"The Life Sciences, Biosecurity, and Dual Use Research"

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Project on Dual Use Research in Life Sciences

- Increased concern about bioterrorism and biowarfare amongst policy makers following 9/11 and anthrax letter attacks
- Discussions about the potential for misuse of biological research and how to prevent it
- Seminar Objective: to encourage an interactive discussion amongst practising scientists and students about the possible malign misuse of the life sciences

In many respects, the events of September 11, 2001 and the anthrax attacks in the US that followed afterwards provide the immediate backdrop for this seminar. As I'm sure most of you are aware, since then there has been a significant increase in attention to threats posed by biological weapons. What some of you may not be aware of is that there has also been heightened attention since regarding the possible security implications of life science research. Questions are being asked internationally whether the research, techniques and knowledge in generated in places like universities might not only *prevent* the spread of disease but might inadvertently *facilitate* it. In this sense, research has a 'dual use' potential. And if that is the case, then what should be done in response?

I want to do two things in the seminar today. The first is to inform you about current 'biosecurity' and 'dual use' debates. The second, and much more important, is to generate discussion about these issues. I hope you will respond a lively way based on your individual experiences. With that, let us more to the first slide and case.

For further information:

American Association for the Advancement of Science *Resource: Science and National Security in the Post-9/11* Environment http://www.aaas.org/spp/post911/

Shea, D. 2003. *Balancing Scientific Publication and National Security* Concerns 10 January Washington, D.C.: Congressional Research Service. http://www.fas.org/irp/crs/RL31695.pdf

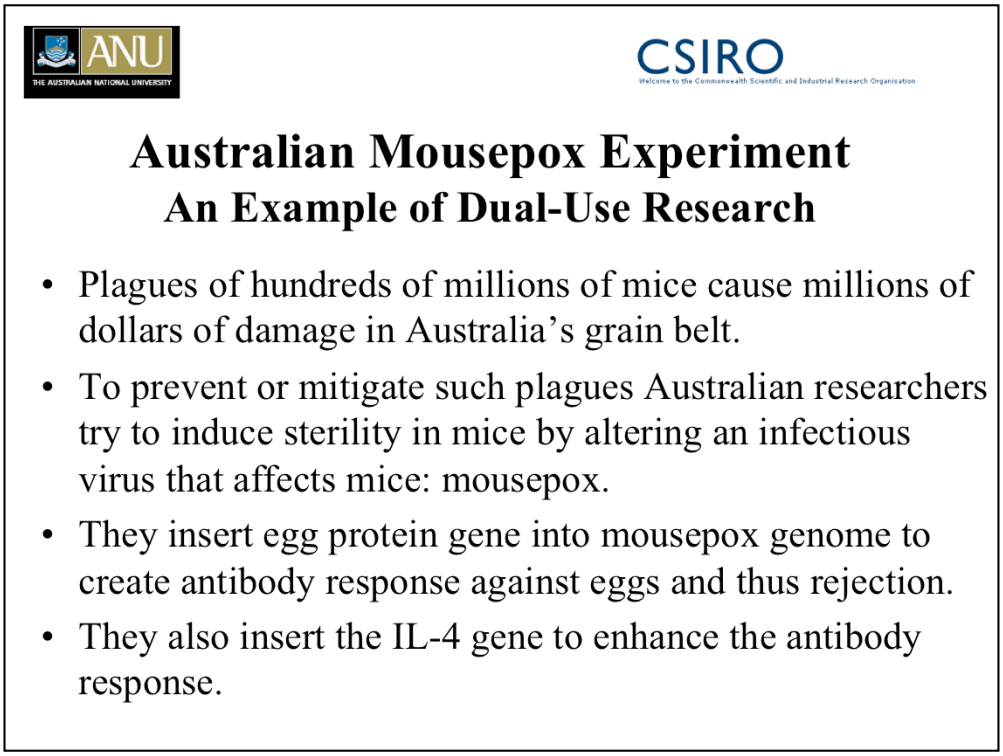
Wellcome Trust. 2003. *Wellcome Trust Position Statement on Bioterrorism and Biomedical Research.* http://www.wellcome.ac.uk/doc_WTD002767.html

Playing Your Role

- Powerpoint slides will address relevant issues in dual-use research and ask questions.
- First respond from the perspective of your character.
- Try to understand the reasons a person might hold these views and the implications of such an opinion.
- If you wish you may state your own views if they differ from that of your character.

Communication

The first set of slides concern the communication of research results. The publication of certain dual use research results have provoked recent discussions about potential misuse.



