CLONING HUMAN BEINGS

Do Research Moratoria Work?

Commissioned Paper
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CONTENTS

PREFACE

On Constitution Avenue in the nation's capital, just inside from Einstein's statue, the workings of democracy looked a lot like bedlam. Protesters sang, "We shall not be cloned" to the tune of "We Shall Overcome." "A banner quoting Adolph Hitler 'We will create the perfect race,' was unfurled and tauntingly waved in the faces of the scientists until one biologist, in a fit of pique, ripped it apart."[1] It was March 7, 1977, at the National Academy of Sciences (NAS), and the subject at hand was governance of recombinant DNA research. Two bills had been introduced in Congress to regulate such research, and fourteen more would follow in the next few years; legislation was deemed inevitable, and the debate was about what it would say not whether it would pass. The city council of Cambridge, Massachusetts, had just a few weeks earlier rescinded a moratorium on recombinant DNA research after a rancorous debate; several other local governments had passed similar ordinances imposing local moratoria. Cambridge Mayor Alfred Vellucci was in Washington to complain about not having been invited to the NAS symposium and to ask who would control recombinant DNA research.

Unknown to those at the symposium, another ruckus was stirring across the continent. At the University of California, San Francisco (UCSF), Axel Ullrich and his colleagues had learned earlier that week, on March 1, that they had inadvertently violated the National Institute of Health (NIH) guidelines for recombinant DNA research. Ullrich had cloned the rat insulin gene in a vector that had been provisionally "approved" by NIH's Recombinant DNA Advisory Committee (RAC) in mid-January but had not yet been "certified" by the NIH director. Peter Seeburg, another UCSF postdoctoral researcher, had also cloned rat growth hormone using the same uncertified vector. On March 19, Ullrich destroyed the bacteria containing the cloned insulin gene, following the recommendation of his lab chief (and department chair) William Rutter, who had discussed the matter with NIH Deputy Director DeWitt Stetten, Jr. Ullrich then cloned the insulin gene again using another, technically inferior and less safe, vector after it was certified for use on April 18. The cloning of the insulin gene, the first mammalian gene so captured, was announced at a triumphal May 23 press conference by UCSF laboratory directors William Rutter and Howard Goodman. Rutter and Goodman did not mention, and reporters did not yet know to ask, about the inadvertent breach of NIH guidelines.

Genetic technology was racing ahead, and government was struggling to keep up. The chaotic spring of 1977 marked the first cloning of a mammalian gene and the launch of a congressional debate that lasted several years. It was a confusing period of political turbulence, buffeting those who did recombinant DNA research, the Members of Congress and executive branch officials who funded and oversaw such research, and those who feared the consequences of its unfettered pursuit. In the end, the nation stumbled into a process for reviewing recombinant DNA research that enabled scientific progress but also ensured public scrutiny and set technical limits. The policy history of recombinant DNA research, including human gene therapy and congressional efforts to constrain fetal research, illustrate how the United States Government has contended with controversial emerging biomedical technologies. This paper recounts some

historical precedents and draws lessons from those experiences, as background for the National Bioethics Advisory Commission's (NBAC's) deliberations about human cloning.

FRAMEWORK OF THIS PAPER

A brief introductory section focuses on a **definition** of "moratorium" that pertains to the accounts that follow. The historical summaries begin with **fetal research**, because this was the first subject of a federal bioethics commission and because it involves many legislative moratoria through both authorization and appropriations statutes, as well as *de facto* moratoria in the executive branch. Fetal research also highlights the importance of regulations governing human subjects in research. **Recombinant DNA research** never became the subject of statutory constraint, but concern about biohazards from such research did lead to NIH guidelines and a new process to monitor compliance with them, separate from but parallel to human subjects review. As concern about the biohazards diminished in the early 1980s, a new controversy erupted over the deliberate introduction of DNA into humans to treat disease, or **human gene therapy**. General concern about human gene transfer, sharply exacerbated by a highly publicized premature human experiment, led to an extension of RAC review into clinical protocols. More than two hundred gene therapy protocols have been approved worldwide, but these have been confined to introduction of genes into cells that do not produce sperm and eggs, so changes are not inherited. The United States, the United Kingdom, and Germany exemplify three alternative approaches to proscribing introduction of DNA into sperm cells, egg cells, their precursors, or early embryos, leading to inherited changes through **germ line gene therapy.**

The discussion of historical background is followed by a summary of **policy lessons** that emerge from the cases. The main body of the paper is confined to factual accounts and limited interpretations, but does not contain recommendations. I have added a brief final section with my own **observations.** This section can easily be removed without jettisoning the earlier background material.

WHAT IS A MORATORIUM?

The *Oxford English Dictionary* lists only one definition of "moratorium," "a legal authorization to a debtor to postpone payment for a certain time."[2] The word is used much more broadly now to include a pause in the action, but it is not clear it should be stretched so far as some decisions covered later in this paper. In some cases, the meaning is appropriate—a suspension of activity pending further analysis or other action; in others it is clear that "moratorium" refers to "a ban I don't want to call a ban," with a deliberately disingenuous implication of transience. Some of the rhetoric surrounding human cloning falls into each category. Some of the cases below are true moratoria, the classic example being the period during which scientists refrained from doing recombinant DNA experiments while guidelines for safe practices were being devised.

In other cases, "moratorium" is not the word that has been used at all, but the case fits into analysis here because the factual similarity merits treatment. Fetal research has been the

subject of moratoria, and partial bans. Germ line gene therapy is banned in several countries, but it is nonetheless relevant for discussion here because in several ways it is the closest historical parallel. The congressional language about embryo and fetal research has been temporary because of the nature of NIH authorization and appropriation, not by intent, which has clearly been a permanent ban on federal funding of controversial experiments, with full knowledge that the same research would go on under private auspices.

The closest analogy to human cloning may well be germ line gene therapy—deliberate changes in human DNA intended to be inherited. This is because it is quite difficult to imagine an urgent clinical reason to clone a human now, much as scenarios for germ line gene therapy were difficult to concoct a decade ago. The motivation for a ban or moratorium seems to be some combination of preserving social values, fear of loss of social control, or harm to the products of the technology (people born from germ line gene therapy or human cloning). And finally, the technological risks appear to be mainly social and moral rather than technical, in contrast to the concern about biohazard to researchers and the public if recombinant DNA were to create uncontrollable replicating pathogens.

The prospect of inherited genetic intervention predates the Watson-Crick discovery that Mendel's inherited elements—genes—are stretches of DNA. A decade ago, the consensus was that no one could do germ line genetic interventions safely and reliably. Transgenic animals existed, but the methods were inapplicable to humans because there was a constant risk of malformed animals and the probability of effecting a desired genetic change was low (and so it remains, although much improved). Opinion split about the prudence of banning germ line gene therapy. On one hand, there seemed little to be lost by banning it, with some prospect of public assurance as a benefit. On the other hand, some voices pointed out that if the technology evolved sufficiently, one might imagine clinical scenarios, however rare, where it could be useful. Policy on deliberate germ line intervention now varies from barely permissive to explicitly proscriptive. In the United States, "the RAC will not *at present* entertain proposals for germ line alternations" [emphasis added].[3] This felicitous turn of phrase, a relic of NBAC member James Childress from a previous role, says the door is closed but RAC might open it in response to an appropriate knock. This was a deliberate decision, as an outright ban was urged by the Council for Responsible Genetics (CRG) in 1985, and the RAC subcommittee elected to stick with its language. German law, by contrast, says that such intervention is a criminal act, period.[4] In the United Kingdom, a licensing authority oversees embryo research, but it precludes licenses to genetically alter germ line cells.

The proposed germ line intervention discussed below commends RAC's prescience. For ten years, RAC has had a *de facto* ban on germ line gene therapy, but last year a concrete, clinically defensible proposal was proposed, and if it proves technically feasible, a protocol might come forward. In this clinical scenario, the harm of germ line therapy is speculative and vague, and most of the risks and consequences long debated do not pertain, yet the potential benefits are straightforward. RAC could simply choose to review the protocol if need be, after announcing a change in policy. In Germany, the parliament must alter a statute before such a move is possible.

Such a proposal comes forward, and indeed the National Advisory Board on Ethics and Reproduction has reliable information that a pregnancy to avoid maternal mitochondrial disease is underway, although not in a setting that uses federal research dollars. In Germany, a couple wanting to use this technique to have a genetically related healthy child would be blocked in exercising their choice by a German law that does not appear to protect any present or future individual from a particular harm. Whether this state involvement is appropriate turns on one's political philosophy, but it is unlikely to comport well with American values.

This recent offshoot of the germ line gene therapy debate exemplifies how language intended to constrain a technology can have unintended side effects. The language used to impose constraints matters a great deal, and yet it is quite difficult to foresee uses of emerging technology with sufficient precision to craft that language. Constraints on human cloning will face this same dilemma. As an alternative to precise legal definitions of what is proscribed, a review process for a broad spectrum of activities can leave judgments of risk and benefit to case-by-case analysis.

CONGRESSIONAL MORATORIA ON FETAL RESEARCH

Research on the Fetus was the first report of the first federal bioethics commission, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.[5] This report was due four months after the Commission got started. Congress in 1974, much like President Clinton in 1997, wanted careful deliberation, but wanted it now. Section 213 of Public Law 93-348, the same statute that created the National Commission, also imposed the first legislative moratorium on fetal research, barring research "on a living fetus before or after the inducted abortion of such fetus unless such research is done for the purpose of assuring the survival of such fetus" until the National Commission had made its recommendations to the Secretary of Health Education and Welfare (which would today be the Secretary of Health and Human Services). The moratorium stemmed from Scandinavian research involving tissue taken from fetuses after induced abortions, followed by revelations that NIH was supporting some fetal research. Outrage greeted press accounts of the research, leading to street demonstrations in Washington. Among those organizing the protests was Eunice Kennedy Shriver, whose brother, Senator Edward Kennedy, was championing the legislation to establish the National Commission.

The National Commission inventoried ongoing fetal research. As the commission countenanced actual research efforts, hard-edged ideology gave way to a search for common ground and criteria that might be used to mark its boundaries. Michael Yesley, executive director, later noted:

> "Fetal research appeared at the outset to be a topic on which the disputants were so far apart that the National Commission would be unable to make recommendations that were satisfactory to all or most of the concerned parties. . . . Many who had expressed outrage at the reports of research involving severed fetal heads anticipated that the National Commission would produce a whitewash of science, while many scientists feared that the National Commission would

> overreact to the public outcry by unjustifiably terminating some areas of valuable research. Instead, the National Commission made recommendations that enabled most fetal research to continue, yet imposed conditions to assure that such research would be ethically acceptable."[6]

The Commission adopted the principle that fetuses intended for abortion be treated equally to those intended for birth, leading to recommendations that only research intended to benefit the fetus or posing "minimal" risk be permitted. The National Commission issued another seven reports and ceased to exist in 1978. Most of its recommendations, including those governing fetal research, were incorporated into federal regulations, which became Title 45, Part 46 of the Code of Federal Regulations (45 CFR 46). 45 CFR 46 is the section of U.S. administrative law that governs human subjects in research. The fetal research recommendations of the National Commission, for example, were incorporated into subparts 208 and 209 of 45 CFR 46. Under 45 CFR 46, institutions that conduct federally funded research involving human subjects sign an "assurance" document with the Office of Protection from Research Risks (OPRR). OPRR is part of NIH, but serves all parts of the federal government for this purpose.

The National Commission made many recommendations for fetal research and about vulnerable populations. The Commission recognized, however, that any firm and fast rules would prove inadequate, so it also recommended that a review body be established to consider waivers to enable research on in vitro fertilization, research that posed more than "minimal risks" for children and fetuses, or otherwise deviated from the standards laid out in the regulations. The National Commission intended to leave the door open for meritorious research in exceptional cases, in subpart 204 mandating "one or more Ethical Advisory Boards" to review research protocols falling outside the other parts of the regulation. These boards became singular in implementation—as the Ethics Advisory Board (EAB)—which was chartered in 1976 and 1979,[7] and operated from 1977 through 1980. The EAB issued reports recommending exemptions from the Freedom of Information Act for some records retained by the Centers for Disease Control and NIH and on fetoscopy (which entailed more than minimal risk and so required special EAB approval).[8–11] The EAB also made recommendations about *in vitro* fertilization and embryo transfer, finding some research acceptable and recommending a change in the regulations to accommodate it, but these were never accepted by the Secretary of the Department of Health, Education, and Welfare (which became the Department of Health and Human Services with the creation of a Department of Education under President Carter).[9] The EAB's modifications to the regulations were not proposed as formal regulations. Instead, section 205 of the regulations continued to prohibit funding of human *in vitro* fertilization unless reviewed by the EAB, which later that year ceased to exist.

The National Commission also recommended establishment of a successor *deliberative* body, another national bioethics commission but with a broader mandate than human subject protections. Public Law 95-622 established the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research (President's Commission). This

large and unwieldy title accurately described the President's Commission's broader mandate. One consequence of creating the President's Commission was the demise of the EAB.

