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DUAL USE RESEARCH OF CONCERN AND MICROBIOLOGY

Singapore, June 14, 2010

Dual Use Research in Life Sciences

Increased concern about bioterrorism and biowarfare amongst policy makers following 9/11 and anthrax letter attacks in the USA

Discussions about the potential for misuse of biological research and how to prevent it

Lecture Objective: introduce practising scientists and students to the concept of awareness about the possible malign misuse of the life sciences

- ***Life sciences research underpins:***
  - **Biomedical and public health advances**
  - **Improvements in agriculture**
  - **Safety and quality of food supply**
  - **Environmental quality**
  - **Strong national security and economy**
- ***However, good science can be put to bad uses***

Definitions

- **Dual Use Research**
  - Biological research with legitimate scientific purpose that may be misused to pose a biologic threat to public health and/or national security
- **Dual Use Research of Concern**
  - Research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment, or materiel

Resources Necessary to Misuse Research

- **Nuclear:** Sophisticated expertise and nation-state resources; damage horrific
- **Chemical:** Lesser sophistication and minimal resources; damage extensive (e.g. methylisocyanate release Bhopal, India, December 1984)
- **Biological:** Lesser sophistication and minimal resources and damage could reach pandemic proportions

Australian mousepox experiment
An example of dual-use research

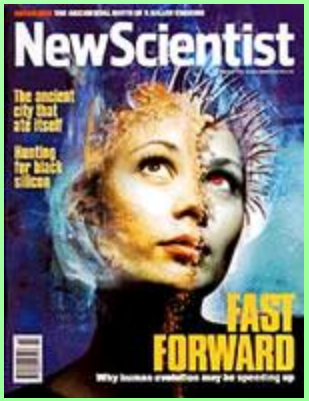
- Plagues of hundreds of millions of mice cause millions of dollars of damage in Australia's grain belt.
- To prevent or mitigate such plagues Australian researchers try to induce sterility in mice by altering an infectious virus that affects mice: mousepox.
- They insert egg protein gene into mousepox genome to create antibody response against eggs and thus rejection.
- They also insert the IL-4 gene to enhance the antibody response (!).

Jackson, R. Ramsay, A., Christensen, C., Beaton, S. Hall, D., & Ramshaw, I. 2001. 'Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox' *Journal of Virology* 75(3): 1205-1210. http://www.pubmedcentral.gov/articlerender.fcgi?tool=pubmed&pubmedid=11152493

Australian mousepox experiment (cont).

- The researchers produced a recombinant virus with greatly increased lethality.
- The virus with IL-4 killed mice genetically resistant to mousepox and those immunized against it.
- Concerns arise because of the potential for increased lethality of other pox viruses, including smallpox

"Disaster in the Making: An engineered mouse virus leaves us one step away from the ultimate bioweapon"



Another example: Production of an Extraordinarily Lethal Form of a Select Toxin

An investigator in the US NIAID/NIH is developing a vaccine against a “Select”* toxin (known to be stable to boiling)

*(Select agent: A biological agent or toxin that has potential to pose a severe threat to public health and safety)

She purifies the toxin from a natural source by a simple but previously unpublished method

When tested in mice the oral LD_{50} is found to be 1000x lower than expected from literature values!

Other examples of published "contentious research"

2002: Total synthesis of poliovirus genome

2005: Genome sequence of the 1918 human influenza virus; effects of recreated virus virus in mice.

2007: Extending host range [human → mouse] of *Listeria monocytogenes* by rational protein design

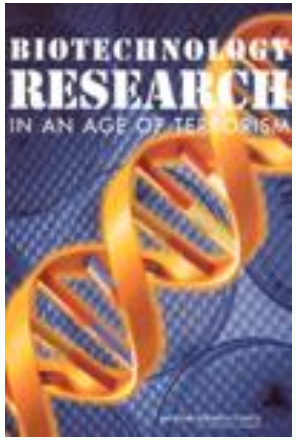
Experiments/Results of Special Concern

1. Render a vaccine less- or in- effective
2. Confer resistance to antibiotics/antiviral agents
3. Enhance virulence, increase transmissibility or alter host range
4. Enable evasion of diagnostic/detection modalities
5. Enable weaponization of biological agent or toxin

World Mortality Statistics

Cause	Incidence*
Communicable diseases, maternal, perinatal, and nutritional conditions	18,400,000
Non-communicable diseases	33,500,000
Injuries (intentional and non-intentional)	5,200,000
Bioterrorism	1

