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Emerging technologies and bio-threats

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Chapter Outline

The role of the Institutional Biosafety Committee: risk assessment and protection of the community through (dis)approval of proposed scientific activities

Scientists voluntarily convened in 1973 (Gordon Research Conference on Nucleic Acids) and 1975 (Asilomar Conference on Recombinant DNA Molecules) to discuss societal concerns surrounding the newly emerging recombinant DNA (rDNA) technology. As a result of these conferences, guidelines, and recommendations were drafted on how to perform rDNA experiments safely without endangering the laboratory worker, the environment, or society as a whole. Institutional Biosafety Committees (IBCs), soon mandated by the National Institutes of Health (NIH) for all entities receiving NIH funding, became a standard at US research institutions as a direct consequence of these recommendations. However, at some institutions, their role has expanded beyond the evaluation of rDNA technology. This chapter will summarize the current challenges that emerging biological agents and emerging technologies present to IBCs in experimental risk assessment and communication, and outline a path forward on how to address them.

In a testament to the foresight of the attendees of the 1975 Asilomar Conference, the text below applies to the challenges of assessing emerging technologies (and agents) almost as well today as it did nearly 40 years ago (emphasis added):

> *This meeting was organized to review scientific progress in research on recombinant DNA molecules and to discuss appropriate ways to deal with the*

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potential biohazards of this work. Impressive scientific achievements have already been made in this field and these techniques have a remarkable potential for furthering our understanding of fundamental biochemical processes in pro- and eukaryotic cells. The use of recombinant DNA methodology promises to revolutionize the practice of molecular biology. ***While there has as yet been no practical application of the new techniques, there is every reason to believe that they will have significant practical utility in the future.***

Of particular concern to the participants at the meeting was the issue of whether the pause in certain aspects of research in this area, called for by the Committee on Recombinant DNA Molecules of the National Academy of Sciences, U.S.A. in the letter published in July, 1974, should end; and, if so, how the scientific work could be undertaken with minimal risks to workers in laboratories, to the public at large and to the animal and plant species sharing our ecosystems.

The new techniques, which permit combination of genetic information from very different organisms, place us in an area of biology with many unknowns. Even in the present, more limited conduct of research in this field, the evaluation of potential biohazards has proved to be extremely difficult. It is this ignorance that has compelled us to conclude that it would be wise to exercise considerable caution in performing this research. Nevertheless, the participants at the Conference agreed that most of the work on construction of recombinant DNA molecules should proceed provided that appropriate safeguards, principally biological and physical barriers adequate to contain the newly created organisms, are employed. Moreover, the standards of protection should be greater at the beginning and modified as improvements in the methodology occur and assessments of the risks change. Furthermore, it was agreed that there are certain experiments in which the potential risks are of such a serious nature that they ought not to be done with presently available containment facilities. In the longer term serious problems may arise in the large-scale application of this methodology in industry, medicine and agriculture. ***But it was also recognized that future research and experience may show that many of the potential biohazards are less serious and/or less probable than we now suspect****.*

(quoted from the Summary Statement of the Asilomar Conference on Recombinant DNA Molecules [1])

At its most basic level, the role of the IBC is to evaluate and ensure the safety of proposed research or scientific activities to both workers and the larger environment where their institutions reside. After the groundwork laid by the pioneers in this field, such risk assessments are sometimes considered routine, and are usually a part of the regulatory and oversight requirements faced by most institutions. However, due to the variable and (occasionally) unpredictable nature of emerging agents and technologies, highly specialized and/or cross-discipline knowledge (e.g., knowledge of niche subspecialties of chemistry, physics, synthetic biology, or even engineering) is sometimes required to adequately evaluate incoming research proposals. Facing proposed research outside their specialized knowledge, IBC members may err on the side of caution, thereby potentially halting or preventing highly promising research. Alternatively, the committee may rely too heavily on the submitter's judgment of his/her proposal and approve risky activities that should receive a deeper level of scrutiny. In such a case, the temptation to consult *ad hoc* reviewers will be great and should

be encouraged. Such consultation can be an excellent solution to a real or perceived lack of expertise on an emergent technological or biological hazard. Unfortunately, at many institutions (especially smaller or isolated institutions), there is unlikely to be an in-house, objective third party that can effectively evaluate highly specialized research proposals on novel technologies or emerging biological threats. Distinct research groups at the same or different locations that are engaging in research with the same emerging agents or technologies often collaborate or compete, raising questions of objectivity – even if only in perception. It was noted without irony that the moratorium on rDNA experiments that culminated in the 1975 Asilomar Conference was "vulnerable to portrayal as the fox set to guard the chicken coop" [2].

Additionally, seemingly similar agents or technologies can respond to manipulation differently in some significant ways, raising questions of the applicability of objectively applied but off-topic expertise. Also, while there is no restriction on bringing in expertise from outside the institution, logistics can be problematic. At a minimum, outside reviewers should be aware of their duty to confidentiality (if not required to sign a statement to that effect), should be vetted for conflicts of interest similar to internal reviewers, and be available and committed to the full term of adjudication in case the matter becomes more complex over time. Geographically isolated research institutions may need to sponsor travel, but will likely handle the review process using technological approaches such as secure email or conference calls. While an IBC cannot cede its review process or judgment to the proposal's authors, it must at the same time be aware of the benefits as well as the potential pitfalls of consulting with external reviewers.

