be the prudent course. One useful ethical resource that might help in considering vector choices is the *precautionary principle*. The precautionary principle has arisen out of the realization that in some scientific endeavors, the enormously complex interactions among a number of systems and factors indicate that some effects may be unknowable in advance – or even indeterminate. An influential statement from the so-called Wingspread conference in Racine, Wisconsin, in 1998, is often cited as a definition of the precautionary principle:

When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically.<sup>21</sup>

Proponents of the precautionary principle believe that, when conditions of uncertainty dominate, important decisions should be taken out of the realm of science and into an ethical or

---

<sup>18</sup> Thompson, 4.

<sup>19</sup> Sheryl Gay Stohlberg, "A Death Puts Gene Therapy under Increasing Scrutiny," *New York Times*, Nov 4, 1999 ([www.nytimes.com/library/national/science/health/110499hth-gene-therapy.html](http://www.nytimes.com/library/national/science/health/110499hth-gene-therapy.html)) 3.

<sup>20</sup> Thompson 2

<sup>21</sup> David Appell, "The New Uncertainty Principle," *Scientific American*, Jan. 18, 2001, 18.

political process that takes uncertainty as a signal for caution to protect against possible harm. The efforts to tighten up regulations *after* the death of Jesse Gelsinger may portend a more cautious approach to gene therapy in the future, but they are not an application of the forethought that the precautionary principle advocates.

- Should a greater emphasis on the precautionary principle be given in gene therapy?
- If the precautionary principle had been operating, would the ongoing approval of adenovirus by the time of the IHGT's OTC trial have been as likely?

### 3. Research protocols and ethics advisories for human studies

The approval process for a gene therapy protocol is extensive. “It has to go through the Institutional Review Board (IRB), Institutional Biosafety Committee (IBC), RAC, and finally the FDA. At each step, there are clear cut rules and guidelines to which the investigator must adhere before approval can be granted.”<sup>22</sup> In 1985, the RAC established its extensive “Points to Consider” in assessing gene therapy protocols from both scientific and ethical perspectives, the most relevant of which are summarized in following central questions:

- What is the disease to be treated, and why is it a good candidate for gene therapy?
- What alternative treatments are available for this disease?
- What is the potential harm associated with the genetic intervention?
- What is the potential benefit associated with the intervention?
- What steps will be taken to ensure that the consent of study participants is both informed and voluntary?<sup>23</sup>

Every researcher who designs a gene therapy trial must answer these questions. Let us focus on the question, “What is the potential benefit associated with the intervention?” In the mid-1990s, a majority of the RAC members seem to have taken the view that a study must offer at least a low probability of benefit to patients who are invited to enter the protocol.<sup>24</sup> But the Penn OTC study illustrates a drift away from that standard, as it offered no lasting medical benefit to the participants, but only to others – infants who could not be subjects because of their

---

<sup>22</sup> Verma, Senate hearings, 3.

<sup>23</sup> Walters and Palmer, 149. Other central questions for gene therapy concern fairness of candidate selection and confidentiality. The influential principles-based approach developed by Beauchamp and Childress, the first four questions are related to the *principle of beneficence*, the duty to help others even as you expect others to help you. The final question, with its focus on the self-determination of participants, relates to the general principle of respect for the *autonomy* of persons, the duty to decide responsibly for oneself about one's own interests. For a discussion of these ethical principles, see Tom. L. Beauchamp and James F. Childress, *Principles of Biomedical Ethics* (4th ed.; New York: Oxford University Press, 1994).

<sup>24</sup> Walters and Palmer, 41.

vulnerability and their inability to give their consent. But there are reasons for the change: in this case, it was patients' advocates who argued that non-terminal OTC sufferers ought to be the subjects of the trial.