* Per annum estimates (2002-2006) from WHO data

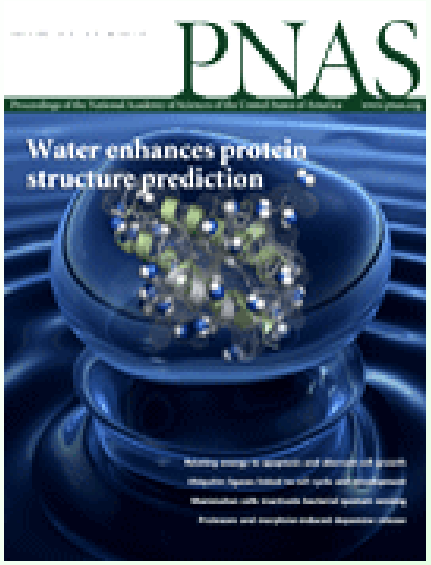


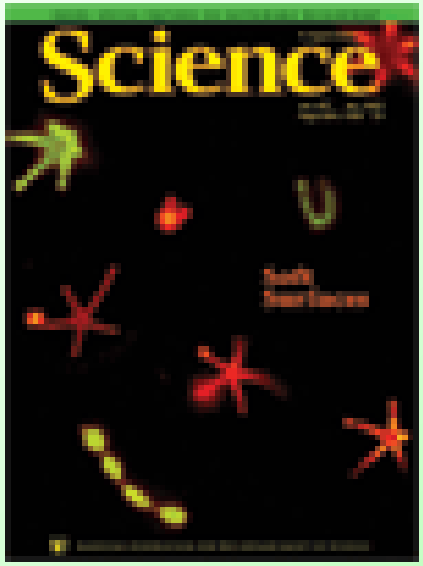
US National Academies (Gerald) Fink Report (2004). *"Biotechnology Research in an Age of Terrorism"*

Recommendations

1. Educate scientific community
2. Review plans of selected experiments
   - Making vaccines ineffective
   - Altering host range or enhancing virulence of pathogens
   - Conferring resistance to useful antibiotics or antivirals
3. Review at publication stage
4. Create National Science Advisory Board for Biosecurity (NSABB)
5. Increased communication between life science, national security, and law enforcement communities
6. Convene international forum on biological security
7. Codes of conduct.

Weighing the Risks and Benefits





- In 2003 thirty-two scientific journals (ASM journals, *Science*, *Nature*) agreed on a process for reviewing, modifying, and perhaps even rejecting research articles where ‘the potential harm of publication outweighs the potential societal benefits.’

- UK Wellcome Trust has taken dual-use potential of research into account in reviewing proposals

Results of Applying Risk/Benefit Analysis

- No publication yet stopped in any journals; though two were modified.
- Wellcome Trust never refused an application or imposed publication restrictions because of dual use concerns
- ‘Extreme’ case: 2005 Sequencing and reconstruction of 1918 Spanish Flu virus: NSABB, *Science*, *Nature* agree benefits outweighed the risk

Will the risks ever outweigh the benefits?

Heightened Attention to Dual Use and Need for Codes of Conduct

- Earlier concerns
  - –Experience with nuclear weapons
  - –Rotblat called for a “Hippocratic Oath” for Scientists

- Long history/experience with codes of conduct (medical sciences):
  - – Hippocratic Oath
  - – Codes of Medical Associations
  - – Nuremburg Code
  - – Declaration of Helsinki
    - →Extremely influential
    - →Largely effective guide to action

Why codes of conduct are important?

Roles:

- Raising awareness (and thus promoting good conduct—and avoidance of bad outcomes)
- Winning trust in science enterprise
- Avoiding over-regulation
- Raising awareness of social responsibilities of scientists

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IUMS Code of Ethics against Misuse of Scientific Knowledge, Research and Resources

- IUMS is opposed to the misuse of microbiological knowledge, research and resources. In particular, IUMS also strives to promote ethical conduct of research and training in the areas of biosecurity and biosafety so as to prevent use of microorganisms as biological weapons and therefore to protect the public's health and to promote world peace

Adoption of the Code of Ethics or no opposition to Code of Ethics
Requisite for membership

Codes of Conduct: Limitations

- Universal codes— “lack substance”, too general to be action guiding
  - Commonsense lists of things (conscientious) people would do anyway
  - Conflicting principles
- If too specific/detailed, then less wide applicability and/or code is more controversial/less widely accepted
- Dangers r/e proliferation of codes (that say different things).
- “Codes not effective”—those who would do what codes prohibit are not the kind of people who listen to codes in the first place. Need enforcement mechanisms.

