

PREDICTING BIOCONTAINMENT REQUIREMENTS FOR THE FUTURE

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ABSTRACT

This paper was first presented as one of four keynote addresses at the 5th National Symposium on Biosafety held in Atlanta, Georgia on January 17-20, 1998 (Richmond, 1998). The Symposium was sponsored by the Centers for Disease Control and Prevention (CDC) and the American Biological Safety Association (ABSA). The original title of the address "Where are we going?" was selected by the Symposium's planning committee. While contemplation of the future can be an enjoyable intellectual exercise, predictions about the course of science and the corresponding future requirements of biocontainment will yield only uncertain results. Contemporary science has demonstrated that revolutions in science occur with spontaneity. The best recent example is the revolution in the biomedical sciences brought about by recombinant DNA in the 1970s. Scientists cannot predict the next revolution, but they are keenly vigilant to discern its occurrence. Biological safety professionals must be equally prepared to recognize major scientific advancements since the future may require swift changes in the practice of biocontainment as was evident in the recombination DNA revolution. To be prepared, biological safety professionals must establish a continuing and meaningful dialogue with scientists. For this to happen, the biological safety professional must become better informed of current knowledge and strive to gain the trust and respect of the scientific community. Biological safety professionals, as partners in science, can ensure that biocontainment keeps pace with new requirements that will most certainly occur in the future.

Future of Biomedical Research

One way to consider the future of biomedical research is to look at how science is conducted in a major research institution like the Howard Hughes

Medical Institute (HHMI). Hughes investigators are given salaries, several positions for post docs and technicians, substantial resources for supplies and equipment, adequate space, and administrative support. This level of support is provided for three, five, or seven years following an investigator's initial appointment as an assistant, associate or full investigator, respectively. Promotions and renewal of support are dependent entirely on the merit of scientific accomplishments determined by peer review. At no time in the course of employment is an investigator required to follow a directed research plan or to submit proposed research ideas to the Institute for approval. Investigators are free to use their creativity and intellect to be adventurous in the pursuit of scientific knowledge.

This approach to basic biomedical research is credited by many distinguished scientists as a formula that can lead to important discoveries. In 1997, in a presentation at the conference on the Future of Biomedical Research sponsored by the Federation of American Societies for Experimental Biology, The Brookings Institution, and the American Enterprise Institute, Nobel Laureate Dr. Arthur Kornberg said that institutionally planned or directed research is "fundamentally flawed because discoveries are commonly serendipitous" (Kornberg, 1997). He went on to say that the great discoveries that have laid the groundwork for "major transformations in the acquisition and application of knowledge" have been discoveries that "have come from the pursuit of curiosity about questions in physics, chemistry and biology, apparently unrelated at the outset to a specific medical or practical problem." For example, the recombinant DNA technology and genetic engineering revolution was based on, in Kornberg's words, "the discoveries of enzymes that make, break and seal DNA." Kornberg's discovery of DNA polymerase, for which he was awarded the Nobel Prize in Physiology or Medicine in 1959, helped create the foundation for this revolution. He readily admits that his wonderful

career in science was motivated fully by the desire to satisfy curiosity.

Kornberg and others believe that recombinant DNA technology and genetic engineering represent "the most revolutionary advance in the history of biological science." Dr. Purnell Chopin, president of HHMI, has said that "the life sciences are experiencing the same historic transformation that occurred earlier in this century in physics. Our understanding of living organisms has been totally recast in the four decades since Watson and Crick determined the structure of DNA." And the distinguished Nobel Laureate George Palade, a founder of modern cell biology, has said that "one must go back to the Italian Renaissance to find a comparable time of human creativity and imagination." This excitement and the abundant creative talent that exists today in the biomedical sciences will most certainly lead to future discoveries that will yet again transform the tapestry of medical science. Scientists are wise enough not to predict the next revolution, but they are keenly vigilant to discern its occurrence.

Biological Safety and Research Interaction

Although the future of biomedical science may be unpredictable, the inexorable pursuit of curiosity by scientists will continue to have a profound affect on the biological safety community. It is appropriate to look to the future when designing new facilities that hopefully will provide safe space for the conduct of science. And it is appropriate to consider potential biohazards that might be associated with new experiments prior to their being carried out. Both of these endeavors require that there be a code of practice accepted by both the biomedical research community and the biological safety community for making biocontainment decisions.