The EAB did issue reports and also review protocols, but the diversion of the EAB's budget to sustain the President's Commission allowed only the deliberative function to continue. Loss of the EAB removed the only avenue for national review for *in vitro* fertilization or review of any protocols requiring waiver of 45 CFR 46 provisions. This, in effect, imposed a moratorium on fetal research posing more than minimal risk, unless expected to enhance the health of the particular fetus.

With the demise of the EAB, the source of the moratorium on any research falling outside 45 CFR 46 was no longer legislative, but caused by the executive branch's failure to establish a review body stipulated in its own regulations. The language of the regulations also introduced a legal lacuna, which was ambiguous but never tested. *In vitro* fertilization (IVF) was prohibited, but other experimentation on human embryos was not, because the fetal research provisions applied to a fetus, defined as "the product of conception from time of implantation" (subpart 203). Conceivably, an embryo created without federal funds could be the subject of research before implantation, and an argument could have been made for use of federal funds in such research.

The regulations applied (and still apply) to institutions that receive federal funds for research involving human subjects. Research on *in vitro* fertilization nonetheless continued, at private research centers funded by clinical fees, donations, and other nonfederal sources. The congressional Office of Technology Assessment (OTA) observed in 1988 that "the effect of this moratorium on federal funding of IVF research has been to eliminate the most direct line of authority by which the Federal Government can influence the development of embryo research and infertility treatment to as to avoid unacceptable practices or inappropriate uses." Failure to fund such research led to inability to control it or even monitor it.

The President's Commission operated from 1980 to 1983. Fetal research was not the theme of any of its 11 reports, although it did point to the problematic nature of a de facto moratorium on certain kinds of research. Even as the President's Commission went out of business in 1983, a debate about replacing it commenced. Representative Albert Gore introduced a bill to create a successor body to review developments in "human genetic engineering." A long and circuitous legislative journey ultimately led to creation of the Biomedical Ethics Advisory Committee in Public Law 99-158. This was a to be a small congressional analytical agency modeled on OTA, governed by a congressional Biomedical Ethics Board. That body operated for eight months, but was never able to get to its mandated tasks, which included a review of the "minimal risk" criterion for fetal research. The same 1985 law imposed a legislative moratorium on research "on a nonviable living human fetus *ex utero* or a living fetus *ex utero*" unless the research was intended to enhance its prospects of survival or posed "no added risk of suffering, injury, or death to the fetus." It stipulated that the standard for evaluating risk be no different for

research on fetuses intended for abortion than for those intended for birth (the National Commission principle, originally proposed by LeRoy Walters).

The legislative moratorium was repeated in the 1988 NIH authorization. A different, but related topic was also the subject of a special NIH review. Preliminary experiments using fetal tissue transplanted into adults to treat Parkinson's disease provoked a controversy in 1988 and 1989. In response to an NIH request to fund such research, Assistant Secretary of Health Robert Windom imposed a funding moratorium until NIH received the report of an ad hoc panel to address 10 questions that he posed. The most contentious of the questions dealt with connections between fetal tissue research and elective abortion. The panel issued a short report containing recommendations that were then accepted by the Advisory Committee to the Director of NIH. The Secretary of DHHS, however, rejected the use of tissue from elective abortions, in a tale recounted by James Childress.[12] Since he is an NBAC member, NBAC has direct access to much more intimate knowledge of the proceedings, and there is little virtue in recounting it here.

The fetal tissue transplantation controversy and a House hearing convened by Representative Weiss, drawing on OTA's 1988 infertility report, almost led DHHS Secretary Otis Bowen to charter a new EAB. He intended to do so but left office just before signing the charter. (As an aside, this EAB was chartered to combine the deliberative and protocol review functions, which may have doomed it even if it had come into being.) The 1985 legislative moratorium on fetal research remained until early in the Clinton Administration.

Newly elected President Bill Clinton urged Congress to lift the legislative ban on fetal research in January 1993 (*Federal Register*, vol. 58, p. 7468), and the relevant provisions were indeed removed from that year's NIH reauthorization, Public Law 103-43. NIH's first moves were cautious, however, in part because of a breaking controversy. Plans to assemble a panel for advice took shape in September 1993. In October, press accounts of research involving the "cloning" of a human embryo at George Washington University caused a public stir. NIH contemplated reentry onto this treacherous turf with understandable trepidation. In early 1994, NIH established a Human Embryo Research Panel to advise it about how to use its restored funding authority.

That panel's experience was reminiscent of the fetal tissue transplantation panel five years before. Recommendations were forwarded to the Advisory Committee to the Director of NIH, which recommended their adoption to NIH Director Harold Varmus. Within hours, however, President Clinton stepped forth to reject one recommendation of the NIH panel, saying, "I do not believe that federal funds should be used to support the creation of human embryos for research purposes, and I have directed that NIH not allocate any resources for such research," in the same statement that first announced his intention to create NBAC (Presidential statement, December 2, 1994). The President was silent on the panel's many other recommendations. The panel recommended that a group inside NIH review compliance with the guidelines. The Human Embryo Research Panel's deliberations are chronicled by R. Alta Charo as "The Hunting of the Snark."[13] She is an NBAC member, and so further review here is unnecessary.

The President's venture into the ethics of fetal research does not end the story. The Republican landslide in the 1994 congressional elections brought with it renewed interest in legislative constraints on fetal research. NIH was up for reauthorization in 1996, but the bills proved controversial, and fetal research provisions were among the sources of controversy. The NIH authorization was not a sufficiently high legislative priority, and NIH can operate for most purposes under a standing authorization, so no reauthorization bill was passed. A legislative moratorium on fetal research was restored, however, via language in the NIH appropriation for both fiscal years 1996 and 1997. These appropriation provisions were extremely controversial, involving floor debate that invoked allusions to Nazi atrocities (by proponents of the ban) and the Flat Earth Society (by opponents). The fetal research funding bans were in and out of House and Senate appropriation bills at different stages, but the final version included the Dickey-Wicker amendment proscribing embryo and fetal research, which survived a July 1996 attempt to excise it, and was passed in the final funding resolution in September. That language precludes use of NIH funds for "the creation of a human embryo or embryos for research purposes; or research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses" [in 45 CFR 46].[14]

In sum, a legislative moratorium imposed to allow the National Commission to report on fetal research gave way to criteria for fetal research in human subjects regulations, with a "safety valve" CEAB review of protocols that posed greater risks or involved *in vitro* fertilization. The EAB operated for three years, but its recommendations were never approved by the Secretary. The EAB was allowed to die in 1980, creating an executive branch ban on *in vitro* fertilization and fetal research outside the criteria specified in 45 CFR 46. (This was often called a *de facto* moratorium, but it was a ban). In 1985, a legislative moratorium was reimposed, pending comment from a congressional bioethics committee, via NIH reauthorization. The congressional committee was defunded in 1989 without having issued a report, and the moratorium became a ban until 1993, when Congress lifted the ban. During 1994, NIH accepted funding proposals for review while its Embryo Research Panel met. In 1995, a legislative ban was reimposed, this time not in the NIH authorization statute, but through the appropriations process. Whether the appropriations language will be included with 1998 appropriations is not yet clear, and NIH reauthorization may also be considered this year in Congress, although controversial features such as fetal research could preclude passage or even serious committee action.

MORATORIA ON RECOMBINANT DNA RESEARCH

When biomedical researchers think of research moratoria, they are apt to think first of the recombinant DNA story of the mid-1970s. It began with an experiment that Stanford molecular biologist Paul Berg proposed in 1970 to Janet Mertz as a graduate student research project. It would have entailed splicing together a monkey virus, SV40, and a bacterial virus (phage) and inserting the new construct into bacteria. Mertz discussed the experiment at a course she took in June 1971 at Cold Spring Harbor Laboratory on Long Island, one of the birthplaces of molecular biology. Her classmates and instructors, especially Robert Pollack, were worried that this might enable the bacteria to copy and transmit potentially harmful genes. Pollack called Berg to dissuade

him from the experiment. Worry about the hazards of working on tumor viruses were the subject of a January 1973 meeting chaired by Berg at Asilomar, but recombinant DNA was not the focus there. Berg and Mertz's gene-splicing experiment was dropped, but concern was rekindled with the advent of gene-splicing experiments in bacteria a few years later—as the recombinant DNA era dawned in 1973 with the work of Herbert Boyer of UCSF and Stanley Cohen of Stanford (they first conceived their collaboration in a cafe on Waikiki in November 1972). (This paragraph and the following account derived from several sources.[15–20])

A Gordon Conference in June 1973 was the first nationally conspicuous event in the recombinant DNA debate, initiating a public discussion through a letter to the President of the National Academy of Sciences, Philip Handler, and David Hogness, President of the Institute of Medicine. The letter was drafted by the conference co-chairs, Maxine Singer of the National Cancer Institute and Dieter Soll of Yale, and circulated to the conferees in July before being sent to Washington. It urged formation of a committee to formulate guidelines for the safe conduct of recombinant DNA experiments. Handler referred the Singer-Soll letter to the newly formed Assembly of Life Sciences of the National Research Council (the operating arm of the Academy). The Singer-Soll letter was subsequently published in *Science* that September,[21] greatly expanding the audience for the debate about recombinant DNA. The notion of potential biohazard from gene splicing was new to many in that audience, but not to Singer, as she was a friend of Paul Berg's. They had worried together over his proposed SV40-phage splicing idea in 1970. When the Academy asked her advice, she suggested that Berg chair the proposed committee, and he was contacted.

The resulting committee met in April 1974 at MIT, and included four past or future Nobelists in addition to Berg (a Nobelist six years later) and three other scientists. The committee reported in July. They recommended a moratorium on certain experiments until their hazards could be better assessed, that NIH establish a committee to craft guidelines and review proposals, and that an international meeting be convened to discuss potential biohazards.[22, 23] This set the stage for the famous Asilomar conference of February 1975.

Whereas the first Asilomar conference dealt with biohazards of viral research but did not address recombinant DNA, the second and far more famous Asilomar conference focused on biohazards of recombinant DNA specifically. The conference was again organized by a committee chaired by Paul Berg. The second Asilomar conference brought together biologists, mainly molecular biologists, with a smattering of lawyers and reporters. The Berg committee invited 150 participants, 60 from outside the United States; 16 were reporters who agreed not to file reports until after the meeting was over.[18] When the conference ended on February 27, 1975, it was immediately followed by a press conference, and the reporters who had attended were free to start filing their stories. A final report from the Asilomar conference was submitted in late April, was formally reviewed by independent sources, approved on May 20, and rushed into print in the June 5 issue of *Science* and that month's *Proceedings of the National Academy of Sciences*.[24, 25] The day the Asilomar conference ended, the NIH's Recombinant DNA Advisory Committee (RAC) met in Bethesda, Maryland, adopting the draft statement of the Asilomar conference as its interim

rules for federally funded research. The RAC had been born and began to walk, if only on shaky legs.

The voluntary moratorium, largely conceived and imposed by the molecular biology community on itself, thus was supplanted by a federally sanctioned set of guidelines and a prospective group review process. No violations of the voluntary phase of the recombinant DNA moratorium are known to have occurred. There were two known violations of the RAC guidelines for federally funded research, plus one alleged infraction at Harvard that was widely publicized but turned out to be a bureaucratic snarl rather than a real infraction. These cases shed light on different aspects of research moratoria.

The first two cases were about laboratory experiments that either actually took place outside the guidelines (University of California, San Francisco) or without proper NIH authorization documents on file (Harvard). The third case, involving University of California, Los Angeles (UCLA) physician Martin J. Cline, entailed introduction of recombinant DNA into two thalassemic patients, one in Israel and one in Italy. Of these, only Cline's actions were found to be deliberate violations of recombinant DNA guidelines, and even here, the violations of human subject protections were much more significant than infraction of the recombinant DNA guidelines. The Cline debacle set the stage for RAC's prospective review of human gene therapy protocols.

Cloning Rat Insulin and Growth Hormone in pBR322 at UCSF

Two genes, for rat insulin and rat growth hormone, were cloned using the plasmid pBR322 before it was certified by the NIH director. These experiments took place in January through March 1977, following a January RAC meeting at which pBR322 was provisionally "approved" pending further data. This was an action of the RAC, but the guidelines called for "certification" by the NIH director before a cloning vector could actually be used. Alex Ullrich cloned insulin and Peter Seeburg's growth hormone. Most of the attention, both scientifically and in the investigations of infractions in late 1977, focused on the insulin gene.

Axel Ullrich, a German postdoctoral researcher who had been in the United States only six months, apparently did not understand that approval was not the same as certification when he started his experiments. The information was relayed by phone, first from Miami (after the RAC meeting) to a postdoc in the Boyer laboratory, and then again from that laboratory to Ullrich. Even formal certification decisions were often communicated by phone, not only at UCSF but at most universities, because of the intense scientific competition (necessitating very fast communication) and also because the NIH Office of Recombinant DNA Activities was, by its own admission, "desperately understaffed."[26] The fact that two different people at UCSF took the same action suggests both that the competitive urge to use state-of-the-art methods was shared, and that neither Ullrich nor Seeburg was alone in his misunderstanding of the rules. The infractions took place at UCSF mainly because that is where the pBR322 vector was created and one of the places where gene cloning methods were most advanced.