In a seminal paper, Dunning and Kruger outlined a "dual burden" of the unskilled: "Not only do these people reach erroneous conclusions and make unfortunate choices, but their incompetence robs them of the metacognitive ability to realize it." This became known as the Dunning–Kruger effect. However, a relevant corollary to the noted effect was that intelligent people often under-rated their abilities in relation to their peers [3]. This lack of confidence in one's own abilities could lead individual IBC members (or entire committees) to inappropriately cede their judgment(s) to third parties that may be no more capable than the committee members themselves. It must be remembered that science (mostly) progresses slowly, in incremental steps aimed at fulfilling the scientific method; as such, novel topics are generally going to be accessible to a scientifically educated committee member with a willingness to undertake some research and analysis in the performance of due diligence. At the inception of the rDNA Advisory Committees (RACs) and IBCs, members had to acquire a basic understanding of knowledge current researchers now take for granted in assessing recombinant or synthetic nucleic acid research proposals. Today, members must be reminded of those approaches when examining complex or novel studies. An example may be a proposal on intercalating drugs that drive RNA viruses to "error-extinction" by disrupting the quasispecies population beyond its ability to carry genetic informational identity into the next generation [4]. A basic understanding of the nature of genetic identity and the redundant genetic code, coupled with research on the nature of replication fidelity of RNA viruses, will make the concept of disruption of information-carrying capacity accessible to anyone with a strong

and relatively current biological educational foundation. Further, an understanding of (or research concerning) the nature of viral genomes and viral replication versus the intracellular sequestration of those activities will allow the committee to assess the risk of the proposed drug to the workers developing it.

Several factors will be relevant to this risk assessment. For instance, whereas a high-molecular-weight drug (actively delivered to the cytoplasm) that binds to RNA will likely bind to all RNA, it will likely be excluded from the nucleus and endoplasmic reticulum (ER) by normal cellular processes, and will therefore intercalate preferentially into viral mRNAs, rather than cellular mRNAs. Conversely, a small-molecule drug that crosses the cellular membrane passively will likely cross the nuclear/ER membrane as well, and therefore might be considered more hazardous to cellular processes in the absence of other information. While not a guarantee of absolute safety, the process exemplified above is a part of a viable and robust assessment of the risk of a proposed scientific activity, and meets the duty of an IBC in protecting workers and the public.

Ideally, IBC evaluation of emerging technologies will be based on scientifically acquired knowledge alone. The transgenic research community has already faced difficulty in this regard, with examinations of public attitudes about genetically modified organisms (GMOs) finding that "(t)here are only weak correlations between knowledge and attitudes and knowledge and acceptance of GMOs, and a strong correlation between attitudes and acceptance" [5]. Other critical reviews declared that GMOs are "the new food safety concern which, despite the intense reactions from Non-Governmental Organizations (NGOs) and consumer organizations, have entered our lives with inadequate legislative measures to protect consumers from their consumption" [6]. Efforts to educate the public and reframe discussions away from uncertainty about the unknown to the societal implications of the work, as well as attempting to instill a fundamental understanding of transgenic organisms as the logical extension of rDNA technology, have proven difficult. Polls continue to show a tragic mistrust of the scientific community on this issue. This ongoing conversational confusion has been propagated into the realm of synthetic biology ("The danger is not just bioterror, but 'bioerror'" [7]), "gain-of-function" research on infectious agents ("The same people continue to make the same arguments, and some scientists 'feel like they're treading water'" [8]), and the use of recombinant proteins as growth or production promoters in food and fiber animals ("Cynical activists have unfairly stigmatized a scientifically proven product that has consistently delivered economic and environmental benefits to dairy farmers and consumers" [9]). The IBC can and should play a critical role in communicating the fundamental scientific aspects of such novel work, the risk assessment process, and the essential truth that we, as a society, are safer, more adaptable, and more responsive to natural or man-made threats through increasing our knowledge of the world around us. Simultaneously, it is our thesis that we are made less safe, less adaptable, and less responsive by closing off viable and valuable avenues of research. IBCs have, and should continue to have, the "Power of No"; however, they should use that power only when their decision is based in rational and scientific reasoning absent from partisan or demagogic influence.

