

**Managing the Destructive  
Potential of Biotechnology**  
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Research**  
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# Conception of the Fundamental Problem

- Rapid progress in basic molecular biology is apparently enabling extraordinarily consequential applications, including **in principle** deliberate intervention in the process of evolution.
- The same basic science simultaneously identifies both **therapeutic** and **destructive** possibilities.
- The extended consequences of this situation are potentially large but cannot be determined with confidence.
- Those consequences will assuredly involve social dynamics as well as basic science.

- Recent reconstruction of the 1918 influenza virus is currently the leading instance of the more general problem.
  - Work actually motivated by “historical curiosity” but does have potentially important therapeutic implications.
  - Has highly destructive applications as well.
  - Degree of oversight and containment applied does not appear commensurate with the magnitude of risk entailed.
    - Reconstructed strain is substantially more virulent than standard reference strains.
    - SARS has escaped BSL 3 containment at least 3 times.
  - Decision on publication made with no intermediate option available.

# Evident Implications

- The scale and character of potential consequences mandate more advanced protective procedures than have yet been devised.
- In principle appropriate procedures should:
  - Prevent the deliberate or inadvertent creation of pathogens more destructive than those that have naturally evolved.
  - Assure prudent exploration of protective and therapeutic applications.
  - Assure equitable access to all constructive applications.

# The Basic **Principle** of Protection

- Since the potential for constructive and destructive application of biotechnology cannot be categorically disentangled, effective protection depends on reinforcing and existing behavioral rule:

**Biotechnology must not be used to do deliberate harm under any circumstance for any reason**

- Categorical rule must be adapted to specific context to be meaningfully applied.

- That basic principle is reasonably well established as a universal norm.
- Has been authoritatively articulated:
  - The Hippocratic Oath.
  - The 1925 Geneva Protocol.
  - The 1972 Biological and Toxin Weapons Convention.
- Is broadly upheld and not expressly rejected.
- Nonetheless must be substantially strengthened if it is to be the practical foundation for protection.

# Recent Developments in the US

- 2003 report by US National Academy of Sciences -- *Biotechnology Research in an Age of Terrorism (Fink Committee)*:
  - Acknowledged the extraordinary consequence and inevitably associated danger of biotechnology.
  - Noted that current US regulatory procedures do not provide for independent review of the social consequences of fundamental research.

- Recommended extending current RAC review process to examine social consequences for 7 “experiments of concern,” ones that might:
  - Render a vaccine ineffective.
  - Confer antibiotic or antiviral drug resistance.
  - Enhance the virulence of a pathogen.
  - Increase the transmissibility of a pathogen.
  - Alter the host range of a pathogen.
  - Evade diagnostic detection.
  - Enable weaponization.



- Noted that effective oversight measures would have to be global in scope.
- Urged international discussion of that requirement especially within the scientific community.

- 2004 Biosecurity initiative established the National Science Advisory Board for Biosecurity (NSABB) to :
  - Develop guidelines for local and national oversight.
  - Develop code of conduct for scientists and lab workers.
  - Develop education and training programs.
  - Develop guidelines for dissemination of results.
  - Promote international extension.

- National Biodefense Analysis and Countermeasures Center (NBACC) established in 2005 incorporating four components:
  - Biological Threat Characterization Center (BTCC)
  - Bioforensic Analysis Center (BAC)
  - Biodefense Knowledge Center (BKC)
    - Livermore National Laboratory
  - Agricultural Biodefense Center (ABC)
    - Plum Island Animal Disease Center

- BTCC and BAC are to be housed at a new facility under construction at Ft. Detrick MD
  - 160,000 ft<sup>2</sup> total floor space,
  - 20% of which will be devoted to BSL – 4 containment laboratories.
  - Suggests research efforts in the \$100 million range annually.
  - Entire facility to be operated as a Secure Compartmentalized Information Facility
  
- BTCC mandated to explore the destructive potential of biotechnology to identify what potential terrorists might attempt.
  - Projected efforts include genetic manipulation of pathogen virulence and aerosol dispersion of agents.

# Evident Problems

- Oversight procedures recommended by the Fink committee and projected by the NSABB:
  - Would **not** be comprehensive within the US – would not include commercial and biodefense research.
  - Would **not** be mandatory and therefore probably not adequately financed.
  - Would **not** apply beyond the US.
  - Offer **no** metric for dimensions of concern.

