

Xenotransplantation, Zoonosis, and Dual-use Dilemmas

Honor 2510, Spring 2009
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Outline

- Xenotransplantation
 - Benefits and risks
 - Immune system
- Zoonosis
 - Origin of many diseases
 - Problems and manipulations
- Dual-use Dilemmas
 - Saving the world and bioweapons
 - Balancing two needs

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Xenotransplantation

- The transplantation of living cells, tissues, or organs from one species to another.
 - Tissues & Cells: brain/tissue/blood source, tissue grafts, veins/arteries, etc.
 - Organs: heart valves, hearts, livers, lungs, etc.
 - Applications for cancer, diabetes, liver failure, Parkinson's, etc.
- Rationale
 - Clinical need for organs, tissues, cells
 - ~60% of patients waiting for replacement organs die while on the waiting list. Human sources limited (~5,000 donors vs. ~50,000 on waiting lists)
 - Alternative source for tissues
 - Non-human sources of tissue/organs may make for reliable resource for medical uses, overcoming issues of harvesting or experimenting on human derived materials.

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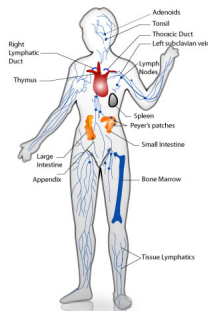
Ethics of Xenotransplantation

- Animal Rights/Welfare
 - Concerns over the use/manipulation of non-human animals, abuses, welfare, and possibility of rights (e.g., "Great Ape Project").
- Immune Response
 - Foreign bodies introduced into humans may produce a dangerous immune response that could reject the tissue/organ and/or kill the patient.
- Zoonosis
 - Transmission of infectious disease from one species to another, potentially causing wide spread disease (pandemic).

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Immune System

- Your immune system is designed to defend you against invading bacteria, microbes, viruses, and parasites. (You vs. them)
- Three different ways:
 - Create a barrier that prevents invasion;
 - If barrier is surpassed, detect and eliminate invasion before it can reproduce;
 - If reproducing, eliminating invasion before lethal.



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White blood cells

- Produce **antibodies**, y-shaped proteins that each respond to a specific **antigen**, binding to it disabling that antigen (bacteria, virus, toxin).
- Examples:
 - **B cells**: develop in bone marrow, produce antibodies specific to an antigen, which can clone rapidly.
 - **T cells**: develop in bone marrow, migrate to other areas, identify infected (viruses) cells and destroy them; also producing a chemicals that signal immune response.

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Immune Response

- Normal immune response
 - Effectively identify and combat infections, and in some cases developing immunity (adaptive or acquired immunity)
- Dangerous immune response
 - Over respond: producing too much, or attack wrong cells (e.g., autoimmune diseases and allergies)
 - Under respond: weakened immune response (immunodeficiency) or complete lack of immune system (e.g., SCID)

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Xenotransplantation

- The risk of inducing a dangerous immune response as a result of introducing foreign tissue into a human is always a risk in transplantation. (Add the risk associated with the use of immunosuppressant drugs during transplantations.)
- The specific concern about **xeno**-transplantation is that it potentially introduces novel pathogens into the human system with which humans have no immunological history.

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Zoonosis

Zoonotic Diseases

- Transmission of infectious disease from one species to another, potentially causing wide spread disease (e.g., **pandemic**).
- Many diseases are the result of cross-species infection.
 - Examples: Lyme disease, rabies, Ebola hemorrhagic fever, hantaviral disease, anthrax, cholera, smallpox, measles, plague, typhus, West Nile virus, strep, Yellow Fever, AIDS via HIV, influenza, common cold, etc.

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Some Viruses & Likely Origins

| Disease | ~Xenogenesis |
|--|--|
| Creutzfeldt-Jakob disease (vCJD) | Cows (bovine spongiform encephalopathy: "Mad Cow Disease") |
| Ebola and Marburg virus (hemorrhagic fevers); Human immunodeficiency virus (HIV) | Monkeys, Chimpanzees |
| Nipah viral encephalitis (1999 Malaysia) | Pigs |
| Severe acute respiratory syndrome (SARS) | Wild cats, bats, and ferrets |
| Spanish flu (1918), Avian flu (now) | Birds (poultry) |
| Hanta virus & smallpox | Rodents (fleas) |

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Spanish Flu, 1918



- **Global Pandemic**
 - ~20% of world population infected
 - 28% of Americans infected, including President
- ~50 million dead globally in 2 years (~3% world population).
 - Victims dead in hours to days; suffocated.
 - 3x total killed in WW1
 - US average lifespan decreased by 10 years.
- Spread by troops moving in/out of Europe in WW1.
 - "Spanish" b/c first reported case in Spain.
 - Severely taxed health system
 - In US, entered via Boston in Sept. by Oct. 200,000 dead.
- Origin:
 - Probably China
 - From avian source

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Why was 1918 flu so lethal?