The Penn researchers met with a group of families with OTC children, called the National Urea Cycle Disorder Foundation (NUCDF). NUCDF's panel decided unanimously that the study should go forward and that, because the OTC trial was to develop a treatment for critically ill babies, "it should be conducted in adult, stable individuals who had partial deficiency, because these subjects could give informed consent and because they had metabolic abnormalities in which changes could be examined following gene transfer." Penn's own ethics advisors concurred. This approach was presented to the RAC and approved by the FDA.<sup>25</sup>

- Did the ethics advisory get it right, choosing adult, non-terminal subjects for OTC?
- Was the ethics oversight adequate at Penn in general? How might it have been strengthened?

#### 4. Disappointing results, and pressure for a breakthrough

"We must ask if there is an atmosphere of unrealistic expectations with regard to gene therapy."  
 – Senator Bill Frist, chairman of the U.S. Senate Public Health Subcommittee<sup>26</sup>

In the first 10 years of genetic treatment, the hyperbole has exceeded the results. No gene therapy products have yet come to market. There is an air of general uncertainty and risk in the field. "There was initially a great burst of enthusiasm that lasted three, four years where a couple of hundred trials got started all over the world," says gene therapy pioneer Dr. French Anderson, now at the University of Southern California. "Then we came to realize that nothing was really working at the clinical level."<sup>27</sup> In 1995, an NIH committee reviewing NIH's investment in gene therapy concluded that "Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host."<sup>28</sup>

Could this environment of disappointment have pushed Wilson and other researchers to go further faster, taking unwarranted risks to try and prove the method's viability and win needed praise for the field?

- Have the large technical deficiencies of the gene therapy process, and the disappointing results after ten years of hype, led researchers to tolerate greater risks and unknowns in their determination to arrive finally at something impressive enough to prompt continued funding?
- Would such behaviors be accentuated by the larger pressures of the globally competitive marketplace of medical research?

<sup>25</sup> Minutes of the Recombinant DNA Advisory Committee, 12/8 – 12/10/1999, 20.

<sup>26</sup> Senator Bill Frist, U.S. Senate Subcommittee on Public Health, Feb. 2, 2000, 1. (<http://labor.senate.gov/Hearings/feb00hr/020200wt/frist0202/frist0202.htm>)

<sup>27</sup> Thompson, 1.

<sup>28</sup> Stuart H. Orkin, M.D., of Harvard Medical School and Arno G. Motulsky, M.D., of the University of Washington in Seattle, in Thompson, 3.

Many of the questions raised in this study guide lead indirectly outward to the larger pressures of the globally competitive marketplace of medical research. In section 6, we consider how researchers' conduct is affected by commercial incentives. Here, let us consider how the industry and regulators are impacted by dependency on a market demanding its return. "Science has been commodified. What we've created in the last 10 or 15 years is a science that has a goal of global economic competitiveness," says Carolyn Raffensperger of the Science and Environmental Health Network.<sup>29</sup>

Paul Gelsinger, Jesse Gelsinger's father, described his perspective on these pressures to the Senate's Public Health Subcommittee:

I understand how important competition is in the world of business, I can understand the temptation to influence government, and I realize the desire of some to make a name for themselves. However, when lives are at stake, and my son's life was at stake, money and fame should take a back seat. The concern should be not on getting to the finish line first, but on making sure no unnecessary risks are taken, no lives filled with potential and promise are lost forever, no more fathers lose their sons.

- How do market pressures accentuate the perception of a need for more rapid progress in gene therapy?
- What ethical and regulatory philosophy would be most likely to secure long-term support for gene therapy – by protecting it from adverse results and the pressures that can bring them on?

## 5. Regulatory gaps and failures of adverse event reporting

In the aftermath of Jesse Gelsinger's death, the realization set in that many researchers were failing to report adverse events to the NIH as required. Penn researchers failed to immediately report that two patients had experienced serious side effects from the gene therapy – a disclosure required in the study design. Probably the clearest evidence that the system to protect research subjects was not working was that only 37 of 970 serious adverse events from gene therapy trials were reported to the NIH – fewer than 5 percent (a fact that Senator Bill Frist called "inexcusable").<sup>30</sup> Paul Gelsinger described the consequences of this illicit nondisclosure from his perspective: "I learned that a pharmaceutical company had conducted experiments similar to the one Jesse was in and had obtained adverse results, which, if disclosed, would have fully informed Jesse and me of the real risks in this procedure."<sup>31</sup> There were allegations of other unreported deaths caused by genetic treatments, at least six in all. Repercussions were felt at a number of institutions: in one example, the FDA suspended gene therapy trials by run by Tufts University School of Medicine in Boston, "because scientists there failed to follow protocols and may have contributed to at least one patient death."<sup>32</sup>

---

<sup>29</sup> Appell, 19.