By the time Ullrich confirmed that he had succeeded in cloning insulin, on March 2, 1977, he had known since a laboratory meeting on February 4 that pBR322 was not certified for use. At a March 1 meeting in Utah, William Garland of NIH confirmed to laboratory director Howard Goodman that pBR322 was not certified for use. After a conversation between William Rutter and NIH Deputy Director DeWit Stetten, Ullrich destroyed bacteria containing the pBR322 vectors that included the insulin gene inserts–the first mammalian gene ever cloned.[1, 27, 28] In the end, the experiments that broke the guidelines were technically safer than the ones that experiments using other cloning vectors. The vector designers turned out to be right about its safety, although that was not confirmed by empirical data until May 1977. The vector pBR322 was certified for use in cloning experiments on July 7, 1977.

The violations came to light on September 30, 1977, when *Science* reporter Nicholas Wade ran a story.[29] This led to wide media coverage for several months, and Senate hearings that November. Investigations at UCSF and NIH resulted in "no further action" being taken.[30] Further information about the infractions came to light in a federal patent case decided against the University of California last December.[31] New facts and documents were uncovered through legal discovery proceedings, court testimony, and expert analysis of data in the June 1977 *Science* paper and the related U.S. Patent 4,652,525. That case remains under appeal in the Court of Appeals, Federal Circuit. It was argued orally on January 6, 1997 (docket number 96-1175), and a decision is pending. Several relevant facts and interpretations remain in dispute.

Most of the disputed facts have little bearing on NBAC's interest about whether infractions of research moratoria take place. None of the parties to this litigation dispute that the infraction took place and was initially inadvertent; the disputes center on what took place when knowledge of the infraction became known. The final outcome of this case may, however, influence judgments of what happens when infractions do occur. The continuing dispute is not about whether an infraction occurred (it did), whether it was initially inadvertent (it was), or whether it posed a real risk to safety (it did not). Instead, this case shows how new regulatory or legal constraints imposed on research can complicate scientific discovery, influence scientific competition, and may even bear on patent rights—in this case, whether the patent on the first cloned mammalian gene is judged valid. The December 1995 decision of the judge explicitly calls into question findings from the UCSF and NIH investigations of late 1977, statements in the November 1977 Senate hearing, and completeness of the patent disclosure (see appendix C). The federal judge's decision hinges on facts that the NIH and UCSF investigations failed to bring to light, and thus implicitly raises doubts about the adequacy of previous investigations. Relevant sections of the judge's decision are reprinted as Appendix A.

Recombinant DNA Experiments without a Memorandum of Agreement between Harvard and NIH

Another guidelines infraction was alleged soon after the UCSF case was reported in *Science.* Charles Thomas at Harvard Medical School was one of the early users of recombinant DNA methods. He sat on the NIH committee that developed the guidelines. He believed the dangers of

recombinant DNA were "imaginary" or "totally conjectural,"[32, 33] and made no secret of this. A Freedom of Information Act inquiry from the Environmental Defense Fund discovered that no formal "memorandum of agreement" covering his experiments was on file at NIH.[34] His outspokenness no doubt made him a juicy target. The revelations were covered in the scientific press, then spilled over into the mainstream media and became the subject of a Senate hearing.

Investigations at both Harvard and NIH ultimately concluded that "at no time were Dr. Thomas' [sic] laboratory practices out of compliance with the applicable guidelines or conducted in a manner that would constitute a hazard." Dr. Thomas admitted that he "misspoke" to the Harvard biosafety committee. He claimed that NIH grants were being held up pending approval of his laboratory at the next-to-highest physical containment specifications (ventilation was insufficient, and it was never so certified, but in the meantime, Dr. Thomas departed Harvard for the Scripps Clinic and Research Foundation). Dr. Thomas' strategy was a transparent attempt to pressure the Harvard biosafety committee to approve his laboratory by leading it to believe their approval process was holding his research grant hostage. This manipulation, while unethical, did not bear directly on the allegations of violating the recombinant DNA guidelines, and says little about respect for the moratorium. Researchers in his laboratory were interviewed, and none asserted that he ever failed to abide by the NIH guidelines, whatever he thought about their merit. He publicly chafed at the rules, but all agreed that he played by them.

Dr. Thomas had many documents on file at both Harvard and NIH, including an agreement that was not forwarded to NIH a month before the case came to light. In the end, this was not an infraction of the guidelines but a bureaucratic tangle, and responsibility was shared among NIH, Harvard, and Dr. Thomas. Dr. Thomas's grants to do recombinant DNA research (not all work) were put on hold for five months while the investigations were underway. When those investigations were complete, the recommendation was to allow Dr. Thomas to resume recombinant DNA research using NIH funds.[35] In the end, Dr. Thomas was vindicated. From the documentary record, it appears he endured research constraints while under investigation and suffered bad publicity for being obstreperous and Machiavellian, but he neither violated the guidelines nor broke the earlier voluntary moratorium.

Introduction of Recombinant DNA into Thalassemic Patients in Israel and Italy

In July of 1980, UCLA physician Martin J. Cline inserted recombinant DNA into two patients with the blood disease thalassemia, one in Israel and one in Italy. In doing so, he violated the U.S. recombinant DNA guidelines (which covered any experiments using molecules created with federal research dollars) and human subjects regulations (which cover research by investigators at institutions with a signed human subjects agreement, regardless of whether the work is federally funded or not and whether or not it takes place in the United States). As a consequence, Dr. Cline resigned as chair of his department, had several grants terminated early, and for three years had to submit the report of the investigation to those reviewing any proposals he made to do recombinant DNA, to do research involving human subjects, or to request NIH funding.[36, 37]

REVIEW OF SOMATIC CELL GENE THERAPY PROTOCOLS

The most significant aspect of the Cline case was its violation of human subjects regulations, but its main impact was on how gene therapy entered the world, under the framework of the recombinant DNA guidelines. A month before Dr. Cline did his experiments abroad, the general secretaries of the three major U.S. religious denominations (Protestant, Roman Catholic, and Jewish) wrote to President Jimmy Carter.[38] Their letter opened, "We are rapidly moving into a new era of fundamental danger triggered by the rapid growth of genetic engineering" and went on to note, "Those who would play God will be tempted as never before." From a group of august theologians, that statement carried some weight. The clerics then turned to public policy and process, "We believe, after careful investigation, that no government agency or committee is currently exercising adequate oversight or control, nor addressing the fundamental ethical questions in a major way." Among other things, they were concerned about the 1980 Supreme Court decision allowing patenting of a bacterium, the famous *Diamond v. Chakrabarty* case.

As the President's Commission was beginning to operate, Alexander Capron, Executive Director, got wind of the letter. The President's Science Advisor, Frank Press, turned the letter over to the Commission. The letter became one origin of its report *Splicing Life.*[39] The Commission addressed public fears and pointed to the distinction between somatic cell therapy (which would affect only the person treated) and germ line treatment (which could be inherited). It discussed reconfiguring or augmenting RAC, with appointment of a Genetic Engineering Commission to "deal solely with this field" and also the possibility of a successor bioethics commission (the President's Commission was slated to go out of existence several months hence).[39] The report was released, became the subject of a House hearing before Representative Gore (at which Dr. Cline presented a defense of his work),[40] and led ultimately to the creation of the Biomedical Ethics Advisory Committee, and thence NBAC, through a long and complicated lineage.

The President's Commission report was commended to the RAC, which in 1984 set up a Working Group on Human Gene Therapy chaired by LeRoy Walters of Georgetown University's Kennedy Institute of Ethics. That Working Group was reconstituted as a RAC subcommittee, which went on to produce the first document laying down guidelines for RAC's review of gene therapy protocols, the "points to consider" document that raised over one hundred questions in seven main areas.[41] This document survives as Appendix M to the recombinant DNA guidelines, having been modified several times, but not fundamentally changed.[3] With diminishing duties other than gene therapy, the subcommittee was merged into the full RAC in 1991.[41] As of December 1996, RAC had considered 149 protocols.[42] Last year, NIH Director Harold Varmus proposed to dismantle the RAC, leaving review of gene therapy protocols to the Food and Drug Administration (FDA).

FDA does review gene therapy and somatic cell alterations,[43] and Varmus observed that protocol review by NIH was redundant and that public purposes could be served by hosting national conferences to promote dialog. Dr. Varmus's proposal met opposition, and RAC will be

retained in smaller form, reducing membership from 25 to 15. RAC will be responsible for "(1) Identifying novel human gene transfer experiments deserving of public discussion... (2) Identifying novel ethical issues relevant to specific human applications of gene transfer and recommending appropriate modifications to the *Points to Consider*... (3) Identifying novel scientific and safety issues... (4) Publicly reviewing human gene transfer clinical trial data... [and] (5) Identifying broad scientific and ethical/social issues... for Gene Therapy Policy Conference topics" (Office of Recombinant DNA Activities, 1997 #15; Office of Recombinant DNA Activities, 1997 #94).

MORATORIA ON GERM LINE GENE THERAPY

The President's Commission set the tone for much of the subsequent debate about gene therapy. Its distinction between germ line and somatic cell therapy guided the policy discussion, most notably in the form of Council of Europe Recommendation 934, citing a right to inherit a genome that "has not been tampered with," but also open to therapeutic interventions (with the suggestion that a list might be drawn up of conditions possibly warranting gene therapy).[44] Second thoughts about the moral and clinical significance of the somatic-germ line distinction began to appear with the 1990 Declaration of Inuyama, the statement resulting from an international meeting. It noted that germ line alteration would be "technically much more difficult than that of somatic cells and is not at present in prospect. However, such therapy might be the only means to treat certain conditions, and therefore continued discussion of both its technical and its ethical aspects is essential. Before germ-cell therapy is undertaken, its safety must be very well established, for changes would affect the descendants of patients."[45, 46]

The final clause about safety was added not only to note multigenerational impact, but following discussion of a serious problem faced by germ line therapy but not somatic therapies—the fact that any inserted genes would have to go through all of embryonic and fetal development without triggering a developmental mishap. This was a high hurdle indeed, since no animal models of human development can fully simulate the timing of intricate gene regulation, and controlled expression of many genes not expressed in adults. The thinking at Inuyama was that debate about germ line gene therapy would become serious with progress toward technology for extremely specific replacement of mutated genes with their exact non-mutated counterparts, leaving the genes in the same chromosomal site and subject to the same local regulatory effects. If such a technique were developed—and it would surely be developed first in other organisms—then it would quite likely be safe throughout development (and virtually no other technique would be). At that point, some clinical scenarios would become sufficiently safe to make possible application in some rare situations.

Walters and Palmer devote a chapter to possible scenarios for germ line intervention. Their book also includes a survey of targeted genetic alterations in other organisms, by molecular biologist Mario Capecchi of the University of Utah, because it is the key enabling technology necessary before human germ line changes make sense.[47] One such scenario discussed in Inuyama involved two parents with recessive disorders wishing to have a child without the disorder.

Another was to address diseases requiring genetic change in many different organs whose cells do not divide in adults (such as muscle, heart, and nerve cells), requiring modification before organs differentiate during embryonic development (Wivel 1993, 95).

All nations that have explicitly addressed germ line gene therapy have opted to constrain it. In the United States, the "will not entertain proposals" language of RAC prevails. As noted before, Germany, Denmark and some other nations have made germ line alterations in humans a criminal act. In the United Kingdom, the experiments are subject to a licensing authority that was created by law. The licensing authority has discretion, but only within statutory parameters. The legislative language has caused some problems in the case of a mother who desired fertilization using the sperm of her husband, whose sperm was obtained and frozen after he was comatose and could not give written consent for its use. The artful solution in this case has been to export the sperm to another European Union country, where the fertilization and insemination can take place.

The proscriptions on germ line intervention were largely academic but edged toward more concrete form in 1995, when Donald Rubinstein and colleagues proposed "a nine step protocol at the germ-line level for the curative treatment of a genetic disorder."[48] The protocol was unexpected because it focused on mitochondrial disease, thus framing germ line intervention in a new way.

Mitochondria are small membrane-enclosed organelles inside most cells in the body. They contain several dozen genes, some of which cause diseases when mutated. Mitochondria are not inherited with the other chromosomes, but reside in the mother's egg at time of fertilization, and so inheritance is exclusively maternal. All children of an affected woman are at high risk, although expression can be variable, depending on the severity of the mutation, on whether all mitochondria are mutated or there is a mix of mitochondrial gene types, and on modulation by other genes.

The proposed protocol would fertilize the egg of an affected woman with her husband's sperm, thus making the nuclear genes the usual 50-50 mix of mother's and father's genes. The nucleus of the mother's egg would be removed, however, and placed into the enucleated egg of another woman before fertilization. This would replace the mother's cytoplasm, containing the mutated mitochondria, with the donor woman's just before fertilization. Like other children, the resulting child would retain the nuclear genome of the mother and father but all mitochondria would derive from eggs of the donor woman.

