Viral Pathogens
Bioscience in the 21st Century
Peter R. Shank, Ph.D.

Professor Emeritus of Medical Science
BMC/GG 595
Phone (401) 863-2765
Email: Peter_Shank@Brown.edu
What we are going to discuss

- Viruses as human pathogens
- What defines a virus
- Influenza
- Smallpox
- Polio
- HIV
- Ebola
- MERS
Why study viruses?

■ Some make people sick
■ There are a whole lot of them and we don’t know most of them
Sir F. Macfarlane Burnet
Former Director of the Walter and Eliza Hall Institute
Sir F. Macfarlane Burnet was an Australian virologist/immunologist who shared the 1960 Nobel prize for Medicine and Physiology. He made several seminal discoveries in the 1930s including that there were multiple distinct strains of polio virus not just one.
Burnet wrote in the introduction to the third edition of his book *Natural History of Infectious Disease* published in 1962:

“…the late 20th century would be witness to the virtual elimination of infectious disease as a significant factor in social life”.

To write about infectious disease… "is almost to write of something that has passed into history."
How could he have been so wrong?

- Think of when he wrote *i.e.*, 1962
- What was happening in medicine in the mid 1960s?
  - Fleming discovers penicillin 1929 and widespread use occurred in the second world war
  - Polio vaccine licensed 1955
  - Measles vaccine licensed 1963
  - Mumps vaccine licensed 1967
  - Rubella vaccine licensed in 1969
- Evidently antibiotic could kill all bacteria and vaccines could prevent all viral disease
There are a lot more viruses than many people thought

- Most estimates suggest there are around $10^{31}$ virus particles in the world
- A significant number of those exist in the ocean
- $10^{31}$ is a BIG number
Yet infectious diseases still kill a lot of people.
When Were Viruses Discovered?

- In 1879 Adolph Mayer transmitted a disease of tobacco plants with an extract from diseased leaves.
- In 1892 Dimitri Ivanovksy transmitted the tobacco disease with a filtrate *i.e.*, a “filterable agent”.
- Ivanovskv wasn’t convinced he was on to anything and speculated the disease was caused by a toxin, not a new form of pathogen.
- A Dutch scientist diluted the filtrate and showed the agent recovered full infectivity which a toxin could not do.
Also in 1898 Freidrich Loeffler and Paul Frosch demonstrated foot and mouth disease was transmitted by a filterable agent – the first animal virus.

In 1900 Walter Reed showed yellow fever was transmitted by a filterable agent – the first human virus.

In 1906 Negri showed smallpox was caused by a filterable agent.

In 1908 Ellerman and Bang transmitted leukemia in chickens with a filtrate of the serum – the first retrovirus.
What is a Virus?

- From the Latin
- slimy liquid, poison, stench
Peter Medawar, who shared the 1960 Nobel Prize with Burnet defined viruses as:

“…a piece if nucleic acid surrounded by bad news.”
The late Salvador Luria, Nobel laureate in 1969 for his work on viral replication and genetics said:

“Viruses are entities whose genome are elements of nucleic acid that replicate inside living cells using the cellular synthetic machinery and causing the synthesis of specialized elements than can transfer the genome to other cells”

What does that mean?
Who was correct?

- The mechanism of viral **replication** separates them from all other replicating elements
- Other microorganisms replicate *via* binary fission
- Viruses essentially kill themselves during replication
Unique aspect of viral replication
Viruses, cells and microbes on a size scale

Newly described viruses blur the boundary even more

Used with permission of Henry Holt and Company, LLC.
Mimivirus

- Recently described virus
- Large virus 800 nm
- Large genome ds-DNA 1.2Mbp
- Encodes ca. 1,000 genes
- Associated with pneumonia
Bacterial and Viral genomes

![Bar graph comparing genome sizes of bacteria and viruses](image_url)
Influenza virus
Death rates in the US 1900-2000
The 1918 Flu killed more Americans than died in

- World War I
- World War II
- The Korean War
- The Vietnam War
- The Iraq/Afghanistan conflicts
Who was Benjamin Waterhouse and What did he have to do with Virology? Or the College Rhode Island? Or Harvard?