In general, the discipline of biological safety has lagged behind the pursuit of science. For example, the need to address microbes as biohazards became apparent following the recognition by scientists of the problem of laboratory-acquired infections in the handling of human pathogens. The commitment to address potential biohazards of oncogenic viruses was made by scientists at the time this field was expanding. And scientists were first to recognize that potential biohazards might be associated with the early experiments that led to recombinant DNA molecules. In all of these endeavors, scientists advo-

cated two principles of biological safety: biocontainment should be made an essential consideration in the design of experiments involving the use of potentially hazardous microorganisms; and the effectiveness of biocontainment should match, as close as possible, the estimated risk. Professionals in biological safety were sought to help refine the methods and practices for executing these principles. This collaboration often resulted in more stringent biocontainment than could be scientifically justified. This result should not be surprising because a valid safety persuasion is to err on the side of safety. Nevertheless, potentially adverse consequences have accrued from these experiences when this persuasion was taken too far.

Several examples can be cited. A maximum biocontainment laboratory was built at NIH in 1969 as a contingency for the hoped-for discovery of a human cancer virus. Such a virus would be considered a potential lethal risk because a laboratory-acquired infection might lead to incurable cancer. This facility included all secondary barriers now appropriate for biosafety level 4. Cancer virologists of the National Cancer Institute were assigned to this facility and required to follow practices equivalent to biosafety level 3. Most investigators in the facility thought the biocontainment measures were grossly exaggerated in comparison with any plausible estimation of risk. The consequence of this inconsistency was abandonment of the vigilance and commitment necessary to sustain proficiency in safe practices. Biocontainment measures were quickly relaxed with the persuasion of scientists to set a closer match between biocontainment and estimated risk.

The original *NIH Guidelines for Recombinant DNA Research*, issued in June of 1976, set higher biocontainment standards than most scientists thought were necessary. It was anticipated, however, that the *Guidelines* would be quickly relaxed based on the knowledge that would be gained from the many experiments that would now occur in this field. Unfortunately, there was no provision in the *Guidelines* to formally make changes. A public process had to be developed to make modifications. No changes, though scientifically justified, were made to the *Guidelines* for over two years, and then only at a snail's pace.

This experience has also brought unfortunate

consequences that have complicated the interactions between the biological safety community and the biomedical research community. Today, most academic scientists believe the sole role of the biological safety officer is to provide an essential institutional compliance function for certifying that research laboratories meet the BSL facility criteria designated by NIH or CDC for work with recombinant DNA molecules or human bloodborne pathogens. Scientists are reluctant to raise issues of research risks with their institutional biosafety officers for fear of an excessive biocontainment response. They prefer to be reassured about their questions of risk through discussions only with their scientific colleagues. Others agree with the view of Dr. Philip Leder, an HHMI investigator, who made the following statement in a recent HHMI laboratory safety video (HHMI, 1997):

Perhaps our notion of what's dangerous and what's not dangerous and what proper practice should be is distorted from the controversy that surrounded DNA technology. When it was introduced, procedures which most thoughtful people felt should be really addressed with a certain level of safety, were exaggerated perhaps in the public mind. And when there isn't a sufficient justification for a safety procedure it loses its meaning, and you lose respect for it. That is important to overcome because when you do work in a laboratory there are reagents in the laboratory and procedures that are very worthy of the kind of respect that is necessary to deal with them.

One notable example where health and safety professionals developed appropriate biocontainment measures in concert with an evolving scientific program was the U.S. Government's initiative at Fort Detrick to develop a biological warfare defensive capability. During the period 1946 through 1972, under the able leadership of Dr. Arnold G. Wedum, the Fort Detrick biological safety professionals in collaboration with scientists and engineers were responsible for the greatest advancements in the acquisition and application of biological safety knowledge during the twentieth century. A primary mission of Fort Detrick was to protect the health of laboratory workers who handled virulent lethal pathogens in high risk experi-

mental protocols. Most of these protocols required the use of stringent safety practices, gastight cabinets and sophisticated biocontainment facilities. Dr. Wedum was an authority in risk assessment and his organization set the standard for biocontainment effectiveness.