The child's cells would be genetically altered, but not in the way most writers addressing germ line intervention have assumed. This protocol entails manipulation of an egg and not an embryo, but depending on details of language, the technique might or might not be covered by proscriptions intended to thwart embryo research and *in vitro* fertilization. The technique certainly causes inherited changes in subsequent generations, and in that sense is a germ line manipulation. It does not entail recombinant DNA, however, and so would not be subject to RAC review unless

voluntarily submitted to it. It would be subject to Institutional Review Board (IRB) review if conducted at an institution that receives federal funding for research under an agreement with the OPRR, and is thus governed by the U.S. human subject protection regulations. (The reported pregnancy under way using this technique, or a similar one, was apparently undertaken by a private institution. I have no direct information about it, even about whether it is taking place in the United States, nor is the case publicly known). This technique is very likely a criminal act under the German law, which addresses genetic alterations, and also perhaps a Danish law, which addresses manipulations of all or part of an embryo (although since the nuclear transplant takes place before fertilization, it might be exempt). Because it would alter the genetics of an embryo, it appears to be outside the range of experiments that can be licensed in the United Kingdom.

The couple's intent might not be a cure for future generations, but only to rid their genetically related child of consequences from the mother's mitochondrial mutation. If male, the child would not pass his mitochondria on. But any female child would pass the mitochondria inherited from the donor woman's enucleated egg. The technique deliberately induces maternally inherited changes intended to avoid mitochondrial genetic defects, and would be transmitted via germ line (egg) cells. It is, in this sense, germ line gene therapy and would be proscribed by most formulations of bans on germ line manipulation. It is not, however, gene splicing of the kind that was debated and intended to be stopped by those bans. It is hard to argue that the mitochondrial genetic changes carry the moral risk that lies beneath the germ line gene therapy debate, and the case for state intervention seems weak. Yet it is easy to construct reasonable scenarios in which a woman might well want to avoid mitochondrial disease while retaining the benefits of having genetically related children.

If the technique were proven safe in animal experiments (and the developmental safety considerations about mitochondrial inheritance are considerably less worrisome than nuclear genes, so considerations raised earlier do not pertain), then this scenario could present a case lesson in the dangers of premature bans. The desire of a woman (and man) to have a healthy genetically related child could be pitted against existing germ line legal constraints. It is not entirely clear what harm the constraints would be preventing in this scenario, and hard to construct much public benefit, but the damage to the couple's reproductive liberty is quite clear.

In the United States, RAC could simply remove the "will not entertain at present" language in its guidelines by administrative fiat after announcing publicly its intention to do so, or it might choose to construe the protocol as a gene therapy protocol to cure a specific child that has the inadvertent effect of causing changes that female offspring would transmit to their progeny. Most scenarios for use of the technique, however, would not even require RAC review at all, unless the mitochondrial or nuclear genes were altered using recombinant methods. RAC might nonetheless accept such a protocol for review, and judge its safety and technical prospects for success. In the United Kingdom, the licensing authority could also possibly consider the case, subject to interpretation of its statute. In Germany, respecting the couple's reproductive choice would entail a criminal act. Changing the law would require a public process and considerable delay. It would also put a private family decision on public display, and potentially threaten the

personal privacy of the couple if names and other details came to light. Altering national statutes to accommodate reasonable clinical investigations, in any event, seems an awkward route to sensible public policy.

LESSONS FROM OVERSIGHT OF FETAL RESEARCH, RECOMBINANT DNA RESEARCH, AND HUMAN GENE THERAPY

The legislative and bureaucratic history of fetal research is all well and good, but what has it meant to research? Has it led to a real moratorium?

The various legislative bans on federal funding were never expected to block all scientific research on *in vitro* fertilization. If the intention were to ban all human cloning, then this moratorium on federal funding is not the appropriate model. Private sector activity was anticipated and understood by lawmakers to be going on. In many respects, the situation now is much as OTA reported it a decade ago. The federal moratorium has shifted *in vitro* fertilization and related research to private centers that do not receive federal funds for research on human subjects, and so can conduct work outside 45 CFR 46. Thus most of the work takes place outside the research mainstream. With the possible exception of some research undertaken by Mark Hughes that overlapped with activities funded by the National Center for Human Genome Research last year, however, the federal moratorium appears to have held. (The Hughes case may or may constitute an infraction. Federal funding for Dr. Hughes was cut off when this came to light, but the nature, extent, or even existence of work that was federally funded and fell afoul of federal guidelines has not been publicly disclosed. A congressional inquiry has been initiated).

For most of the past 23 years, a ban has remained in place for federally funded *in vitro* fertilization and fetal research of more than minimal risk. This ban has been punctuated by two periods when proposals were considered for federal funding—1978–1980, when the EAB existed to review proposals (including some fetoscopy studies that were approved), and 1994-1995, when NIH assembled a panel to consider what criteria should guide funding for fetal research. The boundaries of the moratorium have shifted slightly with the shift from NIH authorization statute to executive branch back to NIH authorization to ban removal to new bans imposed by annual appropriations. Fetal research has proven irresolvable within Congress, and has provoked repeated fights. With a shift to the appropriations committees, such fights can now be expected to take place every year, meaning more or less continually.

The various moratoria on fetal research were initially imposed by Congress, and subsequent moratoria were either due to actions of Congress or decisions not to act by Secretaries of Health and Human Services (in several cases over the years, usually to spare the President from precipitating controversies that policy change would entail). The various bans were imposed because of ethical concerns, not biohazard danger to patients, or lack of informed consent. The dangers were not palpable to the investigators whose freedom of inquiry was constrained. The risks were to unborn fetuses, and for early embryonic research in particular, the moral standing of the "research subject" was a matter of moral belief, often grounded in theology.

Yet biomedical researchers are by occupation empirical sorts, intellectually contentious and skeptical of assertion not grounded in experiment. Fetal research moratoria have been fought over by factions in Congress and among political appointees in DHHS, and recently joined by the President himself. The terms of the debate have not been framed as risks that might be empirically assessed, as was possible with recombinant DNA. The debate on fetal research has been largely derived from the savage and divisive policy debates over abortion.

Congress has not been able to resolve the controversy, but instead has been itself poisoned by it. With the shift of the moratorium to appropriations language in 1995, the rancorous debate can now affect funding for all of DHHS and the Departments of Labor and Education, bundled with NIH in the same appropriations bill. The shift to appropriations was made because disagreement blocked NIH authorization. NIH has a standing permanent authorization that lessens the need for reauthorization. The funding bills must pass each year, however, one way or another. With authorization blocked, the fetal research battle shifted to the appropriations process. In the past two years, the fetal research provision has been one major reason that a Labor-HHS-Education Appropriations Act has not been passed as a separate law, but instead has been lumped with other incomplete funding bills as the new fiscal year threatens to dawn. With linkage to the appropriations process that must go forward every year, and always faces a daunting schedule, fetal research funding could escalate from a nasty intermittent sting to a hardy perennial controversy.

Fetal research bans and the recombinant DNA moratorium followed by guidelines were research constraints that originated from different sources for different reasons. Both sets of constraints, however, were respected for the most part. In the case of recombinant DNA, this was at first because of genuine concern about biohazard, soon followed by an understanding that a breach of the guidelines could undermine public faith and threaten the research effort. The guidelines were followed not only for federally funded work but on a voluntary basis by those doing research with private funds. While this paper summarized a few infractions and alleged infractions of the recombinant DNA guidelines, the main story here is the remarkable success in creating guidelines that adapted to new knowledge and were for the most part respected throughout the scientific community.

In the case of fetal research, the federal ban has not extended to the privately funded research sector. Many in the research community do not regard the federal ban on *in vitro* fertilization research and fetal research as prudent, but the ban has held out of respect for the legal line-drawing by Congress and surely also some fear of the impact that violating the ban might have on other research. Because of contending moral values, however, this ban is a constant source of conflict.

Respect for constraints on research involving human subjects, in contrast, runs strong and deep. Respect for persons involved in research is fundamentally different from the speculative risks of biohazard attending a new technology or the moral values embedded in a fetal research ban. The human subject regulations derive from principles well understood even before the

Nuremberg Code.[49] The human subject regulations are an accepted fact of modern research. The relevant U.S. regulations, 45 CFR 46, are just two decades old, but two generations of investigators now regard them as a matter of course that ultimately strengthen research. Many conceivable experiments that could produce interesting data simply are not done. Moral boundaries are respected; they may be porous, but they are constantly patrolled by Institutional Review Boards. The Advisory Committee on Human Radiation Experiments discovered that the IRB system is far from perfect and some unethical experiments still proceed (Advisory Committee on Human Radiation Experiments 1995, 97)—and this is one reason for NBAC's existence, to continue an unfinished agenda of human subject protections. There can be little doubt, however, that norms of clinical research have changed over the past few decades.

LeRoy Walters, in responding to a previous draft of this paper, noted that the RAC process could take on even the world's best known experts in an emerging and highly conspicuous field, in part because of its process and stature. Success may have depended on several features of the RAC process (Walters 1997, 98):

open public meetings,

involvement of nationally recognized experts,

expertise spanning biology, medicine, law, ethics, public policy, and consumer advocacy,

appointment of experts familiar with the field but not direct competitors,

use of expert *ad hoc* consultants when needed,

rotation of membership,

regular and accurate coverage by the public media, and

frequent revision of the "points to consider" document.

One lesson from the Cline case is that when the potential rewards are exceedingly large, human subject protections are all the more important, because scientific priority and fame are powerfully seductive. The Cline case tested the IRB and recombinant DNA review processes. The punishment meted out was swift and fair. Cline remained a scientist, but was stripped of his chairmanship, lost several grants, and found getting grants much harder than before his infraction. The main damage was to his reputation and ability to do science. Few molecular biologists would fail to recognize Martin Cline's name even after more than a decade and a half. His censure was meaningful to the scientific community. If indeed Dr. Cline's actions were driven by a desire to enhance his reputation, then the penalty that mainly damaged that reputation was appropriate and proportionate.

SOME PERSONAL OBSERVATIONS

A proposed moratorium on human cloning would share with fetal research a grounding in public outrage over what is much more a moral than a technical or public health concern. The purpose of a human cloning moratorium would be to prevent a moral wrong rather than to save lives or forestall biohazard. Arguments for a human cloning moratorium also hinge on theological and moral beliefs, as abortion and thus fetal research positions often do. The moral standing of the resulting human beings, however, is not in question, and so, unlike the debate about fetal and embryonic research, disagreement about personhood should not be as central, and theological tenets may be less likely to confront deep social divisions. This might diminish the passions, and it may also reduce pressure to impose a moratorium in the first place. Unlike fetal research, however, the object of a moratorium might well be to block *any* human cloning, not just the use of taxpayers' money in its pursuit.

If the object of the effort is to stop all cloning, not just experiments funded by the federal government, then *in vitro* fertilization and fetal research are poor models. Since it is currently difficult to foresee any compelling reasons to go ahead with human cloning, then the main intent of a moratorium might be to thwart an egocentric billionaire. If in some currently unimagined scenario, some benefit could be postulated, then the IRB system, if supplemented by a mechanism for review and debate at the national level, might well be up to the task, addressing the policy concern with only the need to strengthen national review of the existing human subject protections. If that is the problem being solved, then a moratorium on federal funding similar to the one on fetal research would be useless.

The UCSF story paradoxically suggests that a moratorium can matter a great deal, not just because it changed scientists' behavior, but also because it distorted the rules of scientific competition in surprising ways, and planted a seed of discord that is now a factor in patent rights still being decided by federal courts two decades later.

There are limits to the respect scientists will accord a research constraint if they believe strongly in the potential knowledge to be gained. If the recombinant DNA guidelines had been more burdensome, less flexible, or (worse) scientifically suspect, the walls would likely have been breached more than the two times we know about (once deliberately, once inadvertently). Although biohazard was initially perceived to be real, with time the risks appeared more and more speculative while the power of the technology became more apparent. And the rewards were sweet. The races to clone mammalian genes were high stakes. It was one thing to hold position for a few laps under the caution flag, quite another to put a permanent governor on the engine.

If Martin Cline had only violated the recombinant DNA guidelines, his violations would have seemed far less significant. In fact, his case is telling in three regards. First, the recombinant DNA portion of the infraction said more about truth-telling—how Dr. Cline dealt with his collaborators and the people he was "treating"—than it did about the validity of the recombinant DNA guidelines. They were intended to prevent biohazard, but in this case they may have mainly

contributed to weakening an already questionable experiment. When the initial guidelines were extended into the clinical realm, before the Human Gene Therapy Working Group began to grapple with the specific issues in gene therapy 1983, the guidelines were poorly suited for clinical experiments. Second, the bureaucratic decision to exempt the experiment from review was perverse because it removed scrutiny while weakening the likelihood of clinical benefit, which was already extremely low. Third, and most on point when contemplating rules governing human cloning, the Cline case revealed the pathologies of multiple parallel reviews.