- BTCC mandate is of questionable legality under provisions of the 1972 BWTC.
  - US would consider the NBACC equivalent in any other country to be *prima facie* illegal.
  - Evident double standard promises to incite both objection and emulation.
- Constructive discussion by the international community has become more urgent but is not yet organized.

# Basic Features of an Effective Alternative

- Strong expectation that oversight will eventually be imposed as the fundamental method of protection.
  - That technique is applied to virtually all matters of high consequence.
    - Financial transactions
    - Handling of nuclear explosives
  - Can be based on established procedures for scientific peer review.

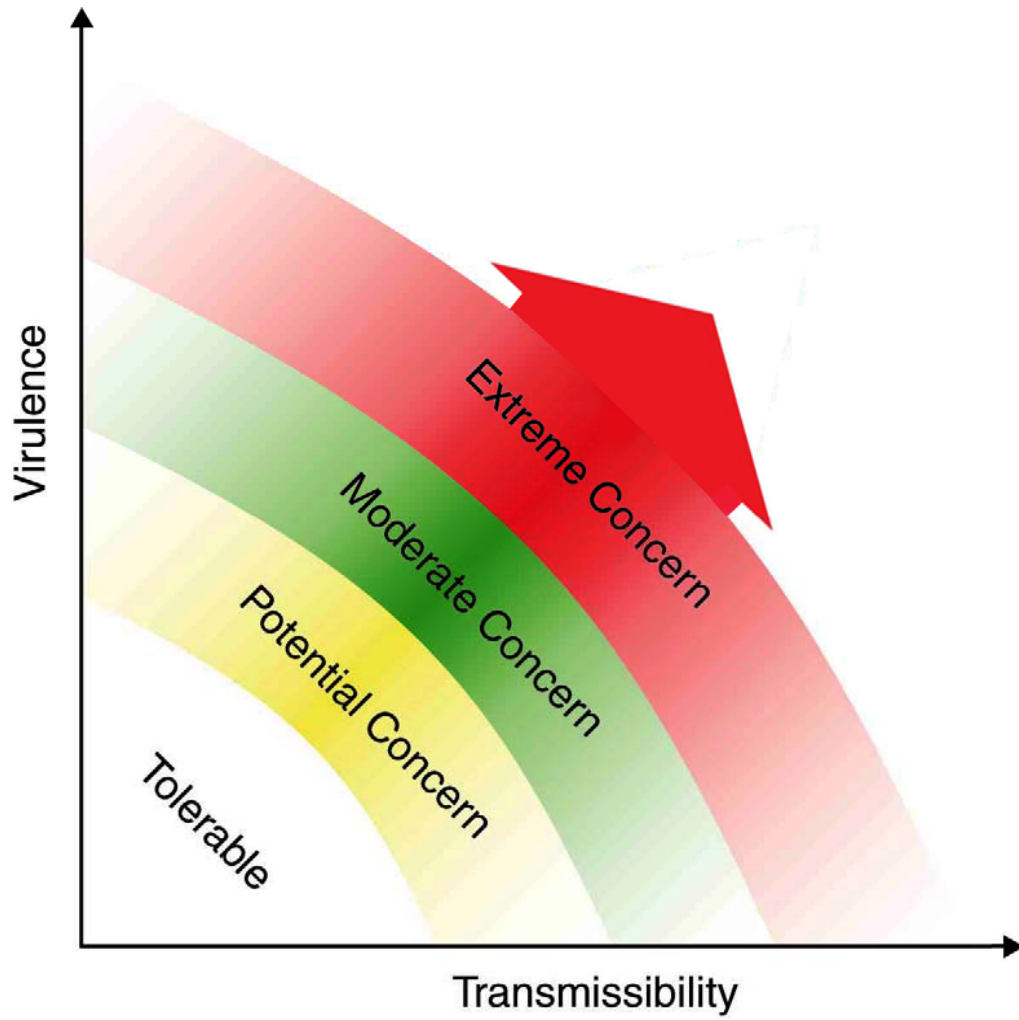
- To provide maximum protection at acceptable cost an oversight process would have to be:
  - Global in scope of application – all parts of the world
  - Categorically inclusive – all relevant research activities.
  - Credibly focused.
  - Legally mandatory.
  - Actively practiced.
  - Efficiently organized.
  - Appropriately constrained.