When investigators propose to work with novel agents or biotechnologies, authors and reviewers must conduct their discussions openly and pursue direct communication

with all stakeholders. Often, such transparency both raises and resolves legitimate concerns. A high standard of communication is necessary, and authors must try to anticipate the needs of reviewers and submit relevant information in a way that allows a scientifically educated reviewer who is not an expert in a specific area to fully assess possible risks of the proposed work. Many laboratory activities are seen as routine, especially by investigators, based on long experience with them or knowledge about their implications to the natural world. However, it must be remembered that these routine activities were once novel technologies that may have created anxiety in reviewers or the public, and might still do so today. For example, in the early days of rDNA manipulations in bacteria, the inclusion of a β-lactamase-encoding gene in plasmids to achieve ampicillin resistance for selection of transformants was seen as highly controversial [10]. That controversy disappeared once it was highlighted that β-lactamases are widespread in nature, and that this fact had been known since 1947 [11]. While a β-lactamase gene could (theoretically) "escape" from a laboratory, it is logical that such a release is in all likelihood inconsequential based on its natural prevalence. The standard for communication of such facts was higher when this technology was novel than it is in current times, when plasmids containing β-lactamase genes are present in commercially available, unregulated kits.

On the other hand, novel uses of biological agents as components of emerging technologies may be proposed by scientists who know relatively little about these agents and may not be able to provide adequate information for review. For example, using a filamentous virus as a molecular engine to aid in the creation of nanomaterials [12] may put a physicist in the position of submitting to an IBC for the first time in his/her career. In this situation, an IBC can – and we would argue should – provide guidance on biological safety to the submitter, such as suggesting alternative organisms consistent with the Asilomar conference findings to limit the risk of rDNA experiments through "the use of biological barriers [such as] non-transmissible and equally fastidious vectors (plasmids, bacteriophages or other viruses) able to grow only in specified hosts" [1]. Such guidance should be provided to facilitate the review process, but the committee must be open to an ongoing discussion of how and why the author designed the experiments as submitted. For example, expert IBC members might suggest the use of tobacco mosaic virus instead of a virus pathogenic to humans or animals as the molecular scaffolding for nanowire assembly. The researcher may accept this recommendation or respond with biological details of the originally proposed virus that are integral to the hypothesized success of the experiments. However this conversation resolves, in this situation, the IBC's follow-up role of ensuring that working conditions mitigate risks and meet safety requirements may be more important than the proposal review role.

IBCs cannot consider any laboratory activities with live pathogenic organisms or viruses (or recombinant nucleic acids for those IBCs with an originalist scope) to be beyond review, even if the organisms are attenuated in healthy, adult humans (the *BMBL* standard for susceptible hosts in biosafety level classification [13]), or thought incapable of causing disease. When a veterinarian in the western United States hears hoof beats, it is not wise for him/her to search for a zebra. However, that same veterinarian must be aware of the existence of zebras (or adult humans that aren't healthy,

or children, etc.), and be open to the possibility that there may be one in the vicinity. Tragic failures of biosafety have been extensively reported, some due to failures of work practice [14] and some due to unexpected biological interactions [15]. Thus, no work with live pathogenic organisms is (or should be) beyond IBC review. While rare, exposures, infections, and deaths in the setting of laboratory research may be prevented with strict adherence to general biosafety practices along the lines of Standard Precautions in healthcare delivery. Recent biocontainment failures might also have been avoided with adherence to well-established laboratory protocols requiring inactivation of biological agents before transfer [16] or implementing proper inventory/cataloging provisions for pathogen collections [17]. The US government's response to these biocontainment failures will likely reduce the prospect of any further issues similar to those that occurred, at least in the near future. However, this response does not include a general mandate to anticipate and solve tomorrow's problems using generally applicable tools and technologies available today [18,19]. At a minimum, it must be remembered that even research largely considered low-risk (e.g., with exempted organisms such as *Escherichia coli* K-12 vector systems) must be evaluated for risk by the researcher. Most IBCs will require the researcher to document that review to the IBC, either before work begins, or (more commonly) concurrent with the work through an expedited review process, to ensure that the committee concurs with the researcher's opinion. Very few IBCs will not review such experiments at all.

Experiments with emerging agents and/or technologies are, by definition, situations for which very little experience, previous critical examination, and/or previous review exists. It took many years to understand that the "bad air" that spread "mal-aria" in the Americas is, in reality, mosquito vectors of specific species, with defined biting behaviors and competencies for transmission of the actual malaria-causing plasmodia. In more recent times, transmission puzzles still abound; as one example, the newly discovered porcine epidemic diarrhea virus (PEDV) is spreading like magical "bad air" through the swine industry, which has a reputation for practicing a high level of agricultural biosecurity (i.e. pathogen exclusion techniques). Using some traditional and some modern approaches, PEDV was rapidly discovered to be an alphacoronavirus, suggesting transmission modes similar to other porcine alphacoronaviruses (e.g. transmissible gastroenteritis virus [TGEV] and its predilection towards spreading via aerosol or contact exposure). However, as of this writing, measures effective against TGEV have proven to be of limited efficacy against PEDV spread [20].

Facing this kind of uncertainty, IBC members might be tempted to take a very stringent approach to review proposals including isolates of emerging biological agents. However, such an approach could unnecessarily hinder valuable research that could be conducted in an attempt to understand and control disease outbreaks. As PEDV became present in an increasing number of states, at what point does it transition from being an emerging pathogen to an endemic/established virus? Should each IBC of each PEDV research institute be made aware of the local epizootiology and change its risk assessment accordingly, and perhaps dynamically? Each committee would have to come to its own individual and collective decision on such matters, but should be reminded that the 1975 Asilomar Conference attendees believed that "the standards of protection should be greater at the beginning [of our understanding of

agents/technologies] and modified as improvements in the methodology occur and assessments of the risks change" [1].

