The issue of what to do with the smallpox virus has engaged many of us over a number of years; what benefits do we accrue by retaining it? What risks do we incur should it be released

After more than a decade of support for the policy of smallpox virus destruction – indeed for many years as principal advocate of this policy, the U.S. this year [attempted to] reversed its position. Not only advocated retention but ~~according to press accounts, stated~~ that, whatever the decision on the matter, by the WHA, the U.S. would retain its virus stocks. The WHA agreed that destruction could be deferred until 2002.

This surprised the world community and, indeed, angered many and this is reflected in the resolution passed at the WHA – more later.

To understand the issues and the players, it is helpful to see the evolution of the argument in historical perspective.

Stocks of pox virus at 2 sites.

During the program – several collaborating laboratories doing research – 2 designated labs.
Programs: products to labs.
11 labs – inventory of all labs with smallpox virus
and then, pursuant to a resolution of the WHA, efforts to persuade destruction or transfer.

From 1980 – Pressure esp. from developing world countries to destroy the virus
U.S. + Soviet Union
Why do you want to keep it. – doing no research with it.

OVERHEAD –

The message conveyed has been that [by some] a WHO Expert Com. [in 1994] ~~arbitrarily~~ precipitously & capriciously decided that the virus should be destroyed – ~~end of story~~ [illegible]

WHO Committee on Orthopoxvirus Infections

Post -eradication policies

1980 Eradication declared

- 8 meetings between 1981 and 1999 – Broad agenda ← removed cases archiving book
- 1986 (5th mtg.)

  Proposed destruction of variola virus stocks:

  +As soon as cloned DNA fragment libraries completed
  +After soliciting views of member governments

  Hoped that this might take place in 1987

- 61 governments wrote in agreement; none dissented
  Financial constraints delayed WHO committee meeting until 1990

  U.S. not paying its dues

WHO Committee on Orthopoxvirus Infections

Post -eradication policies

- 1990

  Committee unanimously recommended variola virus destruction on 31 December 1993 after:

  Nucleotide sequence analysis of 4 strains

  + Asia variola major
  + South America variola minor
  + African high virulence variola
  + African low virulence variola

  Consultation with major science and public health organizations

My views – Russian support – science/nobody working c̄ it
Many. – CDC – dangerous pathogens lab
BSL 4 labs.

→ note parenthetically – ō hypothetical value in retaining the virus – all agreed.

Endorsement of Destruction of Variola Virus
1993

- International Union of Microbiological Societies - Executive Board
- American Society of Microbiology - Council
- Russian Academy of Medical Sciences
- National Center for Infectious Diseases/ CDC -

  Board of Scientific Counselors
- American Type Culture Collection - Board of Directors

WHO Committee on Orthopoxvirus Infections

Post -eradication policies

- 1994

  Committee agrees unanimously that smallpox virus should be destroyed on 30 June 1995

  2 of 10 members favored a delay until 1999.

  Report with recommendations sent to WHO Director General and Executive Board

Dec 94 Synopsis of NSC. mtg 2. — Jan 95 EPB.
Concern expressed by one dept. —
• Vaccinia not derived from spx - not destroying vaccine
[redacted]
• Signature

Ad hoc NSC Conference call --22 December 1994

Participants:

DHHS -- Varmus, Fauci, Mahy, Henderson
USAMRIID -- Jarling, McClean
DOD --Kadilac, Kerkorian
Other -- Lederberg, Zelicoff, Shelekov, Monath

Unanimous agreement re: stocks of smallpox virus

1. Hypothetically of possible scientific value

2. Not required for diagnostic tests

3. Not required for development of more effective or safer vaccines

4. Not required for development of diagnostics or vaccines to deal with a recombinant or altered smallpox virus.

Sum: Not necessary to retain the virus for national security reasons

– U.S. position to EB –

1995 EB –

1995 - Meeting of DHHS and DOD Civilian Advisers

Board of Scientific Counselors of NCID/CDC and
Armed Forces Epidemiological Board

Members: Cassell, Halvarson, Russell, Ascher, Chin, Wolfe

Conclusions and recommendations:

1) Strong support for ultimate destruction of stocks

2) Defer destruction until specific information available on three issues:
   - ✓ Efficacy of vaccine following high-dose aerosol challenge
   - ✓ Development of animal model for possible vaccine and anti-viral tests
   - ✓ Efficacy of currently available anti-viral drugs

3) Focussed CDC-USAMRIID research program

4) If research program cannot be given sufficient priority to complete work in 3-5 years, variola stocks will not be needed

DHHS - DOD Committee

Animal model
Diagnostics
Antiviral drug.