# An Illustrative Design

- An oversight process meeting those requirements might operate in three tiers:
  - International jurisdiction over research activities of **extreme concern** that might generate pathogens more lethal or otherwise more consequential than those currently extant in nature.
  - National jurisdiction over research activities of **moderate concern** – the more lethal of currently regulated agents.
  - Local jurisdiction over activities of **potential concern** involving agents that might be elevated to moderate or extreme categories by use of advanced manipulation techniques.

- Using a conceptual definition of danger based on:
  - Spontaneous transmissibility =  
capacity to propagate between hosts and penetrated immune defenses under standard conditions.
  - Virulence =  
capacity to generate a lethal or otherwise hostile effect within an infected host.



- Such an arrangement:
  - Would license relevant individuals and research facilities.
  - Would subject individual projects to prior review.
  - Would set conditions for the conduct of research and for the dissemination of results calibrated to the degree of danger involved.
  - Would initiate procedures of harmonizing the review judgments made in separate jurisdictions

# Practical Implementation

- Criteria for determining oversight jurisdiction:
  - **Activities of Extreme Concern (AEC):**
    - Any work on the variola virus (smallpox) or a comparably virulent agent that has been eradicated in nature,
    - Any spontaneously infectious agent requiring BSL 4/ABSL 4 level of containment,
    - *De novo* synthesis of any agent matching the above characteristics,
    - Expanding the host range of an agent or changing the tissue range of an agent that would otherwise be assigned to a lower tier category,
    - Constructing vaccine resistant or antibiotic resistant strains of agents that would otherwise be assigned to lower tier categories.

– **Activities of Moderate Concern (AMC):**

- Increasing virulence of listed agent or related agent.
- Insertion of host genes into listed agent or related agent.
- Increasing transmissibility or environmental stability of listed agent or related agent.
- Powder or aerosol production of listed agent or related agent.
- Powder or aerosol dispersal of listed agent or related agent.
- *De novo* synthesis of listed agent or related agent.
- Construction of antibiotic- or vaccine-resistant related agent.
- Genome transfer, genome replacement, or cellular reconstitution of listed agent or related agent.

## – **Activities of Potential Concern (APC):**

- Work with listed agent— or exempt avirulent, attenuated, or vaccine strain of select agent — not covered by **AEC/AMC**.
- Increasing virulence of non-listed agent.
- Increasing transmissibility or environmental stability of non-listed agent.
- Powder or aerosol production of non-listed agent.
- Powder or aerosol dispersal of non-listed agent.
- *De novo* synthesis of non-listed agent.
- Genome transfer, genome replacement, or cellular reconstitution of non-listed agent

- A survey of US grant applications and research publications 2000 – 2005 indicates that under these criteria of jurisdiction a total of 310 research facilities and 2,574 individuals would have been subjected to oversight, of which:
  - 12 facilities and 185 individuals would have been assigned to international oversight;
  - 14 facilities and 133 individuals would have been assigned to national oversight.
  - 231 facilities and 2,119 individuals would have been assigned to local oversight.
  - 53 facilities and 137 individuals would have encountered multiple jurisdictions.



- **Criteria for risk-benefit assessment:**
  - Biosafety Rating: whether proposed research plan minimizes risk to public and environment.
  - Adequacy of Research Plan: whether there are scientific reasons why same outcome cannot be pursued through other means.
  - Public health rationale: whether research will advance understanding of disease causing properties of existing pathogens.
  - Biodefense rationale: whether work being done in response to validated or theoretical threat.
  - Current necessity of work: whether there are medical countermeasures available for use against agents to be constructed.
  - Potential impact: whether proposed results will inform policy

# Current State of the Problem

- Momentum of the research process is continuously generating highly consequential lines of inquiry.
- Immediate terrorist threat is comparable to or less than the natural incidence of infectious disease
  - and can be addressed by enhanced public health measures.
- Hostile competition among national threat assessment programs is a more serious immediate concern than potential terrorism.
- Exclusive subordination of national threat assessment activities to public health jurisdiction and application of transparency rules are urgent priorities.

# Impressions from May workshop in Hungary

- 30 participants from 15 European countries, WHO, OECD and UNESCO.
- General agreement that an effective oversight arrangement would have to be comprehensively applied.
- Broad support for:
  - Codes of conduct among scientists
  - Education and training programs on dual-use dilemma
  - Independent peer review of consequential projects
  - Transparency as the basic principle of protection.

- Concern about overly intrusive regulation.
- Disagreement about:
  - The adequacy of existing regulatory arrangements
  - the relative merits of voluntary and mandatory measures
- Interest short of endorsement in the global oversight outline presented.