Dr. Cline's experiments were either safe and likely to work or not, and the most important considerations were those that an IRB should review, not whether recombinant DNA was involved or not. Yet the local UCLA IRB encountered serious difficulty in reviewing the protocol, in part because it was an experiment with national, even worldwide implications, but review was local. When RAC shifted to reviewing human gene therapy, it in effect became a national IRB for such experiments. This was highly beneficial for the science and for the protection of the human subjects involved, for several reasons. Human gene therapy has always been "hot," and those who do it are local stars because they attract money, prestige, and publicity. It can be difficult for local IRBs to contend with the local star, but when review moves to the national level, NIH can bring in the nation's best minds without worrying as much about local impact. The procedures generally get more thorough technical review at a higher level of expertise. The RAC process is open and visible because unlike FDA review it is public. And it is credible and accountable because the deliberations are covered by the media, especially when major decisions are made or when controversies come to light. It is good for the science because the right information is gathered to comply with the "points to consider" document, which was itself drafted and revised following an open process.

These positive aspects of gene therapy review highlight the consequences of not having an EAB to perform the same functions for other kinds of research. Gene therapy demonstrates that a national IRB can function, despite the fact that RAC was technically operating under recombinant DNA guidelines rather than human subject regulations. Yet this came to be only because the trivial and marginally relevant fact that recombinant DNA was involved in gene therapy. That fact enabled a national committee to construct a document that addresses the same points IRBs should be concerned about.

If NIH had clicked its heels twice, it could have had a review process for difficult research issues all along. The successful national review model grew out of recombinant DNA, but if history were logical, it should have grown out of the human subjects' protections. In the past decade, NIH has careened from crisis to crisis about embryo and fetal research, research involving the cognitively and emotionally impaired, and fetal tissue research. FDA has been excoriated over its handling of RU486, use of placebos in drug trials for schizophrenia, and insufficient regard for AIDS patients and cancer patients to get access to clinical trials. Yet the nation has in its handling of gene therapy a credible model for a transparent and accountable system of national review. The lesson for NIH is the need for the ability to convene national-level IRBs to review particularly vexing research areas. The lesson for FDA is to make its rulemaking and deliberations more open.

The lesson for human cloning may be that it is just one of many possible issues to arise in doing research that involves people or people-to-be. Creating another *ad hoc* committee or new process may well create the kinds of bureaucratic difficulties, with ambiguously overlapping jurisdictions that appeared in the Cline case.

All three efforts to impose research moratoria must confront an uncomfortable fact: they work well in general but may be violated by isolated individuals.

As a final personal opinion, the temptation to blend functions of national deliberation and analysis with review of complex research protocols that raise difficult issues should be resisted. The gene therapy review process under RAC served well by first posing the right questions about clinical protocols and then reviewing protocols. On a few occasions, RAC has also attempted to mediate a national debate, but with no success comparable to the National or President's Commissions. The Ethics Advisory Board also issued some reports, as well as serving to review protocols, but these reports did not have nearly the impact of the National and President's Commissions. The National and President's Commissions, the radiation experiments committee, and now NBAC are spared the review of specific protocols, so they can commission papers, discuss options, and concentrate staff effort on gathering information, writing reports, and the business of policy analysis.

The Ethics Advisory Board did a bit of both deliberating and protocol review. It was arguably closer to success in protocol review than effecting change through its reports. The Ethical, Legal and Social Implications Working Group of the NIH and DOE was successful in helping launch a research program, but had minimal success in its policy forays—with scant publication and no systematic information gathering, report writing, document review, or other features associated with credible policy analysis. The Ethics Advisory Board, as laid out in the 1988 proposed charter, would have mixed analysis with the traffic cop role. So would the EAB functions laid out by the 1993 NIH reauthorization. We have examples of successful public policy deliberation about topics in bioethics, and relatively successful review processes for protocol review for human subjects protections and for gene therapy; but models for doing both are not promising.

NBAC's engagement with the human cloning question demonstrates the virtues of having a deliberative commission in place. NBAC was there to catch the ball. The key missing element seems to be national protocol review. The local infrastructure for human subjects review already exists in the form of IRBs, but the national superstructure of an EAB does not. If concerns about human cloning justify further action, the most pressing need may be to formulate guidelines or terms of a moratorium or ban, and then to review protocols if benefits are plausibly in prospect. This is just what the gene therapy working group did fourteen years ago. In that case, the fear was that without such guidelines, the technology would rush ahead. In the case of human cloning, there seems no pressing clinical or other practical need for the technology but rather a need for reassurance that whatever progress occurs in genetics and cloning technology, there is a credible process for assessing its technical merit and social impact before experiments are tried.

APPENDICES
APPENDIX A: THE UCSF CASE

The UCSF infractions of recombinant DNA guidelines were caused by confusion over regulatory permission to insert mammalian genes into the recombinant plasmid pBR322, named for Francisco "Paco" Bolivar of Mexico and native Californian Raymond Rodriguez. Bolivar and Rodriguez were postdoctoral researchers working in Herbert Boyer's laboratory who designed a circular DNA molecule (plasmid) that dramatically simplified gene cloning. It contained genes to enable selection of bacteria containing it, with a gene conferring penicillin resistance and another gene for tetracycline resistance whose disruption by insertion of a foreign DNA would cause bacteria to stop growing but not to die. It also had splice sites for a variety of DNA-cutting enzymes.

Many of the cloning vectors still used today are direct descendants of this cleverly craf-ted plasmid. It was easier to use than other vectors available at the time, and Bolivar and Rodriguez also reasoned that it would be less liable to pass from bacterium to bacterium, reducing the risk of proliferating outside deliberate control. But it was also new, and the RAC review process meant formal certification, with review by the committee and formal certification by the NIH director. Confirmation of the plasmid's safety awaited data produced by Stanley Falkow and Jorge Gros at the University of Washington. The data showed pBR322 plasmids in weakened bacterial strains to be "the safest plasmid-host systems currently available."[50] Those data were not available until May 1977, and the vector was not certified until July 7.[30]

The competition to clone mammalian genes was intense. Gene jockeys were not so named just because of alliteration. Molecular genetics was characterized by long hours, and as a marathon neared the finish line—the cloning or sequencing of a gene, for example—work went on around the clock. The insulin race was particularly competitive, with a UCSF group contending with Walter Gilbert's Harvard crew, another group at the City of Hope Hospital, and who knew who else? The urge to use the technique most likely to work best and fastest was strong. This day-by-day, hour-by-hour competition was a stark contrast with the quarterly RAC meetings.

Boyer attended a Miami Winter Symposium in January 1977, and the RAC was scheduled to meet afterward. Boyer had sent a letter requesting approval of pBR322 in December 1976. The RAC met January 15-17. It provisionally approved pBR322, but RAC wanted more data before certification by the NIH director. Boyer phoned from Miami to Rodriguez in the UCSF lab with the news. Rodriguez phoned Ullrich. Ullrich proceeded to begin the multi-step cloning procedure, starting from some isolated DNA thought to contain rat insulin genes. By the end of February, he thought he had the gene. Howard Goodman then attended a conference in Park City, Utah, where RAC's executive secretary, William Gartland, unambiguously stated that pBR322 was not certified for use. Goodman then knew for sure the experiments had violated the recombinant DNA guidelines.

Just days before the Washington NAS meeting that began this paper, Ullrich confirmed he had cloned the insulin gene by examining DNA sequence data from one pBR322 clone. After an

internal debate among UCSF collaborators, Ullrich destroyed bacteria containing the pBR322 vector with its insulin-gene inserts on March 19.[1, 27] He cloned insulin in another vector, pMB9, after that vector was certified in April. That cloning effort was announced in May 1977 and published in *Science* that June.[51]

These parts of the story are not contested. Appendix C, the federal district court's decision, includes information about what happened after it became apparent an infraction had occurred. The contested findings cover a few points relevant to this paper—what was done with any DNA *derived from* the insulin-containing pBR322 constructs (as opposed to the destroyed bacterial clones), the chronology of events, the accuracy and completeness of various statements about these events, and the disposition of patent rights.

Had the violations come to light in the spring of 1977, the legislative outcome might have been different. Congress was considering bills to impose more stringent and permanent constraints on recombinant DNA research. NIH director Fredrickson was doing all he could to keep review flexible and locate it at research institutions to the degree possible. The Washington clamor was at a perilous juncture. From Fredrickson's perspective, if the scientists didn't like RAC, they should try what Congress had in mind. News of the UCSF violation at this critical juncture might have scuttled the strategy and led to legislation with more central and less flexible review.

Analysts offer several different reasons for the loss of momentum for legislation. First, RAC began to operate and its initially technical membership was broadened to include nonscientists. At the same time, scientific consensus began to grow that the dangers of inadvertent biohazard (as opposed to deliberate biological warfare engineering) were quite low. Gene exchange that took place in nature even without recombinant DNA was demonstrated. And the first successes in gene cloning, including the insulin and growth hormone genes, were announced.[18, 52] Those successes shifted some attention from possible risks to obvious benefits. Finally, the scientific community mounted a spirited lobbying effort against legislative action, spearheaded by Harlyn Halvorson, a former president of the American Society of Microbiology.[19]

Had the UCSF events become widely known as they occurred or soon after, they could well have undermined the RAC process even as it was just getting started. Or they might not have undermined confidence, if it were clear that the infraction was obviously inadvertent. Faith in scientific self-regulation was arguably the most important factor attenuating calls for legislation and stringent regulation—but this case might have played out as an example that scientists could not be trusted, or that the processes worked to surface and remedy even minor infractions. The impact of public disclosure of the inadvertent infraction might well have turned on how it was handled at least as much as what had actually occurred. An open and transparent process is generally more credible than a secret and opaque one. One thing is clear, however. In retrospect, heavy-handed regulation or inflexible statutory restrictions on recombinant DNA research would have been a serious error, as recombinant DNA research has proven enormously useful scientifically as well as and socially valuable. The putative biohazards have not proven substantial. The lesson here is not that the recombinant DNA guidelines did not work, only that they

influenced the conduct of science and that procedures for communicating them, investigating infractions, and enforcing compliance were incomplete.

APPENDIX B: THE CLINE CASE

This account of the Martin Cline case is mainly based on Larry Thompson's book *Correcting the Code*,[53] as supplemented by NIH case files[54] and old OTA files.

On July 10, 1980, Dr. Martin J. Cline infused 700 million blood cells treated with recombinant DNA into Ora Morduch, a 21-year-old Iraqi Kurdish Jew and patient activist living in Israel. The experiments took place at Hadassah University Hospital. The treatment was repeated the next day. Each treatment involved taking blood cells, incubating them with calcium phosphate in the presence of the DNA, radiating Ms. Morduch's bone marrow with 300 rads to kill native cells, and reinfusing the treated cells. On July 15 and 16, at the University Polyclinic in Naples, Italy, Dr. Cline administered a similar treatment to Maria Addolorata, a 16-year-old from Torino, except that a smaller body surface and lower dose of radiation were used (200 rads). The next day, the University of California, Los Angeles, IRB rejected Dr. Cline's proposed clinical protocol.

The IRB action culminated a 14-month struggle. In May 1979, Dr. Cline and his UCLA collaborators submitted a clinical protocol to the UCLA IRB proposing gene therapy for sickle cell disease and other hemoglobin disorders. This was based on a mouse experiment in which cells treated with recombinant DNA (by incubating them with DNA precipitated in calcium phosphate and rendered porous by electrical currents) were inserted into mice whose bone marrow had been entirely killed by radiation. The mice were also treated with the cell poison methotrexate that killed cells unless they had taken up the recombinant DNA—containing the globin gene linked to one that conferred resistance to methotrexate. Under this strong selection, the mice expressed low levels of the globin gene transiently.

Dr. Cline was chairman of the department of hematology at UCLA. The department had a history of several confrontations with UCLA's IRB. Moreover, the protocol was initially subject to both IRB review and the local Institutional Biosafety Committee, which oversaw compliance with recombinant DNA guidelines. The committees initially deferred to one another. Cline and collaborators decided to avoid the biosafety committee, and thus the recombinant DNA guidelines, by fragmenting the DNA before insertion into patients, so it would not longer be "recombined" in a vector. This modification, while avoiding a bureaucratic impediment, was arguably both more dangerous and less likely to provide benefit because chromosomes tend to incorporate such DNA fragments as large redundant arrays. Since one concern was gene regulation, and such tandem arrays are even less subject to control than single copies, this element could have introduced a new risk of unregulated gene expression. At the least, this needed testing. This protocol as proposed for human patients was never tested in animals, nor was the experiment without full-body radiation and without methotrexate selection, although these were essential features of the human experiments.

The IRB initially requested external expert review of the protocol, but Dr. Cline resisted, wishing to keep his ideas secret from scientific competitors. The back-and-forth led Dr. Cline to

propose the IRB seek advice from an expert panel. The four external consultants who reviewed the experiment were picked after Dr. Cline was allowed to reject direct competitors. All four consultants judged the experiment as premature.

In the experiments he conducted in Israel and Italy, Dr. Cline decided to go ahead and use recombinant DNA instead of cutting it into fragments as promised. He lacked facilities to fragment it, and did not personally know how to do it as proposed in the UCLA protocol. His promises not to use recombinant DNA had proved important in the review process at Hadassah University Hospital, and he had also told both patients no recombinant DNA would be inserted. This feature was again bureaucratically significant, but technically unsound.