1996 -World Health Assembly Resolution

- Calls for destruction of smallpox virus in June 1999
  After final review by 1999 World Health Assembly

- Hope is expressed that a broader consensus might be achieved by 1999

WHO survey of member governments in 1998 discloses:

74 countries favor destruction
1 country (Russia) opposes
4 countries uncertain (U.S.,U.K.,France,Italy)

Cidofovir "Treatment" Studies

"Treatment"

- Probenacid (30mgs/kg) by oral gavage
- Hydration (SC) by lactated Ringer's solution
- IV Cidofovir (10 mgs/kg)

Results:

3 monkeys "treated" 24 hours after exposure
No disease

3 monkeys "treated" 48 hours after exposure
3 cases of monkeypox; 1 death

Source: Huggins, J. Slide presentation data of 1966 studies

cited as "proof of principle that a therapeutic agent is possible

Cidofovir – not a therapeutic drug.

~~Removed from the vaccine~~

↓

IOM Committee –

What possible uses could be made of antiviral vaccinia virus
Not asked to look at practicability, priority, feasibility

NBAC

Report was misinterpreted to mean that IOM endorsed retention of the virus.
Carpenter. –

How probable is a new anti-variola agent?

- Successful antiviral agents are few and far between
- Early, apparent successes with marboran and cytosine and adenine arabinoside proved spurious
- In 1995, a screen of 20+ compounds turned up 2 possible candidates -- cydofovir and ribavirin. Both proved unsuccessful in models using mammals and orthopoxviruses
- Could an antiviral drug penetrate the vesicles and pustules such as to alter the course of the disease?
- Who will support the $300+ million development cost?
- How can one know for certain that the drug will be effective in treating variola infection in humans?

I. How would an anti-variola drug be used?

- For those who might be exposed or had been exposed as much as 3-4 days beforehand, vaccine is the instrument of choice. Vaccine protects against disease even when given 2-3 days ***after*** exposure and against death up to 4-5 days

- A therapeutic drug would be useful in treating patients after development of rash and might be used for those for whom vaccine is contraindicated.

  It would be of little or no value in containing an epidemic.

II. How would an anti-variola drug be used?

- **Some have argued that all with an immune deficiency problem would require the drug. Once it was the belief that such persons should never receive any live vaccine but, in fact, such as measles, polio and yellow fever vaccines are widely used with few problems. Should vaccinia be any different?**

- ***In brief, under epidemic circumstances, the potential need, even for a fully effective anti-variola agent, is limited indeed.***

Preservation of Genetic Information

- **Libraries of cloned fragments of representative strains**
- **Sequence data from different strains of differing virulence**
- **Clinically, monkeypox and smallpox are indistinguishable, thus providing possibility for relating pathogenesis to the nature of the genome**

Very little work is done in the lab.

Use of variola virus in the laboratory

- There is no animal model for smallpox infection
- BSL 4 containment facilities are now required
- Except for Russia's supposed ex-bioweapons facility, no known research using the smallpox virus has been performed in over 20 years except at CDC.

  + Material for cloning and sequencing
  + Validation of PCR primers
  + In vitro screening of anti-virals

- No investigators have asked to undertake work with smallpox

Who should decide about virus destruction ?

- Is a unilateral decision now appropriate? The decision to undertake smallpox eradication and its execution was a joint effort of all countries throughout the world.

- Who owns the specimens? Virtually all specimens held in Russia and the U.S. were obtained from samples obtained from patients in endemic countries and submitted by their health authorities for examination.

- Who financed the program? Most of the costs were borne by the endemic countries. The U.S. contributed about 12% of the total. Russia contributed about 3%.

IOM Report

Assessment of Future Scientific Needs for Live Variola Virus 1999

"While there are many potential medical advances that could derive from studies using live variola virus, the risks of maintaining and working with the virus (ranging from release due to laboratory accidents to acquisition and use by terrorists) may outweigh the benefits."

Russia & the smallpox arsenal.

Director DEL - "won't be satisfied until 4 have 2 cleared antiviral drugs"
Antiviral drug - the mob of the virus.

World Health Assembly:
Resolution on Destruction of Variola Virus

- Strongly affirms the decision of previous Assemblies that the remaining stocks of variola virus be destroyed

World Health Assembly:
Resolution on Destruction of Variola Virus

- Decides to authorize temporary retention up to but no later than 2002 and subject to annual review by the World Health Assembly…for the purpose of further international research into antiviral agents and improved vaccines...

World Health Assembly:
Resolution on Destruction of Variola Virus

- Further decides that any such research…shall be conducted in an open and transparent manner only with the agreement and under the control of WHO