There have been a number of publications in the life sciences which have caused something of a stir because of their dual use potential. Perhaps the paradigmatic case is the Australian IL-4 mousepox experiment. Briefly, scientists at the Australian National University and the Commonwealth Scientific and Industrial Research Institute were trying to find a way of dealing with the plagues of mice which occur in Australia and cause significant agricultural damage. They came up with the idea of using a relatively benign form of mousepox which is usually not lethal to mice, and then to insert the gene for an egg protein from the mouse into this pox virus. The inserted virus then would create an antibody response by the female mice to her own eggs. This worked, but not as well as they hoped, so the researchers decided to add the gene for the cytokine interleukin-4 into the genome of mousepox and in the hopes that this would then elevate the antibody response.

Communication Questions

- 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.
- Published in *Journal of Virology* Feb. 2001.

Do you agree with the decision to publish?

If so, why? If not, why not?

What follows on from your views?

It certainly elevated the response. What it did in fact was to close down the cell mediated arm of the immune system. They ended up with a recombinant virus which killed mice genetically resistant to mousepox and even those immunized against it. It didn't take very long for the researchers to ask 'Hang on a minute, what if somebody was to do this with smallpox?'. Potentially at least, you might then have a form of smallpox that could overcome existing vaccinations. The first question then is do you think the Australians should have gone ahead and published these results in a standard scientific article in the *Journal of Virology*? If so, why? If not, why not? Would there be any additional follow on implications that would follow from what you said?

For further information:

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

ABSTRACT

Genetic resistance to clinical mousepox (ectromelia virus) varies among inbred laboratory mice and is characterized by an effective natural killer (NK) response and the early onset of a strong CD8+ cytotoxic T-lymphocyte (CTL) response in resistant mice. We have investigated the influence of virus-expressed mouse interleukin-4 (IL-4) on the cell-mediated response during infection. It was observed that expression of IL-4 by a thymidine kinase-positive ectromelia virus suppressed cytolytic responses of NK and CTL and the expression of gamma interferon by the latter. Genetically resistant mice infected with the IL-4-expressing virus developed symptoms of acute mousepox accompanied by high mortality, similar to the disease seen when genetically sensitive mice are infected with the virulent Moscow strain. Strikingly, infection of recently immunized genetically resistant mice with the virus expressing IL-4 also resulted in significant mortality due to fulminant mousepox. These data therefore suggest that virus-encoded IL-4 not only suppresses primary antiviral cell-mediated immune responses but also can inhibit the expression of immune memory responses.

Another Kind of Communication

- January 2001Australian researchers worked with a popular magazine to publish a preview of their paper.
- *New Scientist* published an article with the following title:

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

Rationale: "We wanted to warn the general population that this potentially dangerous technology is available…We wanted to make it clear to the scientific community that they should be careful, that it is not too difficult to create severe organisms." -- R. Jackson

How do you view the decision to popularly publish (why, what follows on from this, etc.)?

Let's just slightly later the line of reasoning. The Australian researchers did not just communicate their results through a standard article in the *Journal of Virology,* rather they did so through the *New Scientist* as well. The month before article appeared in the *Journal of Virology*, *New Scientist* carried an editorial and an article about the experiment. That first article was entitled 'Disaster in the Making – an engineered a mouse virus leaves us one step away from the ultimate bioweapon'. It noted that a forthcoming issue of the *Journal of Virology* would be carrying the scientific article. The logic the Australian researchers used to justify the *New Scientist* coverage was that 'We wanted to warn the general population that this potentially dangerous technology is available…We wanted to make it clear to the scientific community that they should be careful, that it is not too difficult to create severe organisms.'

So what I want to ask you then is not was it a good idea to publish in the scientific press, but should they have gone ahead and 'popularly published' their results?

For further information:

New Scientist 13 January 2001

http://www.newscientist.com/contents/issue/2273.html

Another Model for Communication

- Suggestion that British researchers had previously obtained similar results to the Australian mousepox research.
- The researchers were said to have informed Health and Safety Executive, but deliberately avoided discussing or alluding to bioweapons implications in their publication.
- A literature search revealed a **1998** *Journal of Virology* article that might be research in question:
  - IL-4 insertion in modified vaccinia virus (VRBm)
  - "A mortality of 100% was observed for mice immunized with VRBmIL-4 [modified vaccinia with IL-4 gene]… This contrasted with that for mice immunized with rVV expressing low levels of IL-4…which showed no ill effects…"

What are the merits of this "softly-softly" approach?

OK, up to this stage I have asked questions about whether something should be published or not. Now I want to ask a more nuanced question about how one should publish. There has been a suggestion that similar results to what the Australians found had been achieved elsewhere but communicated in a much different manner. This story involves researchers in the UK who were working with IL-4 in the late 1990s. The idea is that the scientists unexpectedly came across similar results about the lethality of IL-4 in a pox virus, but choose to take a very low key approach to communicating their results. So rather than warning the general population through an article in *New Scientist* or raising flags within scientific communities through their specialized publications, what these researchers did was to inform the Health and Safety Executive of their 'dual use' concerns. The UK Health and Safety Executive is in charge of ensuring laboratory biosafety. Then they continued on with the civilian animal research they were interested in.