Rumors about gene therapy having been tried in Israel percolated among research hematologists between July and October 1980. An NIH scientist also interested in gene therapy, W. French Anderson, heard about the rumors. He talked to the resident bioethicist at NIH's Clinical Center, John C. Fletcher, who decided to call Dr. Cline. He caught up with him by phone at a Montreal hotel. Fletcher told Cline about the rumors that Cline had attempted gene therapy in Israel, and he should come tell the facts to NIH officials if he had done so. At the end of an equivocal conversation, Cline denied having done such experiments.[53] On September 8, Charles McCarthy, director of NIH's office for overseeing human experimentation, wrote a letter to UCLA Chancellor Charles E. Young asking whether Dr. Cline had performed gene therapy experiments. In October, *Los Angeles Times* reporter Paul Jacobs broke the story on the front page, having checked with sources in Italy and Israel and with scientists who had been part of the rumor mill.

This began a series of investigations at UCLA and NIH, which culminated in May 1981, noting the first-ever documented transgression of the human subjects guidelines and also a violation of the recombinant DNA guidelines. Dr. Cline had by then resigned as department chair. The NIH reviewed his ongoing grants, terminated several, and required that future applications for clinical research, recombinant DNA research, and NIH funding should include the NIH committee's report on the investigation.[36]

Several factors cast doubt on Dr. Cline's own account of why he did the experiments: (1) he went abroad to do the experiments after being rebuffed at UCLA, (2) he did them knowing that in all likelihood the protocols would be rejected by the UCLA IRB, (3) he lied about using recombinant DNA to his collaborators and to the patients (setting aside the technically sound judgment that it was more likely to work), (4) he lied to John Fletcher about having done the experiments at all, and (5) he tried to convince his UCLA collaborators to keep mum about using recombinant DNA when the story broke.

Dr. Cline's contention that he acted with the best interests of the patients foremost in mind is undermined by his failure to tell either patient what he was really doing, his failure to produce evidence in advance about the possible harms that could come from overexpression of beta globin

in cells, the extremely incomplete animal model and human *in vitro* data, and his characterization of the trials as phase I.

Phase I trials are intended to test the safety and toxicity of drugs, usually by escalating dosages until side effects emerge in healthy patients. Testing for safety and toxicity in seriously ill patients is nonsensical, as their generally fragile health makes it impossible to know whether ill effects are due to the drug or the severe underlying disease. The Israeli case bears out this point: soon after the experiment took place, Ora Morduch entered the hospital in arrhythmic crisis and could have died. This was much more likely to be caused by excess iron in her heart muscle cells than Dr. Cline's treatments. But who could know? The Cline experiments taught nothing about the toxicity of the methods, and could never have been expected to do so.

The proper framework for the experiments is "compassionate use," referring to innovative therapy for patients with no better alternatives, and so even a small potential benefit can be acceptable. In this framework, the decisive factors are the unavailability of alternative treatments and the plausibility, even if small, of clinical benefit. The Cline experiments fail on both counts. Iron chelation therapy in conjunction with blood transfusion was being tested as Dr. Cline did his experiments. Indeed both patients eventually got and greatly benefited from those treatments, both surviving for more than a decade. Gene insertion was exotic and unlikely to work compared to chelation therapy.

Regarding the potential clinical benefit of inserting genes, the situation was at least as bad. First, exposing both legs to 300 rads of radiation (Israel) or 200 rads (Italy) could harm the patient and certainly could not help, except to "make room" for the infused cells, but this part of the protocol had never been tested. Second, credible evidence would have required either closely similar experimental data from animals or tissue culture evidence of gene expression using the same procedures on human cells. Yet even strong selection in the mouse experiments (total body radiation to kill all marrow cells followed by methotrexate selection) led to only low gene expression for a short time. Dr. Cline's clinical experiments in Israel and Italy involved a much smaller proportionate influx of cells and no selection. And although his Italian collaborator did indeed test gene expression *in vitro*, Dr. Cline did his experiments in patients before those results were known.

APPENDIX C: EXCERPT FROM UNIVERSITY OF CALIFORNIA V. ELI LILLY AND CO.

Source: *U.S. Patent Quarterly* 2d, Book 39, from "A. The '525 Patent" on pp. 1248–1254.

Some background information concerning research involving recombinant DNA must precede discussion of this issue. In the early 1970's when experiments in the area of recombinant DNA were first contemplated many people, including some scientists, were concerned that such experiments might pose medical threats to humans. Tr. at 1295. The National Academy of Sciences eventually "called for a broad moratorium on all recombinant experiments until they could be . . . better reviewed by the scientific community." Id. At a subsequent review of recombinant DNA research in 1975, it was suggested that experiments in that area might proceed if suitable guidelines were promulgated to govern the research. See Lilly Ex. 3547 at HG2 580773.

Consequently, the Recombinant DNA Molecule Program Advisory Committee, previously established by the Department of Health, Education, and Welfare's National Institutes of Health (NIH), held its first meeting to develop safety guidelines. Id. Those guidelines were issued by the NIH on June 23, 1976, and published in the Federal Register on July 7, 1976. Tr. at 1296, 1298; Lilly Ex. 3731 at 000004; Lilly Ex. 3547. "The NIH Guidelines establish [ed] carefully controlled conditions for the conduct of experiments involving the production of [recombinant DNA] molecules and their insertion into organisms such as bacteria." Lilly Ex. 3547 at HG2 580773. For example, the regulations classified types of biological containments (i.e., plasmids) and specified which ones could be used in certain recombinant DNA experiments. The regulations also governed the type of physical containment facilities (i.e., laboratories) in which scientists could conduct particular types of experiments. The safety guidelines mandated that no plasmid could be considered to fall within an approved classification until it had been certified by the NIH Recombinant DNA Advisory Committee. Tr. at 1301.

The guidelines also stipulated that any institution receiving NIH funds was to appoint a principal investigator. Under the guidelines, the principal investigator had certain responsibilities, including "supervising the safety performance of the staff to ensure that the required safety practices and techniques [were] employed" and "investigating and reporting in writing to the NIH Office of Recombinant DNA Activities and the institutional biohazards committee (or biosafety committee) any problems pertaining to operation and implementation of biological and physical containment safety practices and procedures, or equipment or facility failure." Lilly Ex. 3547 at HG2 580791. The guidelines governed the conduct of all NIH supported research in the area of recombinant DNA. The research UC was conducting on rat insulin the research that formed the basis of the '525 patent was NIH-supported. Consequently, UC was to operate within the strictures of the safety guidelines.

By January of 1977, the NIH only had certified the plasmids denominated pSC101 and pCR1 for experiments with mammalian DNA. Tr. at 1301. According to Rutter, UC scientists

delayed their recombinant DNA research, awaiting the NIH green light on use of a more advanced vector either pMB9 or pBR322. Tr. at 127. Rutter said UC representatives preferred to use pBR322. Id. Reportedly, that vector would be the most effective cloning agent. Id. On April 18, 1977, the NIH certified plasmid pMB9 as safe. Lilly Ex. 3554A at 177. On July 7, 1977, the NIH certified plasmid pBR322. Id.

Lilly contends that UC researchers knowingly used a plasmid not yet certified for use PBR322 in conducting its rat insulin experiments. Moreover, Lilly argues that UC researchers misrepresented the origins of their rat insulin data to the public, the NIH, the United States Senate and the PTO in order to conceal their misuse of plasmid pBR322. According to Lilly, the UC researchers' misuse of the plasmid and misrepresentations of the origins of their data are material to patentability of the '525 patent, and the misrepresentations of their data were intended to mislead the PTO. Thus, Lilly argues, a finding of unenforceability based on inequitable conduct is appropriate.

Clearly, UC's scientists used pBR322 in their research before the NIH had certified that plasmid for use. In January of 1977, working in Goodman's laboratory at the University, Ullrich began using pBR322 in his recombinant DNA experiments. Ullrich testified that he began using the plasmid after a colleague informed him by telephone that the NIH had approved pBR322 for use. Tr. at 79798; Lilly Ex. 3420 at HG 002878. The record indicates that prior to his use of pBR322, Ullrich informed Rutter that he had heard pBR322 was approved and that he intended to proceed with his experiments. Dr. Rutter concurred with Dr. Ullrich's plan, without further verification of the status of pBR322. Lilly Ex. 3420 at HG 002870.

Subsequently, during a February 4, 1977, meeting, certain UC researchers including Ullrich and Shine learned that although approval of pBR322 had been recommended, the NIH director's requisite certification of the plasmid as safe had not yet issued. Lilly Ex. 3420 at HG 00287172. Ullrich averred that he earlier had not been aware of the distinction between approval and certification. Tr. at 800. Thus, UC's premature use of pBR322 through February 4, 1977, was a violation of the NIH guidelines, but it was not necessarily an intentional violation.

The record, however, illustrates that UC researchers did not halt their use of pBR322 and/or the fruits of previous experiments with that vector after learning that pBR322 had not been certified. In fact, UC agrees that the experiments continued until at least March 3, 1977. Lilly Ex. 3420 at HG 002871. In its report to the Office of Recombinant DNA Activities (ORDA) concerning UC's premature use of pBR322, UC's biosafety committee stated:

At this [February 4] gathering, the investigators in Dr. Goodman's laboratory (including Drs. Ullrich and Shine) reportedly learned for the first time that there was some confusion about the status of pBR322 . . . However, the initial cloning experiments with pBR322 and insulin cDNA had been completed, and clones had been obtained. After February 4, no new clones were constructed, but those already obtained were grown up and examined for the presence of recombinant DNA.

There is no satisfactory explanation as to why the investigators in Dr. Goodman's laboratory continued experiments with these recombinant plasmids after February 4.

Lilly Ex. 3420 at HG 002872. Moreover, when questioned at trial, Ullrich did not deny use of pBR322 after learning that it had not been certified. Tr. at 824. We find that the record clearly supports Lilly's contention that UC knowingly violated NIH safety guidelines when its researchers continued to use pBR322 in recombinant DNA experiments even after learning that the plasmid had not yet been certified for use.

Additionally, neither Rutter nor Goodman officially reported the unauthorized use of pBR322 to the NIH after the time they became aware of the prohibited use. Rather, Rutter testified that he had an informal telephone conversation with Dr. DeWitt Stetten, NIH deputy director for science, and that he and Stetten ultimately decided against a formal disclosure of the incident. Tr. at 12930. In fact, Rutter testified that the conversation between Stetten and himself "was carried out in a deliberate way to convey the fact, but not to create a need to disclose . . . [t]o make a formal disclosure . . . There was no formal disclosure." Tr. at 246. Rutter also testified that during the conversation, Stetten and Rutter decided that the pBR322 clones would be destroyed. Id. at 131. This conversation reportedly occurred sometime between March 1619, 1977. Lilly Ex. 3420 at HG 002873.

Furthermore, neither Rutter nor Goodman informed UC's own biosafety committee of the misuse of pBR322. Rather, Dr. David Martin, then chairman of UC's biosafety committee, "heard rumors" of the incident through a technician in Rutter's lab sometime in May, 1977. Tr. at 227; Lilly Ex. 3420 at HG 002874. Martin then discussed the matter with Rutter and Goodman. Id. At a June 3, 1977, biosafety committee meeting, Martin reported the UC scientists' use of pBR322. However, an examination of the minutes of that meeting indicates that the committee was not informed fully of the events that had occurred. As UC stated in its committee report to the NIH, [t]he failure of the Biosafety Committee to notify the NIH of the pBR322 incident was primarily a consequence of the fact that the Committee itself was unaware of the details and import of the event. On the basis of the information the Committee had at that time, it was not aware that a violation had occurred. Lilly Ex. 3420 at HG 002874.

Thus, it is obvious that UC representatives did not formally report UC's researchers' violation of the guidelines to the NIH, nor did they provide a detailed explanation of the incident to UC's biosafety committee at its June 3, 1977, meeting. Events occurring later, however, brought the incident to the surface.

On September 9, 1977, Nicholas Wade, a Science reporter, called Dr. William Gartland (Gartland), director of ORDA, asking questions about UC's alleged use of an uncertified plasmid. Lilly Ex. 3731 at 000095. Wade stated that he was writing an article about the pBR322 incident an article that subsequently was published in the September 30, 1977, issue of the publication. Id. at 83, 87. Gartland apparently first learned of UC's inappropriate use of the plasmid during Wade's telephone call to him. Id. at 83.

On October 11, 1977, Gartland wrote Dr. James Cleaver, chairman of UC's biosafety committee, asking for an accounting of the incident. Lilly Ex. 3731 at 00008889. Cleaver responded on October 25, 1977, including in his response a memorandum authored by Goodman and Rutter detailing, as they recollected, the events surrounding the pBR322 incident. Lilly Ex. 3731 at 000090, 000092. In the memorandum, Goodman and Rutter stated that the decision was made to destroy the pBR322 clones. No date was affixed to this decision. Id. However, in the biosafety committee's January 20, 1978, report to the NIH in which the committee answered NIH questions about UC's misuse of pBR322 Rutter and Goodman said that Ullrich, the UC scientist actually working with the plasmid, told them that he disposed of the pBR322 clones on March 19, 1977. Lilly Ex. 3420 at HG 002873.

