LONG STANDING ISSUE - FOR ME - 20TH ANNIVERSARY OF 1ST SERIOUS DISCUSSIONS VS. DESTRUCTION
CONTROVERSIAL -
DECISIONS - MIX OF RATIONAL, EMOTIONAL, POLITICAL
HISTORY INVESTIGATES THIS

Assessment of Future Scientific Needs for Live Variola Virus

Historical Perspective and Overview

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Future Scientific Needs for Variola Virus

An Historical perspective and Overview

- Curtailing availability of the virus 1975-86
- Proposals to destroy known stocks 1986-94
- Efforts to reach a consensus 1994-95
- Executive Board and WHAssembly 1996+
- Main arguments: retention vs. destruction
- Defining "scientific need"

Curtailing virus availability 1975-78

- Before 1975
  - Bioweapons research until 1972
  - A substantial number of diagnostic labs, few precautions
    But few infections—London (73); Munich (75)
- WHO survey in 1975
  - 823 labs on WHO list of labs and *Index Medicus*
  - 74 labs acknowledged they had variola virus
- 1976 WHA encourages limiting number of labs
- 1978 Lab infection in Birmingham, U.K.
  - Aerosol infection of a medical photographer

Curtailing virus availability 1980

- Smallpox eradication declared-- 1980
  - Developing countries urged variola virus stocks be destroyed
- WHO Global Commission recommended-- 1980
  - Destroy or transfer stocks to 4 WHO Centers
  - All labs must have adequate containment provisions
  - Labs to be periodically investigated for safety
- Number of labs decreased
  1978: 18
  1980: 6
  1981: 4
  1982: 2 (Moscow, Atlanta) WHO Laboratories

Curtailing virus availability 1981-86

- WHO Committee on Orthopoxvirus Infections
  - To oversee implementation of post-eradication recommendations
  - 10 members from different countries
  - Met annually from 1981-1986
- Composition of committee (partial)
  - Dr. Frank Fenner, John Curtin School, Australia (Chair)
  - Dr Keith Dumbell, St. Mary's Hospital, London
  - Dr. Svetlana Marennikova, Moscow
  - Dr. Brian Mahey, CDC
  - Dr. Peter Greenaway, Porton Down, U.K.
  - Dr. Kalyan Banarjee, India

Proposals to destroy virus 1986-90

- WHO Orthopoxvirus Committee
  - Foresees desirability of destroying smallpox virus – 1986
  - Calls for organized plan to clone genome fragments (later to sequence genes) from representative strains
- HHS Secretary Louis Sullivan addresses 1990 WHA
  - U.S. to destroy stocks after sequencing completed
  - U.S. and Soviet Union are collaborating in the sequencing
  - Completion of sequencing – end 1993
  - Soviet Union is in agreement with this decision

Proposals to destroy virus 1990

- WHO Orthopoxvirus Committee -- September 1990
  - Reaffirms recommendation for destroying virus in late 1993
  - Requested WHO to inform the scientific world of this action and asked that scientists and others be canvassed
- American Type Culture Collection, Board of Directors
- CDC National Center for Infectious Diseases, Board of Scientific Counselors
- Russian Academy of Medical Sciences, Presidium
- International Union of Microbiological Societies, Executive Board
- American Society for Microbiology, Council

Proposals to destroy virus August 1993

- Workshop on destruction of virus
  IXth International Congress of Virology, Glasgow
  - "Why the smallpox virus stocks should not be destroyed"
    - Wolfgang Joklik, Bernard Moss, Bernard Fields, David Bishop, Lev Sandakchiev *Science* (1993) 262:1225-1226
  - "The remaining stocks of smallpox virus should be destroyed"
    - Brian Mahy, Jeffrey Almond, Kenneth Berns, Robert Chanock, Dmitry Lvov, Ralf Pettersson, Hermann Schatzmayr, Frank Fenner *Science* (1993) 262:1223-1224

Proposals to destroy virus December, 1993

- Letter to DG from HHS Secretary Donna Shalala
  - Sequencing of a number of strains had been completed
  - Recognized that destruction must be delayed beyond December 31 but hoped that delay would be time-limited
  - Asked that the WHO Committee on Orthopoxvirus Infections be convened soon so that a final date for destruction could be set

Proposals to destroy virus *Science Jan. 7, 1994*

"I find it hard to believe that we need to, or even will, continue research of a virus whose release from containment would be such a disaster while its present threat is nil...While I agree that a deeper understanding of pathogenesis will help counter microbial infections, I doubt that we so desperately need to study smallpox that it would be worth the risk inherent in the experimentation... Eradication of the virus as well as its disease will better serve the long-term interests of humanity as the proponents of destruction have argued.

David Baltimore, President, Rockefeller University

Proposals to destroy virus Sept. 1994

Meeting of WHO Orthopoxvirus Committee

Some of many issues reconsidered

Would destruction mitigate risk of virus release?

Is it possible that unknown stocks of virus are still extant?

Might the virus be needed for research not presently foreseen?