This is a story that is told in UK policy circles without any identification of who was involved, so it is not possible to know what research is being referred to in this story. Looking back with a sense of hindsight, though, it is possible to identify research that could fit this description. For instance, a 1998 article in the *Journal of Virology* dealt with the effects of cytokine genes on the immune system. If you read the article closely, you can see the researchers made some interesting findings regarding the

Funding

Ideas of restricting research and publications are generally treated as matters of concern by practicing life scientists. However, the funding of various lines of research has also provoked discussions of interest in relation to dual use research.

What is Being Funded: Keeping Ahead Through Research

US Program: "Biodefense for the 21st Century"

- NIH biodefense research ~$50million (2001)
  ~$1.6 billion (2005)
- National Institute of Allergy and Infectious Diseases in 2005 roughly 190 research awards about therapeutics, diagnostics, host response, vaccines, basic biological mechanisms
- 13 BSL-3 and 7 BSL-4 research facilities under construction
- Other civilian programs under Department Health and Human Services, Departments of Agriculture, Homeland Security, etc. totalling ~$3.4 billion (2006) for research programs and facilities

Is this to be welcomed and why?

OK, well let us shift the topic from communication to funding. In discussions about these dual issues, the point is often made about the need to stay ahead of biothreats through research. Certainly this basic philosophy is central to the recent US program called 'Biodefence of the 21st Century'. Just to give you a sense of its basics, the National Institute of Health is the getting the bulk of the civilian funding under this program. In 2001, it funded about $50 million of biodefense research. By 2005, though, that figure had gone up to over a billion and half. Much of this work is being undertaken by the National Institute of Allergy and Infectious Diseases. In 2005, it granted almost 200 major research awards ranging from applied work in therapeutics and diagnostics to basic biological mechanisms. Other US public agencies are also dedicating significant funds to biodefense. The Department Health and Human Services as a whole, the Departments of Agriculture, Homeland Security, and Defense have budgets for biodefense research which total something like three and half billion dollars for 2006. In any case, what do you think about the merits of this funding program, which has at its heart the idea of staying ahead of threats through research. Is it to be welcomed?

<u>For further information:</u>

Schuler, A. 2005. 'Billions for Biodefense: Federal Agency Biodefense Budgeting,

Oversight

As concerns about the possible misuse of research have grown, attention has increasingly focused on whether new forms of oversight of research are required. The final set of slides address this issue.

Development of Biosafety Oversight

- In 1970's life scientists began to manipulate genomes.
- Many countries have instituted review procedures to ensure biosafety of such experiments.
- In US, Asilomar Conference in 1975 led to NIH funded research subject to rDNA review procedures.

James Watson and
Sydney Brenner at Asilomar

Before getting into dual use specific issues, let me make some initial remarks about oversight in general. Oversight is not a new issue to life science research, indeed concerns about the need for such measures have been around for some time. This slide notes some examples related to the safety of experiments.

US National Academies Fink Report *"Biotechnology Research in an Age of Terrorism"*

- Expand **existing** local and national *biosafety* review for **NIH funded** rDNA research to include *biosecurity.*
- Apply new procedures to 'experiments of concern' in **US** e.g.:
  - Making vaccines ineffective
  - Altering host range or enhancing virulence of pathogens
  - Conferring resistance to useful antibiotics or antivirals
- Establish National Science Advisory Board for Biosecurity to:

  review, survey and educate bioscientists including to 'develop guidelines for the oversight of dual-use research, including guidelines for the risk/ benefit analysis...'

Are biosecurity oversight mechanisms to be welcomed? Why or why not?

In the United States, where perhaps more attention has been given to the issues surrounding the malign use of life science research, the National Academy of Sciences set up a committee to look at what possibly could be done in response. This was headed by Gerald Fink of the Whitehead Institute. After about 18 months of study, they produced a report that has become known as the Fink Report. One of its recommendations was that there should be an expansion of the current NIH recombinant DNA review procedures to include a review of so-called 'experiments of concern'. These experiments would be of concern in the sense that they might come up with findings that could readily and significantly aid malign purposes. Seven categories of research of concern were proposed, of which a few are noted on the slides. The report suggested that the proposals to carry out research in these areas should be submitted to local institutional biosafety for assessment and that there should be a National Science Advisory Board for Biosecurity set up to review any case which could not be handled at a local level. The Bush Administration accepted most of the recommendations of Fink report and established the National Science Advisory Board for Biosecurity to give advice on how such and oversight system should function. By 2006, the Board had had a number of meetings and began to formulate specific recommendations. So the question I would like to ask is: should such an oversight system be welcomed?