Dr. Wedum advocated the principle that scientists espoused for matching risks with biocontainment of appropriate effectiveness. He encouraged biomedical scientists to use their scientific knowledge and discriminating judgment when assessing risks and selecting appropriate safeguards. And he respected their assessments. He was never quick to apply a higher level of biocontainment than what responsible and knowledgeable scientists had concluded would be appropriate for controlling risks in biomedical research. The biological safety community needs to follow Dr. Wedum's example.

Value of Secondary Barriers

Many biosafety officers today may not agree with Dr. Wedum's assessment of the value of secondary barriers. They would argue that secondary barriers should be applied to a broader array of experiments. Dr. Wedum commented on the value of secondary barriers in a guidance document prepared for the NIH Recombinant DNA Molecule Advisory Committee. He said (Wedum, 1996):

Secondary barriers become especially important to personnel within the building when such agents as *Coxiella burnetii*, experimental aerosols, or micronized dry powders are handled, or when there are centrifuging, grinding, or similar aerosol-producing procedures without containment precautions, accidents with lyophilized tubes, animals excreting large amounts of infectious bacteria or virus, or pilot plant operations.

In some laboratories, the secondary barriers contribute significantly to integrity of the experiment by reducing nonspecific or cross-infection of materials or animals.

As far as biohazard outside the building is concerned, most secondary barriers are more for reasons of public relations than for anything else, except for pilot plants or other large-volume production, experimental aerosols, use of tick or insect vectors, and

agents capable of spread to the animal or plant food supply. This view assumes that known infectious liquids, solids, animals, and animal wastes are decontaminated before disposal, as has long been standard practice in all microbiological laboratories.

In reflecting on these values, it is difficult to find justification for increasing the stringency of biocontainment facility criteria that are recommended in the current CDC/NIH *Guidelines* (Richmond and McKinney, 1993). For example, there is no scientific basis for considering adding HEPA filtration to treat the general exhaust air from BSL-3 laboratories as a standard design criterion.

Public concern needs to be addressed when designing research facilities. Biological safety professionals can play a valuable role in this regard. But they should remain mindful that Dr. Wedum's assessment of scientific and epidemiological data enabled him to conclude that the general public had nothing to fear from diagnostic and research laboratories studying infectious viruses.

Attitudes that Undermine a Rational Basis for Biocontainment

Public Fear of Science. There is much public misunderstanding about the role, aspirations and work of the scientific community. This misunderstanding can easily lead to fear when the public perceives that scientific research could unleash a new plaque on humanity. Contemporary fiction about emerging hemorrhagic viruses and deadly infections can exacerbate this fear. These fears are not easily overcome. Statements by scientists that actual risks are controllable often are received as self-serving. The biological safety professional, however, can serve a useful role in communicating the way in which the public health is protected. This is best done by addressing efforts that have been taken to ensure that the principle for matching risks with effective biocontainment has been appropriately applied to the design project. Advocating a higher than necessary level of biocontainment may give credence to unwarranted fear of the public.

Institutional Emphasis on Rules and Enforcement. There needs to be a careful distinction between a rule and a guideline. The exercise of judgment based on experience and knowledge is a valid process for selecting appropriate safety mea-

asures. This process becomes less valuable, however, as the intent of guidelines shifts from being advisory to being obligatory. This shift is occurring both locally in our research institutions and nationally in our governmental agencies. For example, the preamble to the 1st and 2nd editions of the CDC/NIH *Guidelines* (Richardson and Barkley, 1984) defined the intent of the document.

...recommendations are advisory and are intended to provide a voluntary guide or code of practice...the application of these recommendations to a particular laboratory operation should be based on a risk assessment of the special agents and activities rather than as a universal and generic code applicable to all situations.

The preamble was a consensus statement developed by biological safety professionals, clinical microbiologists, and scientists. The preamble was deleted in the 3rd edition. It is also notable that the 3rd edition no longer emphasizes that a laboratory director's *knowledge and judgment are critical* in assessing risks and appropriately applying the guidelines. Changing guidelines to rules unnecessarily will make it even more difficult for the biological safety professional to become a valuable advisor to the biomedical research community on any subject other than compliance. Experience has demonstrated that too rigid safety rules can undermine the credibility of even the most well-intentioned safety program.