- Introduce a novel pathogen into a species with no prior immunity means that species is vulnerable.
- Spanish flu was highly **virulent**:
 - Very effective at infecting an individual;
 - Very effective at spreading between individuals
- Added vulnerability with poor sanitation, international travel, strained health-system, and poor emergency response...

Compare risk associated with xenotransplantation?

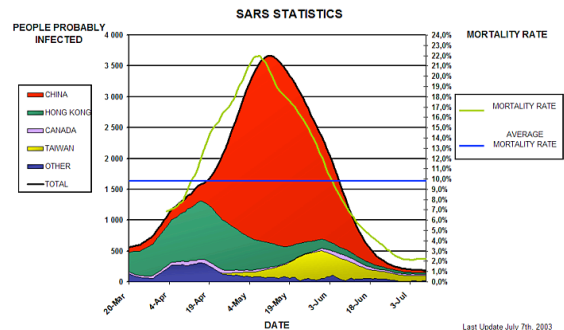
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Recent Developments

- Severe Acute Respiratory Syndrome (SARS)
 - First detected outbreak in China 2002/2003; mortality rate 10%; human to human spread; first denied, but quarantine measures stopped spread; 8,096 known cases of the disease, and 774 deaths.
- Asian/Avian Flu
 - Detected in “Asia”; 24 cases, 19 deaths in 2008 but some report 100s of deaths; extremely high death rate; limited human to human transmission, so far.

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SARS (2003)

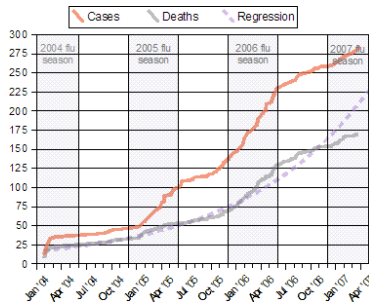


8,096 known cases of the disease, and 774 deaths

Last Update July 7th, 2003

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<http://en.wikipedia.org/wiki/SARS>

Avian Influenza, Bird Flu 2008



24 cases, 19 deaths in 2008

Some reports indicate 100s of deaths attributed to Bird Flu.

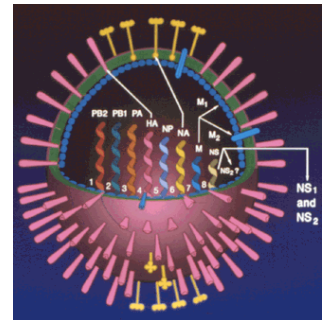
Extremely high death rate
 Limited person to person transmission so far

Graph: http://en.wikipedia.org/wiki/Avian_flu
 Data: http://www.who.int/csr/disease/avian_influenza/country/en/

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Viruses

- Viruses are just DNA or RNA coated with protein (and sometimes lipid/fat)
- Viruses “dock” onto cells using surface proteins to get into (and out of) cells; keyed to specific receptors on cell surface.



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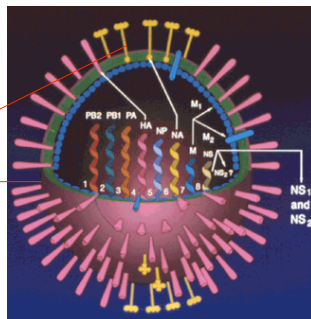
Avian Influenza, Bird Flu

Influenza viruses are named for two proteins on the virus surface:

Hemagglutinin (entry into cells)

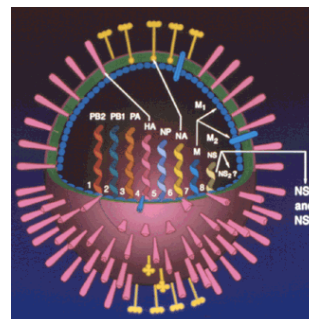
Neuraminidase (release from infected cells)

- Spanish flu is H1N1
- Avian flu is H5N1



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Influenza Evolution



- The virus has 8 separate RNA molecules. If a cell gets infected with two different flu viruses, these can be shuffled into new virus combinations.
- Or random mutations can occur.

<http://www.bact.wisc.edu/Microtextbook/indx.php?name=Sections&req=viewarticle&artid=126&page=1>

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For Public Health

- In order to understand how the Avian Flu (H1N1) might become more virulent, such as in the Spanish Flu (H5N1), researchers reconstructed the Spanish Flu virus:
 - No biological sample of the 1918 virus survived, but able to reconstruct the genome, and thus build from scratch a live virus.
 - Moved Spanish H5 into Avian virus: highly virulent!
 - Moved Avian H1 into Spanish virus: reduced virulence!
 - Published findings, including the genome of 1918 virus!
- Raised some questions:

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Dual-use Dilemma

- An ethical dilemma that results from the potential uses of a technology, when the same technology can be used for both beneficial and malevolent purposes.
- Questions:
 - How should such technology be “controlled” in order to achieve benefits but reduce risks of abuse?
 - Who has control over technology and the knowledge it is built upon?