Enforcement

- Sanctions of professional societies r/e membership and/or licensing
- Enforcement via denial of grants/withdrawal of Federal Funding
- Defacto legal status —“standards of practice”— negligence.
- Formal legislation (perhaps as part of governmental oversight process)

Are biosecurity oversight mechanisms to be welcomed?

If Fink recommendations *not welcomed*, what about…

"We're looking for the scientific community to come forward itself because the government will not do this very efficiently and not do it very well at all. We are looking for scientific community to come forward to help establish these kinds of criteria [for the oversight of research], to debate them openly."

-- Penrose Albright (2003)
Office of Homeland Security
White House Office of Science & Technology Policy

- **At any stage of life sciences research, individuals are ethically obligated to avoid or minimize the risks and harm that could result from malevolent use of research outcomes.**

- **Towards that end, scientists should:**

  - **Assess their own research efforts for dual use potential and report as appropriate;**
  - **Seek to stay informed of literature, guidance, and requirements related to dual use research;**
  - **Train others to identify dual use research of concern and manage it appropriately and communicate it responsibly;**
  - **Serve as role models of responsible behavior, especially when involved in research that meets the criteria for dual use research of concern; and**
  - **Be alert to potential misuse of research.**

Take Home Message

- Recognize that there is a potential problem and that the public is seriously concerned about it
- Be informed about the scientific community's efforts to minimize misuse responsibly
- Remain sensitive to the potential in your own research and in reviewing work of others
- If concern arises, know who to consult

Antibiotic Resistance Case Study

Module 5.0

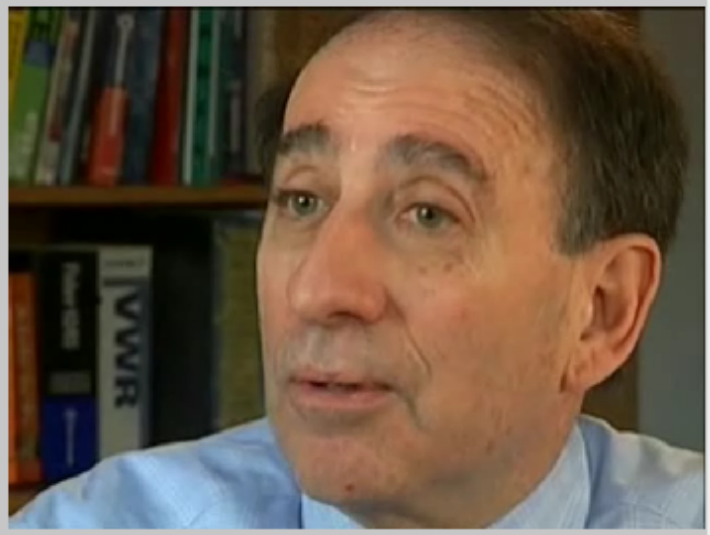
FEDERATION of AMERICAN SCIENTISTS

Topic: Implications

Dual-Use Concerns of Antibiotic Resistance

Video

Click the play video button to view a clip of Dr. Levy discussing dual-use research.



There is a concern that publishing experiments like those done in the Levy paper may pose a biosecurity threat because it provides instructions for a rogue individual or group to create pathogens like *Y. pestis* that are resistant to standard treatment. Making antibiotic-resistant bacterial strains by inserting a plasmid expressing resistance to a specific known antibiotic is routine in most biology research labs. However, Levy was able to show that resistance to six common antibiotics could be transferred from one type of bacteria to another via a single gene. Two of the antibiotics, tetracycline and chloramphenicol, are currently used to treat plague infections.

States or organizations interested in developing biological weapons could cultivate antibiotic resistant pathogens to ensure that if released they would do as much damage as possible. Ken Alibek, a former Soviet biological weapons leader, has reported that during the 1980's the Soviet Union developed antibiotic-resistant strains of plague, anthrax, tularemia, and glanders bacteria. More recently, the Iraqi regime of Saddam Hussein also employed an ambitious bioweapons program focusing on anthrax, botulinum toxin and aflatoxin. The directors of the program, two women known as "Dr. Germ" and "Mrs. Anthrax" were arrested in 2003, shortly after the overthrow of Saddam.

http://www.fas.org/biosecurity/education/dualuse/FAS_Levy/2_A.html

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THANK YOU!

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