Managing the Destructive Potential of Biotechnology

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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.

• 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 ft² 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 of 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 per 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.