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1918 Reconstruction Dilemma

Pro

- Provides insight into how virus works, to improve health care-response to potential outbreak.
- Publishing genome and experiment makes it more likely that knowledge will be gained and used for benefit.

Con

- Publishing genome and experiment makes available information on how to make viruses more virulent; a.k.a., bioweapons.
- Publishing genome and experiment makes technology readily available to people interested in using bioweapons, e.g., bioterrorists.

For quotes and more details about this debate: www.pbs.org/wgbh/nova/sciencenow/3318/02-poll-nf.html

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Bioweapons and Bioterrorism

- Bioweapons
 - Any biological agent (e.g., virus, bacteria, bio-toxins) designed to be used as a weapon.
- Bioterrorism
 - The use of bioweapons for terrorist aims; to cause widespread panic as a means for undermining political/economic system of enemy.



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What are Bioweapons?

- Biological organisms or toxins derived from biological organism used to cause death or disease, usually for military purposes.
- Examples (CDC Category A)
 - Anthrax
 - Botulism
 - Plague
 - Smallpox
 - Tularemia
 - Viral Hemorrhagic Fevers (VHF; e.g., Ebola)

Online NewsHour www.pbs.org/newshour/health/bioterrorism
NOVA Online: Bioterror www.pbs.org/nova/bioterror

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Bioweapons are not new

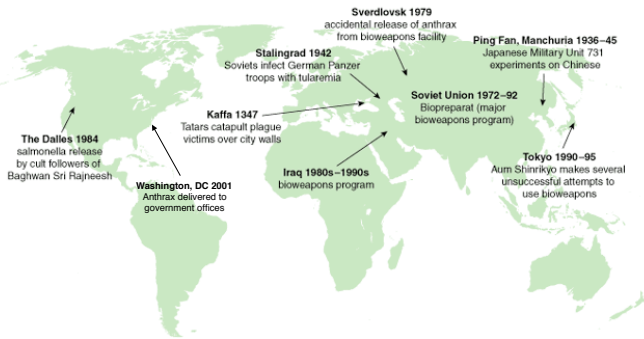
- Ancient & Medieval
 - Peloponnesian War and Earlier in Mesopotamia (poisoning water supply, killing livestock and agricultural fields)
 - 1346/7: Mongols catapult plague contaminated corpses over the wall into the city of Kaffa (in the Crimea), forcing besieged Genoans to flee.
 - 1456: City of Belgrade defeats invading Turks by igniting rags dipped in poison.
- Modern
 - 1710: Russian troops allegedly use plague-infected corpses against Swedes.
 - 1767: During the French and Indian Wars, the British give blankets used by smallpox victims to hostile Indian tribes (Similar tactic used by U.S. in 1880s: Smallpox Blankets distributed to Indian populations, 1000s die.)
 - World War I: (1916-18) Germans use anthrax and equine disease glanders to infect livestock and feed for export to Allied forces. (not very successful.)
 - 1937: Japan creates Unit 731, located in Harbin, Manchuria, killing at least 10,000 prisoners in experiments. (1939 Nomonhan Incident: Japanese poison Soviet water supply with intestinal typhoid bacteria. 1940 Japanese drop rice and wheat mixed with plague-carrying fleas over China and Manchuria)
 - Suspicions that U.S. used BW in Korean War (1950-53)?
 - 1950-51: U.S. tests BW dispersal methods by spraying biological simulants over San Francisco.
 - 1966: U.S. tests vulnerability to BW by releasing harmless biological simulants into the NY city subway system.
 - 1979: Outbreak of pulmonary anthrax in Sverdlovsk, Soviet Union. In 1992, Boris Yeltsin acknowledges outbreak was caused by accidental release of anthrax spores from Soviet BW facility.
 - Salad-bar attacks by Oregon Cult (1984): 751 ill, 45 hospitalized, no deaths
 - Aum Shinrikyo Cult (Japan Subway1995) Several attempts with Aerosolized Anthrax (and Botulinism?).
 - Anthrax Letters (U.S. 2001) 22 victims, at least 5 deaths (Unsolved Biocrime)

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Why use bioweapons?

- Reduce the cost of lives in war
 - Immobilize enemy without great expense of life or material.
 - Reduce destruction of cities, crops, water, etc.
- Deterrent effect
 - Limit enemy's aggression by posing lethal threat (WMD)
 - Requires technology to defend against; often ineffective
- Fear Factor
 - Biological weapons offer a particularly awful and personal way to die
 - Because it is difficult to contain, will produce panic and fear in enemy

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Some historical incidents involving biological weapons. Map by Annette DeFerrari, supplemented by Bryan Benham: <http://www.americascientist.org/template/AssetDetail/assetid/14284?fulltext=true&print=yes#22629>.

