Managing the Promise and Danger of Biotechnology

Presentation for

Regional Biosecurity Workshop

Alexandria, Egypt

February 22 – 24, 2009

John Steinbruner
University of Maryland

Conception of the Fundamental Problem

- Rapid progress in basic molecular biology is apparently enabling extraordinarily consequential applications, including **in principle**
  - Powerful individual therapies
  - Eradication of historical diseases
  - The creation of substantially more lethal pathogens
  - The manipulation of cognitive, emotional and reproductive functions on a mass scale.

- At the level of basic science **therapeutic** and **destructive** applications cannot be disentangled.

- The extended consequences of this situation
  - are potentially large;
  - cannot be determined with confidence;
  - 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 appropriately restricted 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 by any government.

- 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 did not provide for independent review of the social consequences of fundamental research.

– Recommended extending current Recombinant Advisory Committee (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^2 total floor space,
  - 20% of which will be devoted to BSL – 4 containment laboratories.
  - Suggests research efforts in the $100 million range annually.
  - Some unspecified portion of which is to be classified.

- 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.
  - Separate internal review procedures for intrinsic justification and treaty compliance ordered by Presidential directive but not yet implemented.
  - Current projects do not appear to be threatening but could establish the basis for ones that would be.

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 subject to question 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.

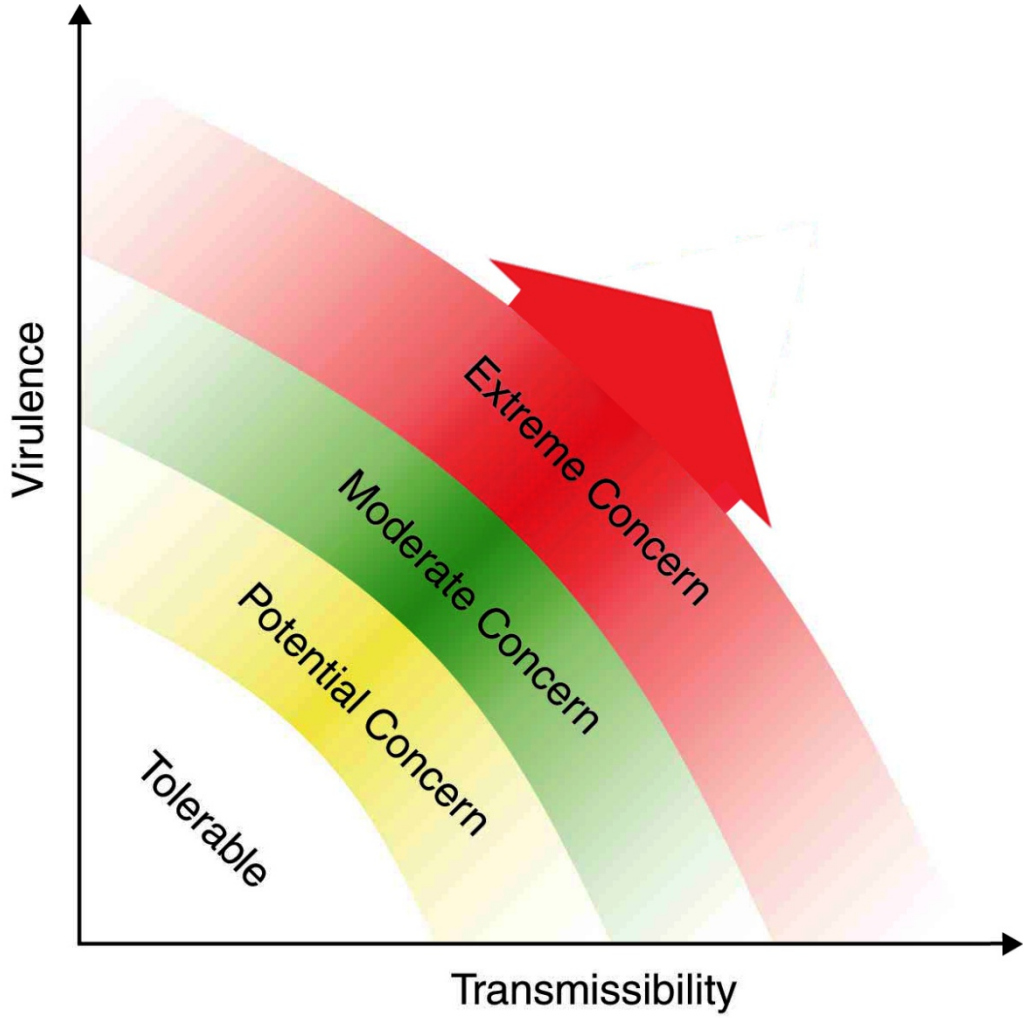
- Using a conceptual definition of danger based on:

  – Spontaneous transmissibility =

    capacity to propagate between hosts and penetrated immune defenses under standard conditions.

  – Virulence =

    capacity to generate a lethal of otherwise hostile effect within an infected host.


Virulence
Extreme Concern
Moderate Concern
Potential Concern
Tolerable
Transmissibility

- 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.

- In all less than 1% of US publications on bacteria, viruses or prions would have been subjected to oversight – a tiny fraction of the relevant biomedical research community.

- 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

- The illustrative Oversight arrangement is presented in: *Controlling Dangerous Pathogens: A Prototype Protective Oversight System*
  - accessible at http://www.cissm.umd.edu/papers/files/pathogens_project_monograph.pdf

Current State of the Problem

- Momentum of the research process is continuously generating highly consequential lines of inquiry.
- Immediate terrorist threat is not greater 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.