A prime example of the dilemma of IBCs is so-called "gain-of-function" research, i.e. research that aims to genetically modify pathogens with specific biological properties to address pressing scientific issues, such as whether a pathogen could easily mutate into a more aggressive or more transmissible form in nature. Two similar experiments, both successful in making a highly pathogenic avian influenza A (HPAI) H5N1 virus more transmissible in an animal model, led to considerable debate about the danger that such a recombinant virus could escape the laboratory. In the end, the debate resulted in a moratorium on certain experiments with H5N1 until the issue was fully debated and a consensus was achieved. For such a debate to be constructive, it must be held to high standards of rationality and scientific theory, free of demagoguery. A wide variety of expertise is needed, encompassing experience with influenza A viruses, animal models for influenza, and influenza A virus biocontainment elements. The moratorium on certain types of rDNA experiments called for in 1974 [21] limited future work. In an unprecedented recommendation, a 2011 moratorium restricted the publication of the data from existing experiments for 6 months, and was extended to restrict work for approximately a year [22–24]. The unavailability of the data due to the moratorium on publication of experimental results, despite the fact that the experiments in question had been reviewed and approved by granting agencies, institutional IBCs, and collaborating researchers, led to a significant amount of uncertainty in the influenza research community with regard to which experiments are permitted and/or publishable. More importantly, the absence of publications at the time made it impossible for the larger scientific community to examine the accumulated data and form a rational assessment of the risks proposed by these influenza A virus experiments. After such an examination by expert panels, the (limits of the) mutagenic potential of the influenza A virus [25], the biotechnological controls designed into the recombinant influenza A viruses [24], and the biocontainment level used at the institutions performing the work suggest that the moratorium on both research and publication was more likely driven by the scientific community's attempts to be responsive to a worried public rather than by substantive concerns among specialists. A similar moratorium was recently instituted based on the emergence of Middle East respiratory syndrome coronavirus (MERS-CoV), and the net was cast broadly to include MERS-CoV, severe acute respiratory syndrome coronavirus (SARS-CoV), and HPAI [26].

Each IBC member should ask the question of how he/she would evaluate research such as these influenza A virus "gain-of-function" experiments. Imai et al. [24] used biological controls in constructing their mutant H5N1 influenza A viruses, consistent with the principles outlined at Asilomar, whereas Herfst et al. [23] used mutagenesis and directed evolution in the generation of their ferret-transmissible H5N1 strain. Studies from the Kawaoka laboratory showed that predictable changes in the genome of influenza A virus could extend aerosol transmission to a mammalian model of human infection; similar studies from the Fouchier laboratory used known but more unpredictable methods to find that multiple sets of mutations might achieve the same biological result. These different approaches lead to different conclusions and answer different questions, but does that difference impact the IBC's risk assessment? Is there

a rational distinction between the two resultant viruses that would argue for a higher containment level for one or the other?

In December 2011, the National Science Advisory Board for Biosecurity (NSABB) recommended that details from the two manuscripts that provided information on mutations which allowed H5N1 influenza A virus to become transmissible in mammals be redacted [27]. Over the course of the next 6 months, continuing deliberations led to the full and complete publication of those manuscripts [23,24] while continuing a moratorium on similar work for another 6 months. While such work was eventually given permission to restart, it is again now subject to another moratorium, this time in funding. The Gordon conference in 1973 and the Asilomar conference in 1975 openly discussed the emerging technology of recombinant modifications, and brought together accomplished experts to chart a path forward that was scientifically ambitious at the same time that it called for safety and critical review of proposed experiments. The decision to call for a redaction of data on mutations that had been theorized or shown to condition host range in influenza A viruses as far back as 1993 [28,29] cannot be seen solely as a rational response to the scientific process, or the data it generated. We support the eventual publication of these data, and it is our belief that the ongoing NSABB deliberations concerning the influenza A virus "gain-of-function" experiments serve the public interest and scientific community's long-term interests. Technical experts from multiple disciplines ultimately made the decision that the data should be published largely unchanged, with recommendations that follow-up research should continue (with a few modifications). Similarly, future experiments and/or technologies should be subjected to rational discourse that both limits the risks of the work through application of technological solutions (e.g. Asilomar's "biological and physical barriers") and facilitates the research in an effort to advance our understanding of the world around us.

Most importantly, such rational discourse should include the public in the case of controversial experiments, and should be conducted prior to research being approved or initiated. It is clear that "controversy" cannot be reliably anticipated, as the experiments in question could be seen as a simple application of existing data about relevant mutations to a virus of concern to public health specialists across the world, which was reviewed and approved at many different levels [30]. However, what became clear is that a larger risk communication initiative is needed, and more robust, formal, and comprehensive review processes are needed to fulfill our duty to both protect and address the concerns of the public at large that funds our research. Several review structures have been proposed, and some of them focus on the IBC as the entity that should perform assessments of controversial research [31]. It would appear that the current entities slated to complete these reviews are the NSABB and the National Research Council of the National Academy of Sciences [26], but each IBC would be well advised to watch for additional guidance on this subject that may direct them to conduct specific review processes or address specific foci of concern.