Gilbert Stuart, ca., 1776
Early in 1799 Dr. John Lettsom, a prominent physician in London, sent his friend Waterhouse a copy of Jenner’s 1798 manuscript *An inquiry into the Causes and Effects of the Variollae Vaccinae*

Waterhouse corresponded with Jenner and received some of the vaccine by 1800.

He vaccinated his five year old son, Daniel.

Waterhouse vaccinated all his children and several servants in 1800.

He tested his experiment by sending his subjects to the Smallpox Hospital in Brookline to be exposed.

They returned with nothing but a sore arms.

Waterhouse believed smallpox was vanquished.

He was wrong.
What Happened Next?

- Smallpox killed an estimated **300-500 million** people in the 20th century
- 1967 the World Health Organization begins a smallpox eradication program
- 1977 the last natural case of smallpox, Ali Maow Maalin occurs in Somalia
- In 1980, **182 years** after Jenner inoculates James Phipps, the WHO announces the end of smallpox
- We should have done better
Polio virus has likely existed for centuries

Egyptian stone tablet from the 18th dynasty (1580-1350 B.C.)
Polio virus
Epidemic polio is a disease of the 20th century.

Why?
The first polio epidemic occurred in Vermont in 1894

There were 132 cases of paralytic disease

Clean water ca. 1900

No longer drinking your neighbor’s feces

Therefore first exposure to polio is later in life

Risk of paralytic polio increases >10 fold in older people

Newborns are like recipients of the Salk vaccine for 12-14 months because of maternal IgG
Unfortunately this is a hypothesis that has been experimentally confirmed.

In the 1960s, we helped the "developed world" by cleaning water supplies.

We created epidemic polio in regions where it was previously unknown.
Poliovirus in the history of virology

■ Was the first animal virus to be completely cloned and sequenced
■ Was the first RNA virus for which an infectious molecular clone was constructed
■ Was the first human virus whose three dimensional structure was determined
■ Was the second virus targeted for elimination from the human population (1988)
Key events in Polio

- In 1908 Landsteiner shows infantile paralysis caused by a “filterable agent” and produces disease in monkeys with human material.
- 1931 Burnett showed there were multiple forms of poliovirus which did not “cross react.”
- 1949 John Enders cultivates poliovirus in non-neuronal cells in tissue culture.
- 1954 Enders and colleagues received the Nobel Prize in Medicine.
- 1954 Salk inactivated polio vaccine.
Ultimately Jonas Won
The Sabin vaccination worked but.....

Vaccine-associated paralytic polio
Attenuation of the Sabin strains

A Derivation of Sabin type 3 attenuated poliovirus

B Determinants of attenuation in the Sabin vaccine strains

C Reversion of P3/Sabin
**B**

Viral (+) strand genome

5' VPg UTR

Translation/processing

Capsid

Proteases and RNA synthesis

UTC

VP0 VP3 VP1 2A 2B 2C

VP4 VP2

2Apro 3Cpro 3Dpol

VPg
A couple of thoughts before leaving polio

- The first *ca.* 140 million doses of the Salk vaccine were contaminated with SV40, a DNA tumor virus.
- Hilary denies it!
Nobel Prize in Medicine 2008

Luc Montagnier Francois Barre-Sinoussi
shared with Harald zur Hausen
Effect of HIV on life expectancy

The graph illustrates the life expectancy at birth for different countries over the years from 1960 to 2000. The countries shown include Botswana, Zimbabwe, Uganda, Zambia, and Malawi. The data indicates a significant decrease in life expectancy for these countries, particularly in Botswana, which experienced a sharp decline after 1990.
HIV and the development of AIDS

Figure 20-13
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company
HIV-1
2011 UNAIDS data

- Infected 33.4M
- New infections *ca.* 2.5M (1.3–2.8M)
- Deaths *ca.* 1.7M (1.5–1.9M)
- *Ca*. 12M AIDS orphans in Africa
- US *ca.* 56,000 new infections
- Overall 60M infections with 25M deaths
- *Ca*. 8M on therapy (15M eligible)
NEW HIV INFECTIONS AND AIDS-RELATED DEATHS

Globally new HIV infections peaked in 1997.
Success of antiviral drugs
SARS returns?
MERS-CoV