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Problems with Bioweapons

- **Indiscriminant**
 - Threat to civilian population (both sides)
 - Difficult to control (self reproducing agents)
- **Disproportionate**
 - No effective civilian defense (catastrophic)
 - Targeting food sources may have global consequences
 - Possible genetic damage (Russian outbreak 1979)?
- **Others**
 - Ineffective deterrent for certain groups (non-state actors)
 - BW programs contribute to (qualitative) proliferation
 - A terrible death

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Conventions

- Geneva Protocol (1925)
 - Prohibits “the use [of]...bacteriological methods of warfare.”
 - Does not prohibit development or stockpiling
- Nixon dismantles U.S. BW program (1969)
- Biological Weapons Convention (1972)
 - Prohibits the manufacturing, stockpiling and use of biological weapons.

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But...

“In the last several decades, the world has witnessed a knowledge explosion in the life sciences based on an understanding of genes and how they work....[The] practical application of this new and burgeoning knowledge base will accelerate dramatically and unpredictably ...Growing understanding of the complex biochemical pathways that underlie life processes has the potential to enable a class of new, more virulent biological agents engineered to attack distinct biochemical pathways and elicit specific effects... [T]he biotechnology underlying the development of advanced biological agents is likely to advance very rapidly, causing a diverse and elusive threat spectrum. The resulting diversity of new BW agents could enable such a broad range of attack scenarios that it would be virtually impossible to anticipate and defend against...”

– (Federation of American Scientists. CIA Panel on the Darker Bioweapons Future, November 3, 2003.)

“The advantage is now firmly with those who would seek to deploy offensive bioweapons; the state of biodefense is relatively weak.”

– (Smith, B. T. et al. 2003. Biodefense R & D: Anticipating Future Threats, Establishing a Strategic Environment. *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science*, 1, 2003; 193-202.)

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Particular Risk

- Compared to other weapons of mass destruction, such as nuclear weapons, bioweapons are easy and cheap to make, and don't require a high-level of scientific knowledge or special technology; and the facilities and products (virus) are easy to hide.
- Given the “genetic recipe” for a virus, the chemical compounds, and some off the shelf lab equipment, anyone can reconstruct the virus.

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Biotechnology

- More Selective Weapons?
 - Difficult to see how genetic/bio targeting will be effective, unless targeting a group including both combatants and non-combatants.
 - No clear biological marker for this selection; but may provide immunity to us and not them?
- Less virulent bioweapons?
 - Most ethically preferable option (still indiscriminate)
 - Problems with vulnerable subjects, typically non-combatants
 - Long-term damage to combatants...
- Dilemma of dual-use technology

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Mousepox

Researchers in Australia studying methods of rodent control introduced the IL-4 (interleukin) gene into the virus that causes mousepox. Unexpectedly the experiment resulted in an extremely virulent strain of mousepox virus that killed mice naturally resistant to the virus as well as those vaccinated against the virus. In 2001 they published their findings in the *Journal of Virology* (Jackson et al., 2001) with a description of the methods and materials used. The mousepox virus is closely related to the smallpox virus, a potential biological weapons agent, so the applications were immediately obvious to anyone with the requisite knowledge. The authors argue that keeping the research secret would have thwarted attempts to develop effective countermeasures; it is better to publish it than not.

- Should the research have been published?
- If you had the power, how would you resolve this issue?

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More Mousepox

- In an article in *New Scientist* (MacKenzie, 2003) it was reported that the Australian research had been replicated and improved upon, producing even more virulent strains of mousepox and rabbitpox.
- Does this change any of your answers to the first question?
- Is this research irresponsible in its handling of potentially dangerous information?

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Polio Virus

- In 2002 *Science* published the results of American researchers' success at synthesizing a polio genome and "live" virus from commercially available strands of DNA purchased over the internet (Cello et al. 2002). The American researchers included a description of the materials and methods in the publication and said they "made the virus to send a warning that terrorists might be able to make biological weapons without obtaining a natural virus."

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Project Bioshield, 2004

- \$6 billion over next ten years to develop bioterrorism countermeasures
- Vaccines, detection, increased laboratory space (BSL2, 3, 4)
- Some worry increased biodefense will increase local risks and result in products not otherwise available to terrorists

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How should we handle this dual-use dilemma in creating viruses?

- Seems clear we can use the knowledge for humanitarian purposes; to address the next major pandemic or create vaccinations, etc.
- Seems clear we should avoid giving terrorists the means and information to create virulent bioweapons that are difficult to track and defend against.

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