Novel biological agents can be (and have been [32–34]) rapidly characterized with existing, broadly applicable technologies. Such characterization can serve as a basis to guide risk analyses of further examinations, and provide early guidance on public/animal/plant health control measures to attempt to limit the spread of emerging

diseases. While not perfect (see PEDV above), such guidance is often useful to both the scientific community as well as the public (e.g. SARS and "social distancing" [35,36]). Such control measures can have a secondary, calming effect on the fear associated with an uncertain field. When it is realized that the same measures employed to fight the spread of "known" diseases such as seasonal influenza are effective against emerging diseases, intelligent but scientifically less educated people may intuit the similarity of biological agents in general, and the (relatively) few methods through which they can be spread from infected to naïve individuals. By linking known diseases with the unknown scourges of "emerging biothreats", we propose that both IBC members and the public will take comfort from the application of knowledge and technologies that are widely available, actualized, and based in the immutable rules of Pasteur's Germ Theory.

True scientists are professional skeptics, but the laundry list of new, emerging, or even as-yet-unknown agents and/or technologies that could threaten humans is large and growing. Scientists must keep an open mind about the possibility of arsenic-based bacteria being able to kill humans ([37], even if methodological problems bring the discovery into question [38,39]); randomly generated synthetic genes that spread through (and impair) whole ecosystems [6,40]; syndromic conditions for which scientists can only establish causation through the use of a modified set of Koch's postulates [41–43]; biologically active nanomaterials [44]; or other truly novel biological agents or technologies that present a threat to our community and, perhaps, our society. However, scientists must not allow these valid and useful precedents (and the thought experiments they engender) to unduly influence the fundamental understanding of probabilities, relative risk, and rational assessment of data that is an essential part of the scientific enterprise and (of course) the IBC review process.

IBCs play a vital role in the pathogen discovery, response, and characterization process. By providing a formal and (ideally) objective assessment of risk, they can facilitate dissemination of existing data that were used in their risk assessment, as well as guide future research in a way that protects laboratory workers, the public, and the environment. IBCs must fully evaluate the safety implications of emerging agents and technologies to fulfill societal expectations of review that derive directly from the promises of the 1975 Asilomar Conference. However, IBC members must also recognize that we are ultimately safer with increased knowledge and tools for response, and facilitate research and technology development as an active initiative to combat ignorance of the unknown. These conflicting priorities necessitate a wide knowledge base that will generate relevant questions that attempt to fully evaluate crucial elements of proposed work, and allow an effective and diligent evaluation without ceding judgment and duty(ies) to the same experts that are being evaluated/regulated. Creative and adaptive thinking – in the context of rational examination of known facts and technological paradigms – is necessary to facilitate research in a society that increasingly mistrusts the scientific enterprise [45,46]. This need is especially stark when that society is faced with truly novel agents or technologies. A full, complete, and robust risk assessment should both ensure rational limits on activities and provide reasonable assurances of safety in the face of rapidly changing scientific conditions or knowledge.

Risk assessment of emerging technologies or biothreats

Researchers, when faced with an "unknown" usually ask the question "what is known about its closest relatives and/or similar technologies?" If a scientist submitting a proposal to an IBC has not provided sufficient information on their protocol/risk assessment, the scientist should be encouraged to submit additional supporting details for review (and the process may well be iterative). At a minimum, the scientist must expressly state the limits of current knowledge about the object of proposed research, fully elucidate hypotheses, and fully describe both experimental approaches and the biosafety controls (e.g. administrative, facilities, work practices, and PPE/safety equipment) to be utilized for the work. The scientist must submit both necessary and sufficient information such that a knowledgeable reviewer can fully assess the work, even though the scientist may desire to limit the submitted information in an effort to decrease their work burden when submitting protocols for review. Guidance documents and committee policy statements can be created to give submitters an idea of the types and depth of information needed for adequate review.

IBCs should evaluate the provided information in the context of its existing knowledge base without falling prey to assumptions that similarities of the "unknown" agent or technologies to known agents or technologies are necessarily predictive of risks. For instance, coronavirus research was a focused subspecialty until the discovery of SARS-CoV – and although much was known about coronaviruses by the time of SARS-CoV's emergence, the lethality of SARS-CoV for humans could not have been predicted, as coronaviruses highly virulent for humans were not known at the time. It is important to keep such examples in mind during a robust risk assessment process concerning novel agents or technologies.