<sup>30</sup> LeRoy Walters, the recently retired head of the Kennedy Institute of Ethics at Georgetown University and former chairman of NIH's Recombinant DNA Advisory Committee., in Thompson, 2.

<sup>31</sup> Gelsinger, 2.

<sup>32</sup> Thompson, 2.

One major reason for this widespread underreporting by researchers is that much of the information that would be revealed is considered commercially sensitive or proprietary (some companies reported only to the FDA, and labeled reports “proprietary” in direct conflict with NIH guidelines).<sup>33</sup> Another reason is that the regulatory structure left gaps in coverage between the FDA and NIH-RAC: researchers seemed to choose to which agencies, and on what terms, they would be accountable. For example, when the RAC approved the OTC trial, it called for the protocol to be revised to deliver the vector intravenously rather than through the hepatic artery. However, the researchers obtained approval from the FDA to use the hepatic route, then failed to come back to RAC to discuss the FDA’s decision.<sup>34</sup> In testimony to the Senate, a former RAC chairman noted the lack of coordination between the NIH and the RAC on the one hand, and the FDA on the other. He said that it was not clear whether the RAC was advisory to the FDA or not, and, if so, whether in a formal or informal capacity.<sup>35</sup>

- What caused the regulatory gaps? Was it just bureaucratic murkiness and unclear jurisdiction? Or was there an unwillingness to look too deeply, motivated by accommodations to commercial pressure and industry potential?

The former RAC chairman, LeRoy Walters, recommended that the role of the RAC in the oversight of gene therapy should be strengthened, including the restoration of its authority to approve and disapprove individual research protocols. That authority had been given over to the FDA in 1997, with the intention of re-forming the RAC into a policy-making body rather than a regulatory one.

- Should the authority of the RAC – or any governing body – be strengthened? And if so, in what ways?

## 6. Commercial incentives and the financial interests of investigators

In the aftermath of Gelsinger’s death, questions were raised about the financial interests of investigators, and whether these interests clouded judgement or influenced decisions that were made. Patents were held jointly by the University of Pennsylvania, individual researchers, and Wilson’s biotech firm, Genovo. No specific charges arose, but the appearance of possible mixed motives was widely noted.

These concerns are widespread throughout the medical research establishment. In August, 2000, Jane Henney, the FDA Commissioner of Food and Drugs, described her concerns about the financial arrangements that have become institutionalized in this field:

---

<sup>33</sup> Paul Gelsinger, 2.

<sup>34</sup> RAC minutes, 20.

<sup>35</sup> LeRoy Walters, Director of the Kennedy Institute of Ethics at Georgetown University and RAC member, testimony to U.S. Senate Subcommittee on Public Health, Feb. 2, 2000, “From October 1997 to the Present: How is the new system working?”, 1 (<http://labor.senate.gov/Hearings/feb00hr/020200wt/frist0202/gelsing/kast/patter/fda-zoon/verma/walters/walters.htm>).

