The Cambridge Model by Sam Lipson

How public oversight of biotech is good for everyone — even business

While it is generally understood that infectious organisms pose a health risk to researchers, and perhaps to those with whom they are in contact, public concern about the immediate public health consequences of scientific research has a short history in the United States. There is a long tradition of non-intervention – if not always trust – in scientific endeavors. Until the regulation of gene-splicing experiments in the mid-1970s, scientific research in the U.S. had never been subjected to local, state or federal law.

At that time, two major dynamics – shifts in public trust and startling advances in molecular biology – combined to change the public's perception of biology. Rising concerns over biotechnology's capacity to cause profound and unwelcome changes in human affairs and the environment spurred demands for science to be held accountable to the public. This new skepticism was further fueled by real and perceived academic arrogance towards public accountability, and by public recognition that no one could honestly answer many of the questions being asked about the potential consequences of new genetic technologies.

While the greatest breaches of public trust were associated with the research and testing of biological and nuclear weapons by the national defense establishment, the medical community had also been implicated in secretive and unethical practices. As research involving human experimentation on prison inmates, people with disabilities, racial minorities, and the public-at-large came to light in the immediate post-Watergate era, many citizens found little reason to accept official reassurances about technologies capable of altering DNA itself. There was a deepening suspicion that real risks posed by advances in science and technology were not being accurately represented to the public.

In the 1960s and 1970s, revolutionary advances increased scientists' ability to isolate, characterize and alter the genomes of bacteria and other organisms, and it became increasingly clear that this knowledge could be widely applied before its consequences were well understood. In 1975, an historic conference took place at the Asilomar Conference Center in Monterey, California, at which molecular biologists discussed the scientific, public health and ethical consequences of new genetic technologies. Among the leading institutions at which this work was being pursued were Harvard and MIT – both located within Cambridge, Massachusetts, one of the most densely populated communities in the country.

While the Asilomar Conference did not result in a consensus even among those most equipped to grasp the science, agreements were made to limit some work thought to be unusually risky, and it was understood that some broad policies and protocols were needed to address the risks and uncertainties posed by this work. Soon after Asilomar, the National Institutes of Health (NIH) assembled a panel of researchers to develop a set of guidelines for research involving recombinant DNA, though even this protocol document was soon subject to further debate and change. In 1976, in Cambridge, even before the release of the NIH Guidelines on Research Involving Recombinant DNA Molecules (henceforth the NIH Guidelines), events began to unfold that led to a series of high-profile, nationally reported public debates and eventually to the country's first regulations involving genetic research. One concern raised in the course of this historic public debate was whether it was appropriate for guidelines to be developed by a research agency composed primarily of those most likely to identify with – or even be associated with – investigators undertaking the research. Further concerns were raised

EXCERPTS FROM THE CAMBRIDGE RDNA ORDINANCE

Section 8.20.010 Purpose.

All use of recombinant DNA (RDNA) in the City shall be undertaken only in strict conformity with the guidelines set out in Section 8.20.020, the other requirements of this chapter and health regulations promulgated by the Cambridge Commissioner of Health and Hospitals (the Commissioner). (Ord. 1148 (part), 1993)

Section 8.20.040 Cambridge Biosafety Committee — Duties and Responsibilities.

The responsibilities of the CBC shall include:

A. Establishing policies, procedures and criteria to aid in the implementation of this chapter;
B. Determining the manner in which permit holders make reports or applications to the CBC, and the type of information required in such reports or applications. Reviewing reports, applications and recommendations by the Institutional Biosafety Committees (IBC) and approving them where appropriate. Carrying out site visits to permitted facilities;
C. Reviewing manuals and worker training programs, approving health-safety programs and monitoring the procedures required by this chapter;
D. Developing a procedure for persons to report to the CBC violations ofthis chapter, the guidelines or any health regulation.

about the limited nature of the Guidelines, which were only intended to govern research funded directly by the NIH.