At the same time, IBCs also must ensure that they are not overestimating risk because too little information is known. Classifying an uncharacterized agent at a high biosafety level based only on the fact that it is uncharacterized is rarely helpful. The possible pandemic of SARS-CoV was (in part) blunted because many studies commenced in laboratories around the world immediately after the virus was isolated, despite the fact that it was a completely novel agent. In the unlikely event that no background or comparative information exists that can be outlined in a research proposal to the IBC, the IBC can suggest a course of pre-experimental actions based on general biological principles to generate sufficient data for consideration. First and foremost, the early events in the SARS investigations instruct us that education, training, and strict adherence to basic laboratory containment practices are essential in the investigation of novel agents, and could have prevented fatal breaches in standard laboratory practice [47]. The original Asilomar attendees anticipated this need and noted that "(p)articularly important is strict adherence to good microbiological practices which, to a large measure, can limit the escape of organisms from the experimental situation and thereby increase the safety of the operation. Consequently, education and training of all personnel involved in the experiments is essential to the effectiveness of all containment measures" [1].

Broadly reactive primer sets or group-reactive antibodies can be used to rapidly characterize novel viruses or bacteria, or (at a minimum) to rule out similarity to

tested groups. Multiple lines of testing should be initiated, examining as many essential (e.g. physical, chemical, and biological) properties of the novel agent as possible. Electron microscopy to detect morphological cues for classification, nucleic acid detection (e.g. group-specific polymerase chain reactions, targeted or random probe hybridization microarrays, etc.) followed by genome sequencing, protein identification (e.g. group-specific antibody testing or sequencing using mass spectrometry), and growth in permissive systems (e.g. intracranial inoculation of suckling mouse brain, cell panels) should all be attempted in the early stages of identification of novel agents. If a successful culture system is found, basic risk assessments can be conducted examining growth in immortalized human-origin cell lines, or perhaps even human organ-system models (e.g., organs-on-chips, 3D cultures) or primary cells (if available).

Similarly, novel technologies must be related to their source in existing, well-characterized technologies. rDNA technologies were examined in the context of the prescient work on horizontal gene transfer conducted in bacteria before the structure of DNA was known [48], and recombinant organisms and synthetic biology derive from (and can draw from the conclusions of) those early technologies. Gain-of-function experiments exist on the backdrop of the parental biological agents; novel diagnostic technologies can be characterized by sensitivity, specificity, and cost; and even the probability of the resurrection of a *Tyrannosaurus rex* can be anticipated (even if only by Hollywood), calculated, assessed, (perhaps) mitigated, and at a minimum communicated to an interested public that likely would fund the research.

Consistent with the original 1975 Asilomar Conference report [1], "(e)stimating the risks will be difficult and intuitive at first but this will improve as we acquire additional knowledge; at each stage we shall have to match the potential risk with an appropriate level of containment". Early characterization experiments should be done at a level of containment that may be in excess of what is used after the risk of the experiments is better known or fully studied. For those novel agents that are recognized due to a human disease outbreak, crucial experiments with live agent that demonstrate susceptibility (or resistance) of the "unknown" agent to possible treatments, cross-reactivity with available vaccines, and/or permissiveness of human cells to infection or biological dysfunction should be performed at a containment level commensurate with the information surrounding the novel agent's/toxin's/technology's discovery/emergence. In a practical sense, novel agents that are recognized due to high virulence, or are closely related to highly virulent viruses, should be initially characterized at higher (e.g. BSL-3 or above) biosafety levels or maximum containment. Those agents that are discovered by research into multifactorial syndromes and/or as adventitious agents not specifically linked to a disease in humans, animals, or plants can be dealt with at a lower containment level depending on an assessment of their risk to laboratory workers and/or the environment. This approach, however, is based on the explicit willingness of an IBC to downgrade the biosafety level at which work is initially performed once sufficient data are available that counter or inform the initial risk assessment. In the past, there have been only a few examples of human pathogens that were initially classified at a high biosafety level and then were downgraded. If downgrading is an unlikely event even in the presence of supporting data, it becomes "risky" for a

scientist to (for instance) suggest BSL-4 classification of an "unknown" that causes significant disease in humans, as the low number of BSL-4 facilities greatly limits research and therefore the development of possible countermeasures. The Asilomar attendees knew, and expressly stated, that "(t)he means for assessing and balancing risks with appropriate levels of containment will need to be reexamined from time to time" [1]. Biosafety classification should therefore be re-assessed over time, weighing new or developing information that may condition scientific or public opinion about the pros and cons of the work to laboratorian (and overall public) health.

Clearly, the above is a simple treatment of the complexity of a true assessment of risk, lacking the depth that will be required in real-world implementation. For example, risk assessment may change based on a scientist's experience with high-hazard agents, the containment level of the facilities available for experiments, and the institutional commitment to biosafety. The simplicity was deliberate, as a prescriptive set of rules will not allow the flexibility and local control that is an essential strength of the IBC system. The basic approach that smart, rational, and honest people should evaluate research activities smartly, rationally, and with a high degree of intellectual honesty was the core promise of the Asilomar Conference attendees to a nervous public. That approach should be strengthened, continued, and should not be subject to an artificial set of external rules that will ultimately poison the intellectual integrity that each committee member brings to the faithful discharge of their duties.