The Bayh-Dole Act of 1980 gives grantee and contractor organizations title to inventions resulting from federal research funding. Thus, the Act encourages more cooperation between government, academia and the private sector, and provides incentives that stimulate the transfer of knowledge and technology that would lead to new product development. Relationships between industry and academia are also becoming more complex. Academic researchers now serve not only as clinical investigators, but also in the roles of sponsors of investigations, inventors named on patents, and product manufacturers .... Patients become increasingly vulnerable as individuals assume the multiple roles of physician, investigator and sometimes sponsor, and when research institutions stand to benefit financially as well. Legitimate questions arise about an investigator's objectivity, and concern for patients, versus his or her concern about the bottom line.<sup>36</sup>

The FDA issued new regulations in 2000 concerning financial disclosure by clinical investigators, which President Clinton described as "steps designed to address the potential financial conflicts of interest faced by researchers." Sponsors submitting applications to the FDA for review now must certify that the investigators have no financial interests in the product or the sponsor, or, if they do, they must disclose those interests.<sup>37</sup>

But beyond these requirements, Henney described a larger question for government regulators and the academic community, as they work together to participate in new product development: "How do we foster and maintain a culture of compliance where our commitment to human subject protection – and our respect for patients' well-being – are first and foremost?" She laid out a series of further questions with this concern in mind:

- Is it enough to inform human subjects of the investigator's financial interest in the outcome of a trial or the success of a particular product?
- Will disclosing that information to patient volunteers make the process any safer for them?
- Can financial conflicts be managed in a way that doesn't adversely affect patient safety or influence the objectivity of the research conclusions?<sup>38</sup>

## 7. Scientific hubris?

Perhaps this case, and much of the past decade of research, have been the Kitty Hawk of gene therapy – a flight into the unknown, portending a bright future, but using rather primitive means. In the early days of aviation, experimentation can and did lead to deaths. But gene

---

<sup>36</sup> Jane E. Henney, Ph.D, Commissioner of Food and Drugs, U.S. Food and Drug Administration, "Human Subject Protection and Financial Conflicts of Interest," Natcher Auditorium, NIH Campus, Bethesda, Maryland, August 15, 2000.

<sup>37</sup> Thompson, 2.

<sup>38</sup> Henney, 2.

therapy is not the same sort of act as trying to construct and pilot a flying machine. Both ventures involve risk, but the ethical responsibility of inventors for the patients volunteering in a medical trial is of a higher order: the ground of experimentation, after all, is *people* – their bodies and their lives.

One of the justifications of gene therapy as an extension of existing therapies, rather than a qualitatively different procedure – and thus of its moral ordinariness – is the perception that it is a “less invasive” approach than other interventions such as organ transplantation.<sup>39</sup> It even works with the patient’s own cells. But perhaps it is only through the physicalist bias of our medicine that we allow ourselves to imagine that changing the code of instructions that to some extent governs our bodies is not an invasive event. If a person’s genes were altered in a diabolical, debilitating way, would we still say that the procedure was, if nothing else, not invasive?

Regardless of the various concerns raised here, the gene therapy community continues to speak in highly optimistic terms about the future. The assumption is that, once the problems that have been revealed are resolved through tighter regulation and ethical oversight, the field will blossom. An article by Larry Thompson in the September-October, 2000, *FDA Consumer* magazine describes the mood:

Not all the news about gene therapy is bad. It’s true that dramatic cures have not been seen to date, but there are tantalizing signs that important advances may be just around the corner. “We do seem to have turned the corner,” says [Dr. French] Anderson, “and there are a number of clinical trials that are starting to show success.” Even as FDA increases its scrutiny of the field to ensure patient safety, there is a sense of advancement. “There is good progress being made,” [Director of FDA’s Cellular and Genetic Therapy Division Phillip] Noguchi says. “FDA thinks that gene therapy will work, but we don’t know for which disease. [Other recent trials] show that if you have the right disease, and can insert the right gene, you can obtain good results.”<sup>40</sup>

These assessments are probably correct. But they are also statements intended to maintain public confidence in an experimental procedure which has been rocked by the magnitude of its internal problems.

- What is the line between justified hopes and scientific hubris?

## Final Comments

I am not at all convinced that, thirty years, from now human beings will be playing with their genomes in anything close to the manner we have been examining here. We may find that genes are not the level at which we should medically intervene in the human makeup; the emerging field of proteomics may eventually reveal that today’s genetic manipulations are the modern equivalent of

---

<sup>39</sup> Walters and Palmer, 27.