Reiterated 1986 and 1990 recommendation

Smallpox virus stocks should be destroyed

Proposed June 30, 1995

Cloned DNA fragments of genome to be retained

Report to be considered at 1995 EB and Assembly

Proposals to destroy virus 1994

- November

  A meeting with a senior figure from the British Chemical and Biological Defense Establishment
- December – NSC meeting

  Agenda – U.S. position on the recommendations of the WHO Orthopoxvirus Committee
  - All concur to continue support of U.S. position except DoD
  - DoD objections:
    - Bodies in the tundra
    - If we destroy virus, how do we know Russians will do so
    - Compromise: each side could destroy all but 50 strains

Proposals to destroy virus — Jan 1995

- WHO Executive Board
  - U.S./U.K./Russia seek to avoid any discussion on the issue of destruction of the virus
  - Problem-- a majority of members both on the Board and in the WHA supported virus destruction
  - Chairman called the meeting to order, announced there was no consensus on the subject and postponed indefinitely consideration by the Board
  - First occasion in memory that the Board had dealt in this manner with a report by an Advisory Committee

Efforts to reach U.S. consensus — April 1995

- Depts. of Defense, HHS create joint groups
  - External committee to review technical aspects
    - Members from Armed Forces Epidemiological Board and CDC Board of Scientific Counselors
  - External committee to decide on research priorities and a time-table for completion
    - Scientists and co-chairs from DoD and HHS
    - Monthly reports to go to NSC through Assistant Secty

Efforts to reach a consensus — May 1995

- External committee to review technical aspects
  - Delay destruction pending:
    - Efficacy of cell-culture vaccines in preventing smallpox in monkeys against high-dose aerosols
    - Efficacy tests of available anti-virals
    - Animal models for testing anti-virals and new vaccines
  - If proposed research program not given sufficient priority to complete studies in 3-5 years, stocks of variola virus would not be needed

Efforts to reach a consensus — Dec.1995

- External committee on research priorities
  - Degree of protection afforded monkeys against high-titer aerosols of (monkeypox) virus
  - Large-scale screening of chemicals in variola-infected tissue-cell cultures
  - More rapid laboratory methods for detecting and identifying smallpox viruses
- Progress
  - A monkeypox/cynomolgus model met the needs of the first objective. The last two studies were reported as having been completed

Executive Board and WHA — 1996

- President Clinton decided that U.S. would support WHO Orthopoxvirus Committee recommendation to destroy the virus
- Executive Board and Assembly agree on destruction but date is postponed to 1999
  - -- All research protocols to be approved by a special WHO Research Advisory Committee
  - – Independent inspectors to visit regularly to assure full compliance with security procedures

Executive Board and WHA — 1998-99

- Preparatory to discussions at 1999 WHA
  - 1998 survey by WHO of 190 member countries
    - Position on destroying smallpox virus
      - Retain: Soviet Union
      - Don't know: U.S.,U.K.,France, Italy
      - Destroy: 74 countries
- IOM Assessment of Future Scientific Needs 1999
  - To consider only future scientific studies requiring variola virus
    - Not to consider risks of retention
    - Not to weigh the relative risk of destroying vs. retaining the virus
    - Not to consider costs or need for facilities for the research
- 1999 WHA resolution--delay destruction to 2002

Executive Board and WHA 20002002

- 2002 U.S. proposed compromise --indefinite postponement until four research objectives met:
  - Licensure of two anti-viral drugs of different mechanisms of action for prevention and treatment
  - Licensure of a new vaccine that provided complete protection and was totally safe
  - Fully developed diagnostic tests and environmental detectors
  - Knowledge base and countermeasures against genetically altered virulent strains
- U.S. agrees on destruction when these tasks accomplished.

Executive Board and WHA 2002-2006

- 2002 Assembly postpones destruction to 2006
  - With the understanding that all approved research would be outcome-oriented and time-limited
- 2006 Assembly
  - Highly contentious with many countries demanding finite date for virus destruction (June 2010); U.S. and others demanding no stipulation be made with regard to destruction of virus
  - Advisory Committee on Variola Virus Research to be restructured to be more representative and to not include staff from the two repository labs
  - "Major review" to be completed for 2010 Assembly

Main arguments: retention vs. destruction

- Retention of variola virus
  - Contributions to fundamental research in molecular viral pathogenesis
  - Needed for development and testing of new vaccines, anti-viral drugs, and diagnostics
- Alternatives to intact variola virus are inferior
  - Surrogate models using monkeypox, mousepox, etc
  - Human clinical monkeypox infection is effectively identical to smallpox but it is not virologically identical

Main arguments: retention vs. destruction

- Destruction of known stocks
  - Diminishes risk of smallpox escaping – absolute security in any laboratory cannot be guaranteed
    - Sends a clear signal that any work with live variola virus could be regarded as criminal activity
  - Availability of cloned fragments, sequence information, monkeypox, other orthopoxviruses permit wide range of studies
  - Many countries doubt the value of research compared to the risk of a virus escape
    - Decision to destroy should be a joint one decided by all countries as was the decision to undertake eradication
    - Two thirds of cost of eradication was born by endemic countries; no country contributed more than 10%

Defining "scientific need"

- From a biodefense utilization policy standpoint
  A number of factors must be weighed in assessing priorities of "scientific need"
  e.g. probable costs. Excluded from 1999 review

Development of a new entity	$ 800 million
Cost of stockpile @$300 per dose	
10,000,000 doses	$3,000 +
Three year shelf-life	$1,000 +
Warm base	$ 500 +

Defining "scientific need"

Prevention

- Uncertainty whether a new vaccine will protect man vs smallpox
- Routine vaccination is not contemplated– do we need another vaccine? Now available: a second generation and two third generation vaccines

Treatment

- Pathogenesis of smallpox suggests drug therapy unlikely to be effective in clinically ill patients i.e. those with rash and fever.
- Who are probable recipients? Those possibly exposed? Those with fever from risk area? Only those with fever and definitive rash?

The charge to the workshop: Evaluation of research progress since 1999? or is the Workshop charged with recommending priorities?

- Key reference

Jonathan Tucker :
Scourge: The Once and Future Threat of Smallpox
Grove Press, New York, 2001