The controversy in Cambridge initially arose over a proposal by Harvard University, in early 1976, to renovate an existing research laboratory for use as a Biosafety Level 3 (then called P3) facility accomodating genetic and viral research. After concerns were raised by members of the Harvard biology faculty and the public, the City of Cambridge conducted hearings in June and July of that year to allow public discussion of this proposal. These meetings coincided with the release of the NIH Guidelines. Discussion focused on whether to allow such research to be conducted in Cambridge, and how the federal protocol could be used. As a result of this process, the City Council created a Cambridge Experimentation Review Board (CERB) and invited lay residents, a social scientist and a medical doctor, also residents, to join this Board. With a moratorium on research involving recombinant DNA (rDNA) in place, the CERB was entrusted to examine the issues and report back to the Council. Following extensive hearings and testimony, the CERB recommended encoding the NIH Guidelines into local law and creating a Cambridge Biohazards Committee (later the Cambridge Biosafety Committee) to oversee enforcement of this new ordinance. In February 1977, by a unanimous vote of the City Council, Cambridge became the first jurisdiction in the U.S. to directly regulate basic scientific research which used recombinant DNA.

National Institute's of Health Director's Advisory Committee meets to discuss recombinant DNA guidelines (1977)

The ordinance was written with small-scale academic research in mind, but the development of gene-splicing techniques necessitated revisiting the ordinance's language when the Biogen Corporation, a genetic engineering firm with headquarters in Switzerland, proposed in 1980 to construct a commercial facility in Cambridge. The CERB and the Cambridge Biohazards Committee (CBC) decided to review this proposal and held a joint hearing in the fall of that year.

In the four years since the original debates had taken place, the tenor of the discussion had changed considerably, and the two review committees adopted a more tolerant and accommodating posture to reflect this shift. In the end, the CERB and CBC recommended that the 1977 ordinance be amended to include safeguards to protect the public from releases of organisms that could escape the laboratory; measures to assure worker safety; and mechanisms for the establishment of a permit-granting process, to be administered by the Department of Health and Hospitals (later the Cambridge Public Health Department). In effect, Cambridge had altered local oversight rules to acknowledge the commercial direction that genetic engineering had taken and would likely take in the future. In the absence of state or federal regulations, the city saw that a more traditional form of health and safety review was appropriate to this new industry.

When asked why they would choose to locate their research and development headquarters in a city with an rDNA ordinance, an oversight committee, and a history of deep suspicion – even animosity – towards genetic engineering research, Biogen officials replied that Cambridge's established review and regulatory process, and the more mature understanding of the field, were in fact part of the community's appeal . A process that was once seen as an obstacle to academic freedom and commercial enterprise engendered an assurance of cooperation and a tacit acknowledgement that such constraints represented reasonable and prudent local governance. What began as an electrifying display of resistance by an energized population became a demonstration of the power of public oversight and private disclosure to benefit all the parties.

Cambridge has now become the *de facto* global capital for biotech research and development, with fifty biotech licenses held by leading biotech and pharmaceutical firms. The presence of so many of the key industry players, and the proximity of Harvard, MIT and several of the nation's most prestigious research hospitals, has transformed much of the city's available industrial land into a collection of campus-like clusters or corridors of research. The industry-academic-healthcare axis has now established Cambridge as an industry-wide think tank and a cross-licensing mecca.

THE CHANGING BIOTECH INDUSTRY IN CAMBRIDGE

Though the Cambridge rDNA ordinance eventually underwent one more major amendment, in which requirements for special large-scale permits were eliminated in 1993, the current enforcement procedures have remained largely unchanged since the 1981 amendments. The Cambridge Biohazards Committee became the Cambridge Biosafety Committee; the Department of Health and Hospitals was granted permission by the Massachusetts state legislature in 1995 to become the quasi-public Cambridge Public Health Commission, also called the Cambridge Health Alliance; and the number of rDNA permits granted has slowly increased. The biggest shift in the impact of genetic engineering research and development in the city involves not how many

licenses have been approved, but rather the scale of the work now being conducted in many of these facilities. Along with an explosion in the capitalization of biotech companies, major pharmaceutical players have acquired many of the more successful start-up biotech firms that made the city their first home. While a number of companies outgrew their Cambridge facilities, most have kept their R&D focus in town while exporting production capacity to less expensive locations in Massachusetts and elsewhere.