It is clear from the record that Ullrich did not destroy all the material associated with pBR322. He saved the purified DNA associated with the use of pBR322 plasmids, and Goodman and Rutter were aware that he did. In registered letters that Rutter and Goodman testified to having exchanged during the events in issue, they admitted that they chose to A [k]eep the cloned DNA since the experiments had already been performed . . . We believed that further sequencing of the DNA clones was acceptable since the hypothetical danger, if any, is not with the DNA itself." Lilly Ex. 3361 at HG 00069192; Lilly Ex. 3363 at WR 1072021; see also tr. at 231234, 11491153. Goodman's letter to Rutter was sent March 25, 1977; Rutter's letter to Goodman was sent March 22, 1977. These "smoking gun" letters could have had no purpose but to keep either of the writers from attributing the misuse to the other.

At trial, Rutter and Goodman testified that although the letters reflect that they chose to retain the cloned DNAs, they actually chose a different course of action. They contended that they destroyed all the cloned DNAs. Tr. at 302, 1111. When asked why he and Goodman did not amend their letters to reflect a different decision, Rutter responded:

Because acqtually we acted on the advice of DeWitt Stetten and destroyed the clones. It was unnecessary to adapt this guideline. We had carried out the activities which we had decided, namely, to destroy the clones for pBR322. Tr. at 302.

We believe the registered letters are reflective of Rutter and Goodman's contemporaneous level of concern over the pBR322 incident. We are far from convinced that the two would go so far as to mail identical registered letters to one another admitting to having taken a course of action that flew in the face of NIH regulations and, subsequently, upon abandoning that course of action, permit those letters to stand uncorrected in their respective files. Moreover, the earlier of these registered letters was dated March 22, 1977. Rutter's telephone conversation with Stetten was, at the latest, on March 19, 1977. Thus, the letters were exchanged after Rutter and Goodman had time to contemplate and decide their course of action and after the time Ullrich allegedly destroyed the tainted materials. In light of the persuasive nature of the registered letters and other evidence of record, we find Rutter and Goodman's trial testimony regarding the letters not credible.

In addition, Ullrich's trial testimony indicates that Goodman and Rutter did not decide to abandon use of the pBR322 DNA clones after they learned of pBR322's uncertified status. After Ullrich's recollection was refreshed by an examination of one of the registered letters, the following dialogue transpired:

Q. Does that refresh your recollection that you were, in fact, instructed by Drs. Goodman and Rutter to continue to work with the DNA even after you learned it was not certified?

A. I wouldn't use the word "instructed."

Q. Would you turn to Defendant's Exhibit

THE COURT: Wait just a minute. What word would you use?

THE WITNESS: It was probably the result of a discussion and an agreement among more than Drs. Howard Goodman and Rutter.

Tr. at 829.

We find by clear and convincing evidence that UC representatives continued to use at least the fruits of the uncertified plasmid in sequencing experiments well beyond the time they learned that such use was inappropriate. The Court believes such use is tantamount to use of the plasmid itself. Next, we must determine whether UC researchers misrepresented the origins of the rat insulin data data on which the '525 patent is based.

On May 9, 1977, Rutter submitted to the journal Science a manuscript in which UC researchers described the isolation of four pieces of rat insulin DNA. Lilly Ex. 3391; Lilly Ex. 3380. The pieces of DNA isolated and sequenced were denominated in the Science article as pAU1, pAU2, pAU3 and pAU4. The researchers stated in their manuscript describing their rat insulin work that they had used the bacterial plasmid pMB9 in their research efforts. Notably, pMB9 was not certified for use by the NIH until April 18, 1977.

Lilly contends that although UC researchers asserted that the work leading to the Science manuscript and, ultimately the '525 patent was done with plasmid pMB9, yet actually the work was done with the uncertified vector pBR322. Lilly argues that the DNA pieces described in the Science article really are those DNA clones obtained by UC's unauthorized use of pBR322. An examination of the evidence and trial testimony leads us to conclude that Lilly's position is well supported. We explain.

Ullrich maintained a laboratory notebook regarding his research activities and in that notebook he described his work with pBR322. See Lilly Ex. 3340. In his notebook, Ullrich specified which of the DNA clones showed a positive result from a hybridization experiment involving microorganisms transformed by the uncertified pBR322 plasmids containing rat islet

cDNA. Id. at HG 000445; tr. at 83437. Ullrich labelled each of the clones for identification purposes. Tr. at 83537. Significant to this discussion are the clones he labelled 113, 39 and 310.

Reference to these same clone numbers, i.e., 113, 39 and 310, was found on certain pages contained in a folder designated "INSULIN expt" from Howard Goodman's files. See Lilly Ex. 3354 at HG 002075. Ullrich admitted that the numbers 113, 39 and 310 "match with the numbers that we had seen before on the hybridization experiment." Ullrich further testified that several of the pages found in this folder contained his handwriting. Tr. at 84041. He also agreed that the page in this folder entitled "Summary of Insulin Clones" includes a diagram that describes where the pieces of DNA from pBR322 started and stopped. Tr. at 841.

At trial, Gilbert, in his expert testimony, relied on Ullrich's lab notes, the insulin experiment folder from Goodman's files, and a handwritten manuscript draft describing an experiment conducted in the plasmid pBR322. See Lilly Ex. 3365. Gilbert compared the sequence data from the unauthorized pBR322 research work with the sequence data reported in the Science article and concluded that the pieces of DNA reported in the article were derived from pBR322 research. Tr. at 1308, 131033. He stated that clone pAU1 listed in the Science article contained the same starting and stopping points as pBR322 clone 113; pAU2, the same as pBR322 clone 39; and pAU3, the same as pBR322 clone 310. Id. Moreover, Gilbert testified that pAU4 identified in the Science article corresponds to other sequence data reported in the pBR322 research. Tr. at 132122.

Gilbert was asked whether a second experiment, conducted in the same way as that with pBR322, likely would result in the isolation of clones having the same structure. Tr. at 1332. Gilbert answered that a researcher might isolate another clone having the same structure as that identified as 39. Tr. at 1333 34. However, he added that the same was not true of clones 113, 310 or that identified as pAU4 in the Science paper. Id. In these fragments, one would have expected variations in other experiments. Id. Even Ullrich declared it highly unlikely that the sequence reported in pAU4 would be duplicated by random chance. Tr. at 87374. UC expert Richards concurred with Ullrich's observation. Tr. at 206.

The Court finds Gilbert eminently qualified and credible. Significantly, we find that the evidence supporting his interpretation of the sequence of events is clear and convincing. Hence, we find that the duplications in the structure of pBR322derived clones and the structure of clones reported in the Science manuscript and the original '525 patent application are not products of random chance. Rather, we find that UC researchers used data derived from the pBR322 experiments in the aforementioned publications.

The Court also believes that comment on Rutter's testimony before the Senate subcommittee in November of 1977 is in order. After comparing the evidence of record against that testimony, we find that Rutter was not candid with members of the subcommittee. For example, Rutter testified that the experiments with the uncertified plasmid were not spurred by

commercial interests. Lilly Ex. 3554A at 219. Rutter also averred that none of the work in the plasmid had any relationship to Genentech, Inc. (Genentech).

Certain evidence of record counters Rutter's averments. The evidence indicates that UC representatives began collaboration discussions with both Genentech and Lilly shortly after learning that rat insulin DNA had been isolated in the uncertified pBR322. For example, on March 9, 1977 eight days after learning of UC's misuse of the plasmid and seven days after learning that an insulin clone actually had been obtained from pBR322 work Goodman contacted Lilly. Lilly Ex. 3400 at WR 10052. In his notes recording that conversation, Goodman wrote: "Have rat clone. Q. How? A. Don't want to say too much now, but can prove it." Lilly Ex. 3343A. Goodman met with Lilly personnel on March 14, 1977. Lilly Ex. 3349. In his notes of that meeting, Goodman wrote that he discussed a plasmid but that when someone asked him what plasmid, he answered, "Can't say." Id. at HG 001462. Additionally, Goodman's notes reflect that he told those present that what he wanted in exchange for what he had to offer included "money for lab" and "consulting." Id. at HG 001465.

Other evidence indicates that Goodman also approached Genentech during the same time period. On March 12, 1977, he met with Genentech representatives; Goodman's handwritten notes of that meeting indicate that Genentech offered Goodman "money for salaries, supplies, equipment, shares (common) . . . [and] consulting for me." Lilly Ex. 3347 at HG 001355. The record illustrates that Goodman called Genentech representative Ron Swanson at home the following day. Lilly Ex. 3348 at HG 001357. Goodman's notes of that telephone conversation state that Goodman "[h]inted [at] we were bringing something very valuable to the co & should be compensated for difference in kind between 'idea' & 'having [it]." Id. at HG 001357. Subsequently, other handwritten notes by Goodman illustrate that on March 15, 1977, he again called Genentech and reported the following: "Problem that in Boyer plasmid. Lay low. Not approved. Can't apply for patent yet." Lilly Ex. 3351 at HG 001364.

Significantly, although at trial Goodman could not recall when Rutter became involved in the Genentech negotiations, he did not dispute that Rutter did become involved. In fact, in Goodman's deposition of May 18, 1993, he testified that while Rutter was not present at the first of the Genentech negotiation meetings that he could recollect, Rutter was involved in all subsequent meetings. Tr. at 123738. Hence, contrary to Rutter's statements to the Senate subcommittee, we find that continued use of the fruits of the pBR322 research was driven by commercial interests and we find that those commercial interests were tied closely to Genentech.

UC asserts that even if the Court determines that the sequence data in issue did stem from work done in the uncertified plasmid pBR322, Lilly still cannot succeed in its inequitable conduct charge. Specifically, UC argues that Lilly cannot prove by clear and convincing evidence not only that UC's act was material to the prosecution of the '525 patent, but also that UC representatives committed the act with an intent to deceive the PTO examiner.

In *General Electro Music Corp. v. Samick Music Corp.*, 19 F.3d 1405 [30 USPQ2d 1149] (Fed. Cir. 1994), the patent applicant, Samick, sought expedited examination of its application because, Samick alleged, the claimed design was being infringed. Id. at 1406. In order to obtain expedited examination, Samick had to file a "petition to make special." Id.

At the time Samick filed its petition, the MPEP [Manual of Patent Examining Procedure] required that an applicant support a petition to make special with an oath or declaration alleging facts showing, among other things, "that he or she had made or caused to be made a careful and thorough search of the prior art or has a good knowledge of the pertinent prior art." Id. (quoting MPEP Section 708.02, II(5)). In light of this requirement, Samick, through its attorney, submitted a declaration stating that a prior art search had been conducted.

However, a jury determined that, contrary to Samick's attorney's declaration, Samick had not conducted a prior art search and, thus, that Samick intentionally had made a material false statement to the PTO. Id. at 1407. The Court entered judgment against Samick based on inequitable conduct rendering its patent unenforceable. Id. at 1408. The Federal Circuit affirmed. Id.

We believe the decision in Samick illustrates that the Federal Circuit's application of the concept of inequitable conduct is not limited to situations in which the patent applicant intentionally misleads the PTO in the context of prior art. Rather, inequitable conduct may be found in a variety of circumstances in which the patent applicant has abandoned his duty of candor, good faith and honesty to the PTO.

We already have determined that certain of the data found in the '525 patent was the result of an experiment conducted in the uncertified pBR322 plasmid. Moreover, in its prosecution of the '525 patent, UC failed to report its use of that vector to the PTO examiner but rather reported use of pMB9 for the data in issue. In light of these findings, the Court must determine whether UC's misrepresentation to the PTO was material to the patentability of the '525 patent.

After considering the facts and the law, we find that there is a substantial likelihood that a reasonable examiner would have considered UC's unauthorized use of pBR322 important in his patentability determination. UC, as an institution that accepted funding from the NIH, was obligated to follow the guidelines issued by that agency; UC was aware of its obligation. Even after UC representatives admittedly learned of their premature use of the subject plasmid, they, nonetheless, continued, at the very least, to use the sequence data they secured from their tainted research. A reasonable examiner easily could have determined that without use of the unauthorized plasmid and the data therefrom, UC's application for the '525 patent would not have acquired its May 27, 1977, file date. Indeed, it is impossible to determine whether UC would have been the first to make patent application had its representatives followed the rules to which its competitors were bound.

The Court also must consider the issue of intent, though the issue need not detain us long. First, we consider UC's forbidden use of pBR322 long past its recognition of the uncertified status of that plasmid. Second, we reiterate our determination that UC representatives incorporated pBR322 data into the '525 patent application an incorporation that was not accompanied by candor or honesty in UC's prosecution of the '525 patent application. Considering the admissions contained in the exchange of letters between Rutter and Goodman, we find no room for doubt that UC's failure to reveal its unauthorized use of pBR322 was intentional. Moreover, the Court finds that such intentional failure necessarily was meant to deceive or mislead the PTO examiner. UC was aware of its violation of the NIH safety guidelines and apparently was concerned that the PTO would endorse neither its experimental use of uncertified pBR322 nor its use of the results of that experiment in the '525 patent application.