A possible role of the IBC: efficacy considerations and resource allocation decisions as representatives of the public interest

The mandate of an IBC is to evaluate the safety of proposed research – specifically the biosafety of the proposed activities. A reasonable expansion of that mandate would be to include a consideration of all safety (e.g. chemical, radiological, etc.) to the degree to which committee members have experience with those hazards. Additionally, IBCs are charged with ensuring that the approved work activities are actually performed as stated in the proposal, through a series of follow-up reports, proposal renewals, inspections, and/or "whistle-blower"-type reporting mechanisms. However, it may occur to readers that an additional expansion of the mandate to consider the likelihood of success of proposed research is logical, especially in today's limited funding pool. We would like to argue against this expansion for two reasons. First and foremost, research that proceeded from the conception stage to the proposal submission stage has already been, or is currently being, considered for likelihood of success by the funding agency's subject matter experts. Secondly, novel research should not be stifled by an additional round of review by those that may have less expertise in the specific field being considered. If a scientist has taken the time to submit a protocol for IBC review, it has probably already been funded, unless IBC approval is required before it will be considered for funding. In either case, an IBC should evaluate the researcher's ability to complete the proposed work safely at their institution only.

Imposing opinions about the success of the research onto an already stringent process is a level of review that is at least burdensome and at most unfair to scientists, as well as the larger research enterprise.

Additionally, the voluntary expansion of the IBC mandate to consider all research at institutions (instead of that research that utilizes synthetic or recombinant nucleic acids) has already taxed many committees, requiring expansion of personnel and increased administrative support. To further increase their purview, with little expected benefit, is not a wise use of the intellectual or temporal resources of the committee members. Consideration of efficacy for proposed activities requires a much greater depth of examination than the consideration of safety protocols, containment, and researcher and institutional commitment to safety that make up the current review process.

The role of the IBC: risk communication and mediating the "science conversation" with members of the public

It is essential to remember that one important but under-utilized role of the IBC is to act as a mediator of the conversation between a scientifically minded workforce, and an intelligent but scientifically less educated public. Science communicators have come to know that there is a proportion of minds that cannot be influenced by rational discussion; however, that percentage is much smaller than one might believe after listening to popular news programs or reading a comment section on the internet. Many people are simply in search of information that is both accessible *and* fills in the gaps in their knowledge in a way that increases their understanding of the world around them. One might be hard pressed to find a better definition of the scientific mind than that simple statement concerning curiosity and Feynman's "philosophy of ignorance":

> *It is our responsibility as scientists, knowing the great progress and great value of a satisfactory philosophy of ignorance, the great progress that is the fruit of freedom of thought, to proclaim the value of this freedom, to teach how doubt is not to be feared but welcomed and discussed, and to demand this freedom as our duty to all coming generations.*

If a scientist working in an arbovirology laboratory received a letter from a member of the public asking whether "the AIDS" could be transmitted by mosquitos, should he/she respond, and if so, how? While it might be tempting to disregard the letter, could this writer's fears be alleviated by a basic discussion of the difference between mechanical and biological transmission of viruses by insects, appropriately targeted to the audience's interest and (presumed) educational level? Would it be better to simply say that while their intuition of blood transmission from one mosquito bite to the next was technically possible, there are several facts that argue against such a possibility in the case of HIV/AIDS? Would the latter invite another question, or would it be satisfactory? And, which would be better?

At its most basic level, the role of the IBC is to evaluate the safety of research or scientific activities proposed, to both the workers as well as the larger environment

where their institutions reside. While robust examination of those activities by members of the community (other than the public committee members) could present interesting communication opportunities, in the absence of a problem or politically charged topic the community often relies on the IBC to represent their interests. Most IBCs take this duty seriously, and value their public members' input.

Conversely, we have seen failures of this conversation that have been chilling to the performance of research as well as to the larger research enterprise. It must be admitted that both scientists (and the larger scientific community) *and* a potentially suspicious public could play a role in disruptions of the normal flow of science. As scientists, we must look to the "natural experiments" that have been conducted on this issue. The actions that culminated in the Asilomar Conference represent an approach of robust self-examination and self-regulation by the scientific community in response to some real (and, admittedly, some perceived) threats of concern to the larger public. These actions and regulatory structures are largely seen as a success of communication and transparency, especially when contrasted with the regulatory burden placed on researchers engaged in either human or animal experimentation, particularly if the research is hotly debated in the public sphere.

Institutions engaged in human or animal research have a large regulatory burden that requires significant financial and human resources support, which is not present in the implementation of the IBC at most institutions. While important, IBC membership is usually a collateral duty to the research, teaching, or corporate activities that are a committee member's primary tasks. However, Institutional Review Boards (IRBs) and/or Institutional Animal Care and Use Committees (IACUCs) are trending towards hiring dedicated personnel (e.g. IACUC Coordinators and/or Compliance Officers, dedicated or collateral-duty Post-Approval Monitoring personnel). These committees are investing significantly in information technology and/or administrative resources for proposal submission and review, and/or entire "Regulatory Affairs" sections dedicated to compliance with the applicable laws, regulations, and/or guidelines associated with those activities. One could argue that the different subject matter (biosafety in the laboratory vs. intentional impact on living systems) is a direct cause of the difference in regulatory oversight; this argument does not account for the consequences of a failure of oversight or verification in the different systems. Ethically questionable human and/or animal experiments are repugnant and damaging to the morals and/or philosophies of different groups or individuals, but they are largely limited to specific laboratories or experiments and do not generally lead to release of biological agents [49–51]. On the other hand, failures in biosafety and/or laboratory containment could have unpredictable effects on the public (e.g., laboratory release of an agent [52–55]) or the environment [56–58], and could be much more consequential to the population as a whole.