<sup>40</sup> Thompson, 2.

stone-age technology. Our predecessors may look back in astonishment at the bluntness and intrusiveness of our interventions.

Perhaps new regulations and closer oversight can curb the risks that the system of competitive incentives seem to encourage in medical research. But I believe that only a far wider public airing of these pressures, and a greater societal consensus about applying the precautionary principle, could institutionalize a noticeably different “go slow” approach. Such a public discussion may be unlikely in America, because the competitive environment for the development of these technologies is global, and Americans are loathe to apply precaution if it means that foreign competitors could get a jump.

It is because of this possible short-sightedness that I would suggest that our society could use a more fully developed ethics for *managing a world of change dominated by world-transformative technologies*. Today, in the realm of genetic research and technology, change is the only constant. We need to better understand the implications of our situation, in which we focus massive resources in advancing technologies, for an enormous range of motives. It seems to me that this investment in change drives a concomitant experimentation with ethics. We are confronted not only with new scenarios for ethicists to consider, but with also new institutional mechanisms such as IRBs and the RAC; legislative and regulatory action in circumstances of uncertainty; and the unresolved practicalities of public participation and input. The death of Jesse Gelsinger has already helped to raise awareness of these issues; how far our society takes its lessons is still an open question.

## BIBLIOGRAPHY

- National Institutes of Health website ([http://www.asgt.org/broadcast/nih\\_guidelines.html](http://www.asgt.org/broadcast/nih_guidelines.html)).
- Recombinant DNA Advisory Committee, minutes, 12/8 – 12/10/1999 (<http://www4.od.nih.gov/oba/rac/minutes/1299rac.pdf>).
- Appell, David, “The New Uncertainty Principle,” *Scientific American*, Jan. 18, 2001.
- Gelsinger, Paul, testimony to U.S. Senate Subcommittee on Public Health, Feb. 2, 2000 (<http://labor.senate.gov/Hearings/feb00hrq/020200wt/frist0202/gelsing/gelsing.htm>).
- Henney, Jane E., “Human Subject Protection and Financial Conflicts of Interest,” presentation at Natcher Auditorium, NIH Campus, Bethesda, Maryland, August 15, 2000.
- Reiss, Michael J. and Straughan, Roger, *Improving Nature? The Science and Ethics of Genetic Engineering*. Cambridge: Cambridge University Press, 1996.
- Stohlberg, Sheryl Gay, “A Death Puts Gene Therapy under Increasing Scrutiny,” *New York Times*, Nov 4, 1999 (<http://www.nytimes.com/library/national/science/health/110499hth-gene-therapy.html>).
- Thompson, Larry, “Human Gene Therapy: Harsh Lessons, High Hopes,” *FDA Consumer Magazine*, Sept.-Oct. 2000 ([http://www.fda.gov/fdac/features/2000/500\\_gene.html](http://www.fda.gov/fdac/features/2000/500_gene.html)).
- Verma, Inder, testimony to U.S. Senate Subcommittee on Public Health, Feb. 2, 2000, 1. (<http://labor.senate.gov/Hearings/feb00hrq/020200wt/frist0202/gelsing/kast/patter/fda-zoon/verma/verma.htm>)
- Walters, Le Roy, and Palmer, Julie Gage, *The Ethics of Human Gene Therapy* (New York: Oxford University Press, 1997).
- Walters, Le Roy, testimony to U.S. Senate Subcommittee on Public Health, Feb. 2, 2000, “From October 1997 to the Present: How is the new system working?” (<http://labor.senate.gov/Hearings/feb00hrq/020200wt/frist0202/gelsing/kast/patter/fda-zoon/verma/walters/walters.htm>).
- Weiss, Rick, and Nelson, Deborah, “Penn Settles Gene Therapy Suit,” *The Washington Post*, November 4, 2000 (<http://www.washingtonpost.com/wp-dyn/articles/A11512-2000Nov3.html>).