- Since April 2012 there have been 536 laboratory confirmed cases of human infections with Middle East respiratory syndrome coronavirus (MERS-CoV)

- 145 cases (27%) have been fatal
Ebola virus EM
filoviridae
Tim Flanigan in Lyberia
former Brown Chief of Infectious Disease

http://www.timothypflaniganmd.com/
Prior Filovirus outbreaks

<table>
<thead>
<tr>
<th>Year</th>
<th>Marburg Cases</th>
<th>% Mortality</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>1975</td>
<td>3</td>
<td>(33%)</td>
<td>Zimbabwe</td>
</tr>
<tr>
<td>1980</td>
<td>2</td>
<td>(50%)</td>
<td>Kenya</td>
</tr>
<tr>
<td>1987</td>
<td>1</td>
<td>(0%)</td>
<td>Kenya</td>
</tr>
<tr>
<td>1998/00</td>
<td>149</td>
<td>(83%)</td>
<td>Zaire*</td>
</tr>
<tr>
<td>2005</td>
<td>252</td>
<td>(90%)</td>
<td>Angola</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>Ebola Cases</th>
<th>% Mortality</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>284</td>
<td>(53%)</td>
<td>Sudan</td>
</tr>
<tr>
<td>1976</td>
<td>318</td>
<td>(88%)</td>
<td>Zaire*</td>
</tr>
<tr>
<td>1977</td>
<td>1</td>
<td>(100%)</td>
<td>Zaire*</td>
</tr>
<tr>
<td>1979</td>
<td>34</td>
<td>(65%)</td>
<td>Sudan</td>
</tr>
<tr>
<td>1994</td>
<td>44</td>
<td>(64%)</td>
<td>Gabon</td>
</tr>
<tr>
<td>1994</td>
<td>1</td>
<td>(0%)</td>
<td>Ivory Coast</td>
</tr>
<tr>
<td>1995</td>
<td>315</td>
<td>(77%)</td>
<td>Zaire* (Kikwit)</td>
</tr>
<tr>
<td>1995/96</td>
<td>37</td>
<td>(57%)</td>
<td>Gabon</td>
</tr>
<tr>
<td>1996/97</td>
<td>60</td>
<td>(75%)</td>
<td>Gabon</td>
</tr>
<tr>
<td>2000</td>
<td>425</td>
<td>(53%)</td>
<td>Uganda</td>
</tr>
<tr>
<td>2002</td>
<td>122</td>
<td>(81%)</td>
<td>Gabon/Congo</td>
</tr>
<tr>
<td>2003/04</td>
<td>178</td>
<td>(89%)</td>
<td>Zaire*</td>
</tr>
<tr>
<td>2004</td>
<td>17</td>
<td>(41%)</td>
<td>Sudan</td>
</tr>
<tr>
<td>2005</td>
<td>12</td>
<td>(75%)</td>
<td>Zaire*</td>
</tr>
</tbody>
</table>

*Newly named Democratic Republic of Congo
Ebola progression this summer

Outbreak reported by 22nd June 2014

Outbreak reported by 26th September 2014

Cases
- 0
- 1 - 25
- 26 - 50
- 51 - 100
- 101 - 200
- 201 - 250

Data Sources: GADM, WHO, UNMIL, OCHA, ACAPS Briefing Note
Map produced by MapAction and ACAPS
A report by the CDC published in MMWR in September caught people’s attention.
Reston made the news in 1989!

- On October 2, 1989, 100 cynomolgus macaques (*Macaca fascicularis*) from Ferlite Farms in Mindanao Island, Philippines were flown from Manila, through Amsterdam to New York, and then transported by truck to Hazleton Research Products' (HRP) Reston Primate Quarantine Unit in Reston.

- Hazelton is a major supplier of primates for biomedical research.

- There had not been any African species quarantined in the Reston unit for many years.

- Several of the monkeys died.

- Serology indicated Ebola.
The company euthanized all the monkeys
Six workers seroconverted
They but presented no symptoms
This variant is highly pathogenic for nonhuman primates but not humans
Ebola has killed thousands of gorillas and there was consideration several years ago about vaccinating gorillas to prevent extinction
Reston Virginia?
VSV Vaccines against Lassa and Ebola Viruses?
Emerging Infect. Dis 21:2 Feb. ‘15