Another shift in the nature of the research conducted within Cambridge in the past decade is the increasing use of laboratory space specifically designed and constructed for the research needs of companies using the facility. Early start-ups in Cambridge were often spun off from Harvard or MIT, and tended to resemble academic laboratories with less than ideal quarters, lax housekeeping practices and slim budgets. Many were poorly funded and forced to make do in old office buildings, basements and other out-dated facilities. As biotech was recognized to have enormous growth potential and several newly patented biopharmaceuticals began to clear FDA approval and reach the marketplace, investment firms lined up to capitalize on these firms. In many respects, this cash-flow has made the task of laboratory review and inspection much easier.

"*One Piece Positive Pressure Ventilated Suits*" *from* National Institutes of Health Laboratory Safety Monograph:A Supplement to the NIH Guidelines for Recombinant DNA Research *(1978)*

Another benefit of this new funding, though not an inevitable one, has been the professionalization of lab staff and increased emphasis on occupational safety and lab safety training. More funding has increased the need to be seen as well-managed and accountable. A larger number of staff with biosafety responsibilities has had formal training in this area, and the pool of experienced biosafety officers has grown dramatically. Smaller start-ups generally did not have the luxury of full-time biosafety professionals, frequently relying on lead scientists to perform administrative functions for which they were not well suited by training, temperament or inclination.

ENFORCEMENT OF THE ORDINANCE

The system for enforcing the Cambridge ordinance has worked well in a changing biotech landscape. The NIH Guidelines impose a great deal of responsibility for protocol and containment decisions within a firm or institution on its own Institutional Biosafety Committee (IBC). Cambridge also relies on the IBC's judgments for assigning appropriate biosafety standards, both physical and procedural, but plays a much more active role in reviewing such decisions and in seeking assurance that community representation on the IBC is maintained. The ordinance requires that the minutes, or proceedings, of each IBC meeting and the annual meeting are submitted to the CBC. Furthermore, any changes in containment level – for example, from a Biosafety Level One to Biosafety Level Two – or in lab location within the city require an amendment to the rDNA permit. The CBC spends most of its time reviewing changes in practices or conditions within previously licensed labs and scrutinizing new applicants.

The process for presenting license requests to the CBC during its monthly meeting is similar for new permit applicants and for those seeking changes to their permits. A template is provided to demonstrate the sort of information and the level of detail sought by the committee. Once hearings are scheduled, applicants must come to discuss the details of their facility and the protocols being followed. They must describe the purpose of their company, the specific technology being employed, the types of biological vectors and host cells being used, and the genes that will be altered. The applicants provide floor plans, medical surveillance programs, subcontracts for waste removal, pest control, instrument validation, and ventilation, and discuss the status of all other required local, state, and federal permits being sought or amended. The sample presentation provides valuable experience for presenters who have never been asked to discuss the details of their work with anyone but venture capitalists or their peers, and helps the committee verify the Risk Group assigned to the proposed work and the final Biosafety Levels that must be established at the facility. Questions from the committee follow the presentation, with occasional requests for further documentation or verification by the applicant.

After the presentation, a site visit is scheduled to ensure that lab areas are fully equipped and properly fitted with signage, safety devices, waste containers, emergency phone numbers, and equipment certification. Site visits are scheduled to accomodate committee members, though CBC staff conduct most inspections. In recognition of the limited time available to CBC members for administrative and enforcement tasks, staff duties are primarily executed by the Director of Environmental Health, a Public Health Department position. All this may sound dry – but the sum of these practicalities ensures the safety of workers and the community.