What Else Might be Done

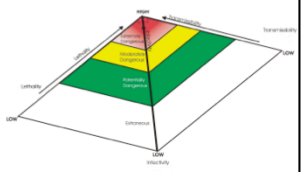
If Fink recommendations *not welcomed*, what about…

"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

OK, given that some of you expressed reservations about the system of community self-governance proposed by the Fink report, I can put up this quote from someone at the US Department of Homeland Security. What Albright said, and it is a sentiment that have been echoed by others in and outside of the US, is that the failure of the scientific community to come up with oversight suggestions will necessitate others stepping in, such as politicians. The implication being: don't complain if this happens. I offer this quote just to see what sort of reactions you might have to it.

What Else Might be Done?
"Protective Oversight System"

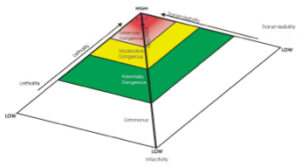


- Former government officials now at University of Maryland and an international team developed a legally based system.
- Three-tiered categorization based on potential consequences:
  - **International** oversight of **extremely** dangerous research = greater than currently active agents.
  - **National** oversight of **moderately** dangerous research = the worst of the current select agents.
  - **Local** oversight of **potentially** dangerous research = agents that might be elevated to moderate or extreme categories by use of advanced manipulation techniques

OK, given that some of you expressed support about the system of community self-governance proposed by the Fink report, by way of testing your reasoning I want to know what you think of a more comprehensive proposal for oversight. This comes from the Center for International and Security Studies at the University of Maryland.

As opposed to the Fink committee recommendations which outline a national system of oversight that included local and national review, the group at Maryland are proposing a system that includes local, national, and international forms of oversight depending on the potential consequences of the research.

"Protective Oversight System" cont.



- **Mandatory** for all relevant facilities including:
  - Military
  - Commercial
  - Government
  - Academic
- Require **licensing** of facilities and researchers on biosecurity grounds including background checks and training

Is this type of oversight system to be welcomed? Why or why not? Implications?

Whereas the Fink report relates to NIH funded research, Maryland recommendations would involve legal requirements for all relevant facilities, be they commercial, government, academic, or whatever. This much more comprehensive system would also require relevant facilitates to seek a license for their activities. This license would be dependent on background checks and biosecurity training. So, I offer this quote just to see what sort of reactions you might have to it. If so, why? If not, why not? Would there be any additional follow on implications that would follow from what you said?

For further information:

Center for International and Security Studies, University of Maryland

http://www.cissm.umd.edu/projects/pathogens.php

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

wellcome trust

Many the proposals mentioned so far have approached the matter of what should be done have advocated that scientific oversight mechanisms -- such as peer review and institutional safety boards -- should identify individual activities of concern, weigh their risks and benefits, and then take any necessary responses on that basis. This framing about what should be done is quite widespread and is likely to have a lasting impact on how dual use issues are thought about for sometime.

This risk-benefit analysis has also been a part of procedures that are already in place. For instance, in early 2003, an informal group of 32 journal editors, including those representing the journals of the American Society for Microbiology, *Science*, and *Nature* got together to think about what to do. The group agreed voluntary guidelines for reviewing, modifying, and if necessary rejecting research articles where 'the potential harm of publication outweighs the potential societal benefits.' The Wellcome Trust, a UK-based major funder of bioscience and biomedical research has considered the possible risks and benefits associated with funding proposals as part of its review process for a number of years.

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?

The result of both these processes though is that nothing has ever been stopped. In the case of the journal editors, as of 2006 apparently two publications of the tens of thousand of manuscript received were requested to be modified in some way.

To offer up what might be an 'extreme' case of dual use research, consider work done on the 1918 Spanish Flu. During 1918 and 1919, this virus was responsible for the deaths of tens of millions of people in a worldwide pandemic. In 2005 two articles were published about it that cause some stir. One was the publication in *Nature* of the sequences for the remaining unsequenced parts of the virus' genome. The second article published in *Science* described the artificial reconstruction of the virus. In both cases the publications went through the journal review process and in both cases it was said the benefits far outweighed the risks. In addition, the virus reconstruction article in *Science* was somewhat informally scrutinized by the established National Scientific Advisory Board which likewise concurred that the benefits outweighed the risks.

So given this experience to date, can anyone image a case where the risks outweigh the benefits?

Thank You & Debrief

For further information about the results of these types of seminars and dual use research issues in general, see www.ex.ac.uk/codesofconduct or contact Brian Rappert at the University of Exeter (B.Rappert@ex.ac.uk)

Debriefing the Role Play

- What role did you find yourself identifying with most strongly? Why?
- What aspects of the role assigned to you did you find easiest to present?
- What aspects of the role assigned to you did you find most difficult to present?
- Do you have additional arguments, insights or opinions that were not represented by people playing the other roles?