Guarded Dialogue about Research Risks. Academic scientists are reluctant to share their concerns about research risks with safety professionals. The recombinant DNA experience, fear of overregulation, enforcement impediments to research activity, and the cost of compliance have all contributed to this guarded position. The biological safety community can be of great value to the scientific community if these barriers to effective dialogue are removed. We must work harder toward developing a more effective interaction with our scientific colleagues. If we are unsuccessful, our potential value in assessing future research risks and in advising on appropriate biocontainment measures will lag behind the scientific vanguard.

Reluctance to Become Well-informed. Biological safety professionals in academic institutions need to become more knowledgeable in the

biomedical sciences, particularly the disciplines of infectious diseases, public health, and recombinant DNA technology. Scientists need to become better informed about the process of risk assessment and the recognition of hazards that may be associated with research activities. One potential problem is that the availability of recombinant DNA kits may result in a larger group of new scientists who are unaware of the scientific foundation of this technology and, therefore, will be less able to effectively assess future risks. The well-informed biological safety professional and scientist will be able to make knowledgeable and discriminating judgments about biocontainment requirements in the future.

Regulatory Bias Against Academia. Although likely unintentional, there is a regulatory bias against academia. The intense enforcement activity of the U.S. Environmental Protection Agency and the U.S. Nuclear Regulatory Commission focused on academia bears no relevance to the inconsequential or remote risk to the public health or the environment associated with chemical, biological or radiation hazards present in academic laboratories. The non-prescriptive regulatory philosophy of OSHA has proven to be a less burdensome approach for controlling legitimate occupational health risks associated with biomedical research. Nevertheless, the composite regulatory burden on academia has been the fundamental reason for why the role of the academic safety officer has shifted toward compliance in the last two decades of this century. It is unfortunate that the traditional advisory and collaborative role of the biological safety professional which resulted in extraordinary advancements in biosafety in the past is now subordinated to essentially a compliance function.

Biocontainment Challenges in Biomedical Research

Although the future of biomedical research may not be predictable with certainty, there are many biocontainment challenges for the biological safety professional to address today and in the first decade of the twenty-first century. Three challenges involving infectious agents, research animals, and gene therapy are cited below.

Infectious Disease Research. Research involving emerging and reemerging viruses and human pathogens that have acquired antibiotic resistance

will continue to focus public and governmental scrutiny on the effectiveness of biocontainment. A concern for public health will argue for a higher level of biocontainment than will be necessary. The challenge is to work toward achieving the proper match between risk and biocontainment. Failing this, research is likely to be constrained and the public will not benefit from the medical advancements that might have come from a fully utilized and curious biomedical research community.

Care of Use of Research Animals. Transgenic animals and other specialty bred research animals will increase in their importance to biomedical research in future years. Facilities to house research animals will expand. Biocontainment will be an integral part of this expansion.

Gene Therapy. The Center for Biologics, Evaluation and Research, FDA, believes the promise of genetic therapy for the treatment and control of genetic diseases can only be fully met if the academic research community can be encouraged to undertake the development and production of vectors and products necessary for gene therapy. This initiative would require building cGMP biocontainment facilities in or associated with academic research institutions. This will be a new challenge for the academic scientists in the areas of safety, process control and documentation. The biological safety professional will be instrumental in the future success of this new endeavor.

CONCLUSION

Extraordinary discoveries in the biomedical sciences will occur in the future, some of which will collectively set the stage for a new era of science. Although it is not possible to predict biocontainment criteria for the future, each new discovery will raise biocontainment issues. In the near-term, the biological safety professional must become better informed of the knowledge that is at hand and work to gain the trust and respect of the scientific community. In the long-term, the biological safety professional must establish an improved dialogue between the biomedical research community and the biological safety community to ensure that biocontainment will keep pace with the rapid acquisition of new knowledge. This will require understanding of the creative nature of the biomedical research

scientist and the value inherent in the pursuit of curiosity. Einstein once said, "The important thing is not to stop questioning. Curiosity has its own reason for existing.... Never lose a holy curiosity." (Seldes, 1993) Perhaps the biological safety community needs to nourish and celebrate a holy curiosity. Without this, pursuit of the goal of a rational basis for biocontainment for the future will be unachievable.

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