The United States Supreme Court has stated that

> . . . a patent is an exception to the general rule against monopolies and to the right to access to a free and open market. The far-reaching social and economic consequences of a patent, therefore, give the public a paramount interest in seeing that patent monopolies spring from backgrounds free from fraud or other inequitable conduct and that such monopolies are kept within their legitimate scope.

Precision Instrument Mfg. Co. v. Automotive Maintenance Mach. Co., 324 U.S. 806, 816 [65 USPQ 133] (1945). We are persuaded that endorsement of UC's conduct by enforcing the '525 patent would counter the public's interest. Hence, we hold that the '525 patent is unenforceable based on UC's inequitable conduct.

These regulations, however, did not pacify everyone. Public debate in Cambridge, Massachusetts about the safety of recombinant DNA research led to a determination that such research was banned from "the City of Cambridge until the citizens of Cambridge and the city council had convinced themselves that it was safe for the research to continue." Tr. at 1299. A citizens committee was appointed to investigate the matter and, in early 1977, the ban was lifted. Tr. at 12991300.

Rutter and Goodman were coprincipal investigators for the research in issue in the instant case. Lilly. Ex. 3420 at HG 002873. Rutter was then chairman of the Department of Biochemistry and Biophysics at the University of California. Tr. at 106; Lilly Ex. 3554A at 200. Goodman was then a professor in the Department of Biochemistry at the University. Tr. at 1106. During some of the time in which the subject research was being conducted, Goodman was out of the country on sabbatical leave. His absence, however, is not relevant to this discussion.

An institutional biohazard committee was established in each institution that received NIH funding. According to the guidelines, such a committee was responsible for, inter alia, certifying,

and recertifying annually, to NIH that the facilities, procedures, practices, training, and expertise of involved personnel had been reviewed and approved. Lilly Ex. 3547 at HG2 580781.

Hearings before qa subcommittee of the United States Senate were held in November of 1977 to examine the potential need for federal regulation governing all recombinant DNA research, including research not funded by the NIH. Lilly Ex. 3554A. At the hearings, Rutter testified about the pBR322 incident. Id. at 20024. Rutter told the subcommittee, inter alia, that the application for the '525 patent was not based on PBR322 research, id. at 21718, and that there were no commercial interests motivating UC to use the uncertified plasmid. Id. at 219.

The record suggests that Goodman actually became aware of the uncertified status of pBR322 on March 1, 1977. Lilly Ex. 3400 at WR 10052. Reportedly, on March 4, 1977, Goodman informed Rutter of the matter. Id.

The way in which ORDA became aware of the pBR322 incident is discussed infra at 7374.

In identical letters Rutter and Goodman exchanged with each other in March of 1977, discussed infra, they state that on March 5, 1977, Ullrich destroyed the "plasmid containing cells and kept only the purified DNA from the clones. . . ." Lilly Ex. 3361 at HG 000691; Lilly Ex. 3363 at WR 10720.

Gilbert also relied on Goodman's notes of a March 14, 1977, meeting with Lilly. Tr. at 131516; Lilly Ex. 3349. At this meeting, Goodman had drawn on the board a plasmid labeled in the same fashion as one in Goodman's insulin experiment folder. Lilly Ex. 3349 at HG 001462. In the experiment folder, the drawing appears under the title, "clone 113." Lilly Ex. 3354 at HG 002081. The Goodman Lilly meeting was on March 14, 1977. Hence, Gilbert concluded that the sequence listed in Goodman's insulin experiment had to exist before that date. Because Rutter testified that UC experiments with plasmid pCR1 were ineffective, tr. at 137, and because pMB9 was not even certified for use until April 18, 1977, the sequence described in Goodman's insulin experiment folder, and later drawn on the board at the Lilly meeting, had to be a pBR322 sequence. Tr. at 1328.

At trial, Lilly introduced certain drafts of research manuscripts found in UC's files. Lilly contends that although these manuscripts purport to arise from research conducted with certified plasmids, yet the data contained therein illustrate that the manuscripts actually were based on work done with the uncertified vector pBR322.

We agree with Lilly that the record illustrates that the data contained in these manuscripts originated in pBR322 research work. However, we already have found that the research work reported in the Science article and, ultimately, in the '525 patent, is based, at least in part, on work done in the uncertified plasmid. Thus, while the common threads in these manuscripts (e.g., identical sequencing errors, identical typographical errors) strengthen Lilly's argument that the

manuscripts all rely upon pBR322 research work, a detailed explanation of those documents and their corresponding features is unnecessary for purposes of this decision.

Genentech, a corporation located in California, is involved in other of the six cases consolidated in this Court for pretrial proceedings by the Judicial Panel on Multidistrict Litigation. See, supra at 12.

At trial, Goodman verified that the notes were in his handwriting. Tr. at 1219.

Evidence of record convinces us that Goodman was referring to pBR322 when he named the "Boyer plasmid." Ullrich testified that scientists in Herb Boyer's laboratory developed pBR322. Tr. at 79798. Moreover, other testimony reveals that the only plasmid with which UC researchers had achieved success by March of 1977 was the uncertified pBR322. Specifically, Rutter averred that UC was unsuccessful in its attempts to clone in plasmid pCR1. Tr. at 137. Furthermore, Rutter stated that UC researchers did not begin using vector pMB9 until after it was approved by the NIH. Tr. at 136. That approval was not received until April of 1977. Consequently, Goodman's midMarch 1977 reference to "Boyer plasmid" must mean pBR322.

It also is interesting to note that by agreement with UC the inventors are entitled to 50 percent of the net profits derived from any royalties or fees received from patent rights.

Lilly contends that UC's inequitable conduct in procurement of the '525 patent should render the '740 patent unenforceable as well. However, we believe UC acted inequitably in the prosecution of the '740 patent itself, as discussed infra. Therefore, we need not consider whether UC's conduct associated with the '525 patent should hinder its ability to enforce another patent in suit.

A NOTE ON SOURCES

This paper was written on short notice, over two successive weekends, in order to meet NBAC's pressing deadlines. I have relied heavily on others' accounts of many of the events, and I am indebted to them. John C. Fletcher (University of Virginia) kindly shared copies of public NIH files bearing on the Cline case,[54] and Rebecca Lawson (Office of Recombinant DNA Activities, NIH) quickly found and copied files on the UCSF and Harvard recombinant DNA guideline cases.[30, 55] Laura Bishop of the National Reference Center for Bioethics Literature did several literature searches on very short notice and emailed the results. Susan Poland from the Kennedy Institute of Ethics at Georgetown University took a late Friday road trip to secure the federal court documents. These generous gestures were immensely helpful in reconstructing the events. I have e-mailed and called many of the principals to ask for corrections to or comments on published accounts and the public record.

With more time, more primary sources could have been reviewed and cited. The accounts are accurate to the extent required here, I believe, because several scholars and policy analysts

have worked hard to construct accounts, and those involved in the debates concur that the accounts are generally accurate. The facts of the UCSF insulin-cloning incident were subject to a formal federal trial, but some findings remain under appeal. For NBAC's deliberations about the merits of moratoria, however, further detail may not be necessary.

The main source for the UCSF cloning story was Stephen Hall's beautifully written and lively book *Invisible Frontiers: The Race to Synthesize a Human Gene*,[1] although some of the facts did not come out until the University of California-Eli Lilly litigation in 1995 (see appendix—and footnote 31). Letters from William Rutter and his attorney Rachel Krevans of Morrison & Foerster and from Kirke Hasson (on behalf of Howard Goodman) helped separate the agreed from the contested facts in the UCSF cloning incidents. The broader history of the recombinant DNA debate is recounted by Bernard Talbot,[20] Sheldon Krimsky,[17] John Lear,[16] and Judith Swazey, et al.[19] Many relevant background documents were collected for the *Recombinant DNA Technical Bulletin* maintained by NIH. James Watson and John Tooze selected many of the seminal documents for *The DNA Story*.[15] And finally, Donald Fredrickson has reviewed part of this history in previous articles,[18, 56] and is working on a book. OTA's 1981 report, *Impacts of Applied Genetics,* includes an excellent brief history of the recombinant DNA controversy and the early origins of commercial biotechnology,[52] although, surprisingly, it does not mention the guideline infractions. The first *Federal Register* guidelines notice also has an expansive and detailed history of events leading up to them.[57]

For background on review of gene therapy, several sources were particularly useful. LeRoy Walters chaired numerous relevant oversight groups for over a decade—the 1984 OTA workshop panel, the Human Gene Therapy Working Group, the Human Gene Therapy Subcommittee, and the Recombinant DNA Advisory Committee. He and coauthor Judy Palmer devoted the better part of a chapter in their recent book to the history of how human gene therapy has been reviewed at NIH and the Food and Drug Administration, and that is the best place to start for a chronology.[41] Scope Note 24, by Mary Carrington Coutts, summarizes the salient literature up to 1991.[58] Eve Nichols's book for the Institute of Medicine and a 1984 OTA report review the process before the first real protocols appeared.[59, 60] And *Splicing Life*, the report by the President's Commission, was the first major public policy statement and remains among the most significant.[39] The recent changes in gene therapy review, with NIH's RAC only reviewing protocols that raise novel issues are stated in official government notices.[3, 61] No discussion of gene therapy is complete without noting the sober December 1995 report that urged more attention to scientific foundations and less to hype.[62]

The best and most detailed account of the Cline case is contained in chapters six and seven of Larry Thompson's book *Correcting the Code*,[53] which was guided by interviews with Cline, his collaborators abroad, the patients and their families, and numerous NIH officials. His account goes well beyond the NIH case file. [36, 37, 54, 63] The early events in human gene therapy are summarized well by John Fletcher.[64] The human gene therapy account in this paper is partly based on files collected for the 1984 report *Human Gene Therapy*,[60] but much more detailed accounts

have been published since. A compendious volume on gene therapy was written by *Chicago Tribune* reporters Jeff Lyon and Peter Gorner.[65]

The tortuous history of fetal research and embryo research is reviewed most concisely and effectively by Constance Pechura,[66] and summarized through early 1994 by the Institute of Medicine.[67] Alta Charo analyzes the results of NIH's Human Embryo Research Panel,[13] and how its findings were rejected by President Clinton. The closely parallel experience of the Human Fetal Tissue Transplantation Research Panel is reviewed by Childress,[12] and the *de facto* moratorium on fetal research due to the absence of an Ethics Advisory Board in DHHS is documented by OTA.[68] The earlier history of fetal research is summarized well by Dorothy Lehrman in a report for the Association of American Medical Colleges,[69] and touched on by a 1989 Institute of Medicine report.[70]

The role of bioethics commissions has generated its own small literature. Michael Yesley comments on the National Commission from his perspective as its executive director.[6] The President's Commission was the subject of a symposium a year after it closed its doors,[71] and many articles have been written about it. The most useful recent synthetic literature comes from a 1995 Institute of Medicine report that contains pertinent background papers, including especially useful ones by Dan Brock[72] and Bradford Gray.[73] Background on federal, state, and international bioethics commissions is collected in the 1993 OTA report[7] which contributed directly to the establishment of NBAC. It includes the legislative language creating the National and President's Commissions and the Biomedical Ethics Board and Advisory Committee, as well as the 1976 and 1979 EAB charters. The point about the separate functions of public deliberation and consensus building versus protocol review and guideline preparation are covered in greater detail, [74, 75] as well as difficulties in steering a research program and attempting policy deliberation in the same group.[76]

A 1996 report, *Understanding Risk*, is highly commended for thinking about how to incorporate risk assessment into public policy.[77]

The following is a record of direct contacts through May 3, 1997.

Phone or face-to-face conversations:

Charles Weiner, MIT, 25 March
Bernard Talbott, NCRR, 25 March
William Gartland, NIDR, 25 March
Judith Swazey, Acadia Institute, 24 March
LeRoy Walters, 24 March
Rebecca Lawson, ORDA, 25 March
John Fletcher, 21 March
Larry Thompson, 2 April
Stephen Hall, New York Times, 3 April
Walter Gilbert, Harvard University, 3 April

Amy Hamilton, Eli Lilly & Co., 9 April
[confidential source, Genentech, 3 April]

Letters:

Kirke Hasson, Pillsbury, Madison & Sutro LLP, 29 April
William Rutter, Chiron Corporation, 30 April
Rachel Krevans, Morrison & Foerster, 30 April

E-mail from:

Axel Ullrich, Max Planck Institute for Biochemistry, Martinsried, Germany, 21 March
Donald S. Fredrickson, National Institutes of Health, 21 March
Barbara Culliton, Editor, *Nature Medicine,* 24 March
Charles Weiner, MIT, 24 March
Larry Thompson, FDA, 25 March
John Fletcher, University of Virginia, 20 March
Laura Bishop, NCRBL (who did literature searches at the National Reference Center for Bioethics Literature, Georgetown University), 26 March
LeRoy Walters, 7 April
Peter Seeburg, Center of Molecular Biology (ZMBH), University of Heidelberg, 11 April

E-mailed to:

Martin Cline, UCLA, 20 March

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