Failure(s) of self-examination and self-regulation have led to a public attitude toward science that has been described as a loss of Aesculapian authority [46,59]. In the past, a physician's order or a researcher's statement of assurance were most often seen as authoritative and definitive statements to calm the fears of the community. That time has clearly (and thankfully) passed, and anyone who counts solely on the authority (supposedly) conveyed by academic or professional degrees lacks

a fundamental understanding of the role and position of science in today's society. Should IBCs play an active role in facilitating this conversation, both to facilitate research as well as to repair the damage to our larger scientific integrity caused by historical failures? Or, should IBCs act only as resources to skilled public relations professionals, receive training in science communication before engaging in debate, or be discouraged from any form of official (or unofficial?) communications with the public? Finally, how will those internal rules relate to the committee's duty to be transparent and accessible to the public, codified in Sections IV-B-2-a-(6) and (7) of the NIH Guidelines? Committees are not required to be proactive communicators *per se*, but the lack of communication presents a hazard to the scientific enterprise that should be decreased or eliminated if at all possible.

Each committee must make its own decision on these questions, but several factors must be fully considered. First and foremost, science communication and the conduct of scientific research require very different skill sets, and those accomplished at both are rare and storied individuals. An unskilled but well-intentioned communicator can still cause damage to the relationship between the scientific community and the larger populace, as can a skilled communicator who does not understand the science he or she is communicating.

Further, many antiscience critics are skilled debaters, and will use opportunities of public debate to engage in a demagogic attack on the scientist, his or her work, and the larger scientific enterprise. It has been stated often, by many different groups, that scientists are limited both by their adherence to the truth as well as their professional tenet that one cannot prove a negative, while the other side of the argument is limited by neither consideration [60,61]. Engaging in debate with a flexible and adaptive opposition, in front of a skeptical and fearful public, is not a recipe for successful communication. Indeed, by engaging in such debate, one gives legitimacy and "air time" to the opposition that might open up the possibility for a discussion that could confuse the facts as well as the listening public.

However, an insular scientific enterprise that just wants the concerns of the public to "go away" does not serve humanity in either the short or long term. A robust and diverse IBC that makes rational and faithful decisions that serve the interest of the public should not be afraid to discuss (or even defend) those decisions if necessary. Removing the veil of secrecy that many feel surrounds the scientific community can greatly enhance the research enterprise in many tangible and intangible ways. Imagine the embattled neurobiologist and animal researcher. While committed to their work, these researchers may reevaluate their chosen career paths when an animal rights group targets the researcher's home and/or family [62]. Would the researcher feel more engaged, more effective, and safer if they were viewed differently? A relevant example that presents more broadly applicable health concerns may be the testing of candidate antiviral drugs or vaccines in an outbreak situation (e.g. Ebola virus disease in western Africa, AIDS in southeastern Asia). Are these scientists viewed as people engaged (as respectfully as possible) in troubling but necessary actions in support of public health and a larger, global just and civil society? Can they successfully navigate the moral, ethical, and (perhaps) legal issues inherent in such work? If one believes such work is moral, and perhaps even ethically required, how is that case to be presented?

The "science conversation" is in flux in today's society due to the ever-increasing accessibility to vast amounts of information on the internet, and thought leaders are emerging and setting this stage (e.g. the National Center for Science Education, the American Association for the Advancement of Science, among others) in ways that build upon the traditions created by the original Asilomar Conference. IBCs must wade into this dynamic activity cautiously and with significant forethought for the benefits and drawbacks. If confronted with a communications issue, IBCs should seek resources in the science of communication just as they would seek external resources for the evaluation of novel technologies or agents. The analogy between safety reviews and scientific communications should not be ignored. Executed incorrectly, both may pose significant hazards to the scientific enterprise and can be addressed and mitigated with similar processes.

IBCs play a pivotal role in the review of research involving emerging technologies and bio-threats. This process exists (and must continue to exist) in the context of changing societal norms and expectations, dynamic and creative research, and competing obligations and duties. Committees must embrace and even thrive in the context of the sum (and, occasionally, the synergy) of these diverse interests. While this may be a seemingly impossible task, alternatives pose hazard(s) to the goals of the scientific enterprise, and the larger societal needs it supports. The IBC resides at the nexus of, and must mediate the interactions between, scientists and the public. The trust that resides with these parties must be protected, respected, and appropriately directed toward decreasing risk, increasing knowledge, and facilitating safe science to advance knowledge, safety, and overall societal health.

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