CONCLUSION

The Cambridge Biosafety Committee has endeavored to improve compliance with the ordinance and expand the knowledge of community representatives and biotech licensees. CBC and the Public Health Department host seminars periodically to provide biosafety instruction, a review of NIH Guidelines requirements, and a discussion of emerging issues in biosafety and bioethics. In September 2002 the CBC conducted a four-evening, 16-hour series on biosafety that drew participants from across New England and included local biosafety professionals from industry and academia, IBC community representatives, and state and local public health officials from throughout Massachusetts. In addition to providing biosafety instruction to attendees, the Cambridge Biosafety Forum offered other lectures on the implications of the USA Patriot Act in academic laboratories and also on the establishment of animal care and use programs, medical surveillance of biotech employees, and panel discussions on biosafety considerations for production-scale biotech firms and on risks and benefits of biotechnology.

The value of the Cambridge Biosafety Committee has also been made apparent by activities in neighboring Boston, where Boston University hopes to construct a controversial federal biodefense facility [*See "Boston University's $1.6 Billion Secret",* GeneWatch *Volume 16, Number 3*]. While Boston has an rDNA research ordinance almost identical to Cambridge's, its enforcement through a standing public biosafety committee has lapsed. Unaccountable to mechanisms of public review, Boston University has severely limited access to details of their proposals, and largely dictated the terms of public debate. Concerned citizens' groups and the Boston Public Health Commission have requested the Cambridge Biosafety Committee's guidance in setting up a system of community oversight.

As an early leader in establishing the right of local communities to regulate biotechnology, the Cambridge Biosafety Committee and the Cambridge Public Health Department continue to maintain a high profile in biotech regulatory affairs. While the ordinance was never intended to regulate or adjudicate the many ethical questions which have arisen from the application of technologies that manipulate DNA, the importance of ensuring thorough regulatory oversight has not lessened.

Over the past quarter century, CBC staff have been contacted by communities around the state and across the country that are adopting or considering local rDNA laws within their own jurisdictions. In Cambridge, it has been shown that a city can address private and public interests in mutually beneficial ways. As new frontiers and controversies in biotechnology emerge, the committee's example of reasonable and meaningful oversight reaches far beyond the city's borders. ■■■

Sam Lipson *is Director of Environmental Health at the Cambridge Public Health Department.*

OUT OF SIGHT, OUT OF MIND BY BRANDON KEIM

How Harvard University exploited rural Chinese villagers for their DNA

Not even the world's most prestigious place of learning is immune to the carelessness and disregard that grow where financial interests and academic inquiry meet without oversight.

In the early 1990s, the impoverished residents of China's remote Anhui province were believed to harbor a twenty-first century version of buried treasure: a large and homogeneous gene pool, isolated for two thousand years. Researchers hoped that the population's relative uniformity would make it possible to link genetic mutations with diseases. Such information could ostensibly then be used to develop wildly profitable treatments. [*For more on this rationale, see "The Genomics Dream in Iceland",* GeneWatch *Volume 15 Number 4*].

When Scott Weiss, a Harvard University respiratory epidemiologist, told Geoffrey Duyk, a geneticist who had left Harvard to join a biotechnology start-up called Millennium Pharmaceuticals, that one of his post-doctoral fellows came from the Anhui province, they quickly saw the possibilities. Harvard and Millennium announced a partnership: Weiss' fellow, Xu Xiping, would direct the collection of DNA in Anhui, for which Millennium would pay the University $3 million. From the blood of Anhui's villagers, they believed, would come clues to the genetic causes of asthma, obesity, miscarriages, and schizophrenia.

Five months later, Swedish pharmaceutical giant Astra AB had swelled Millennium's accounts with a $53 million investment; the company would also receive $70 million from the pharmaceutical company Hoffmann-Laroche. In both cases, Millennium's access to the Anhui population's DNA was critical to securing funding; the DNA's potential was also featured prominently when Millennium went public in 1996, raising $54 million in its initial public offering.