



Lecture One :
History of Virology

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Learning outcomes

By the end of this lecture students should

- **Be aware of the history of virology.**
- **Be aware of the importance of virology in shaping the human history.**
- **Recognize the history of vaccinology.**
- **Recognize the milestone achievements in the field of virology.**
- **Have the knowledge “why we study virology”.**

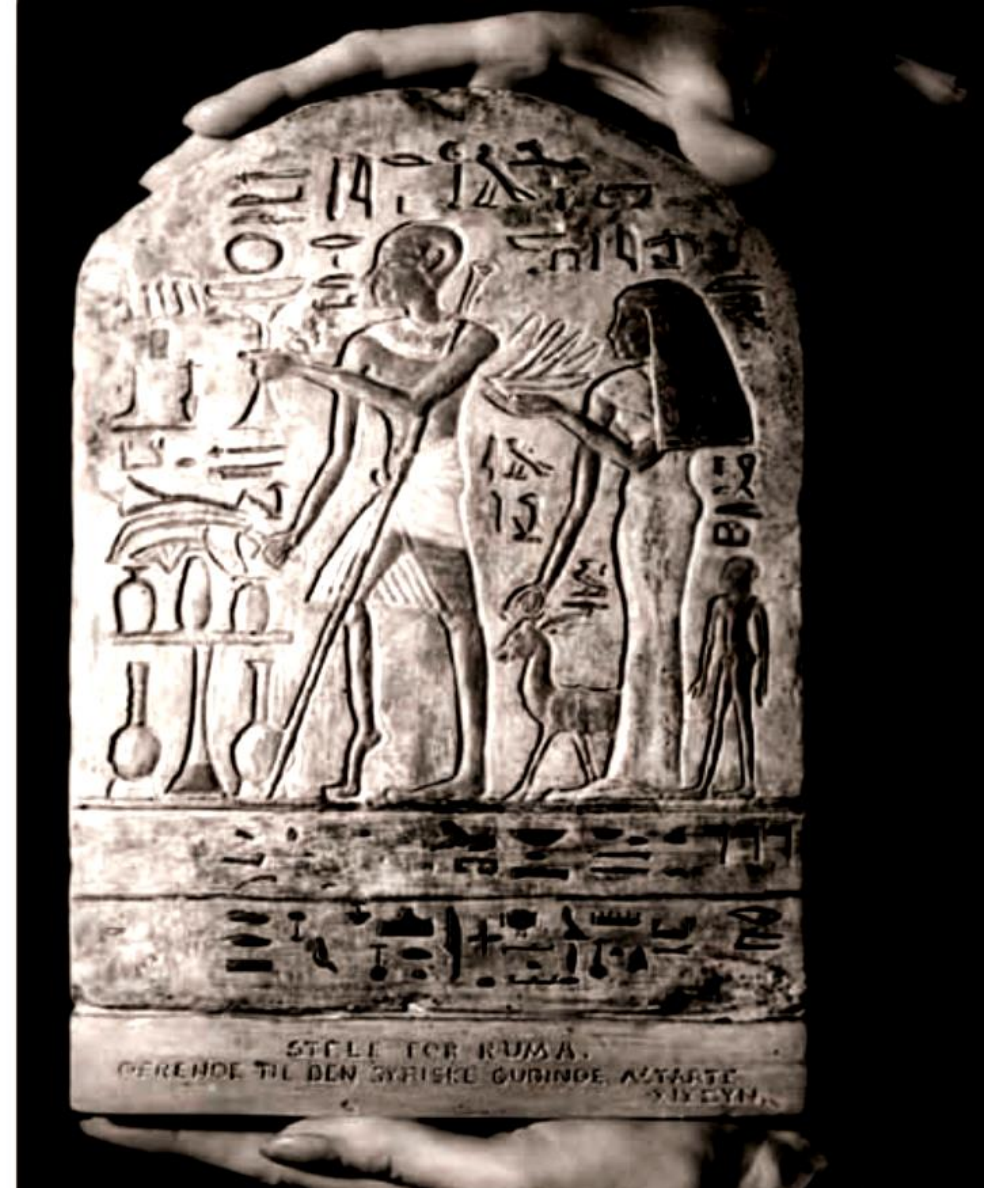
Virus History

Viral Infections in Antiquity

- ❖ Viruses that established themselves in human populations were undoubtedly transmitted from animals, much as still happens today.
- ❖ Early human groups that domesticated and lived with their animals were almost certainly exposed to different viruses than were nomadic hunter societies.
- ❖ Similarly, as many different viruses are endemic in the tropics, human societies in that environment must have been exposed to a greater variety of viruses than societies established in temperate climates.
- ❖ When nomadic groups met others with domesticated animals, human-to-human contact could have provided new avenues for virus spread.




The Greek poet Homer characterizes Hector as “rabid” in the Iliad.



Egyptian stele, or stone tablet, from the 18th dynasty (1580–1350 B.C) depicting a man with a withered leg and the “drop foot” syndrome characteristic of polio.

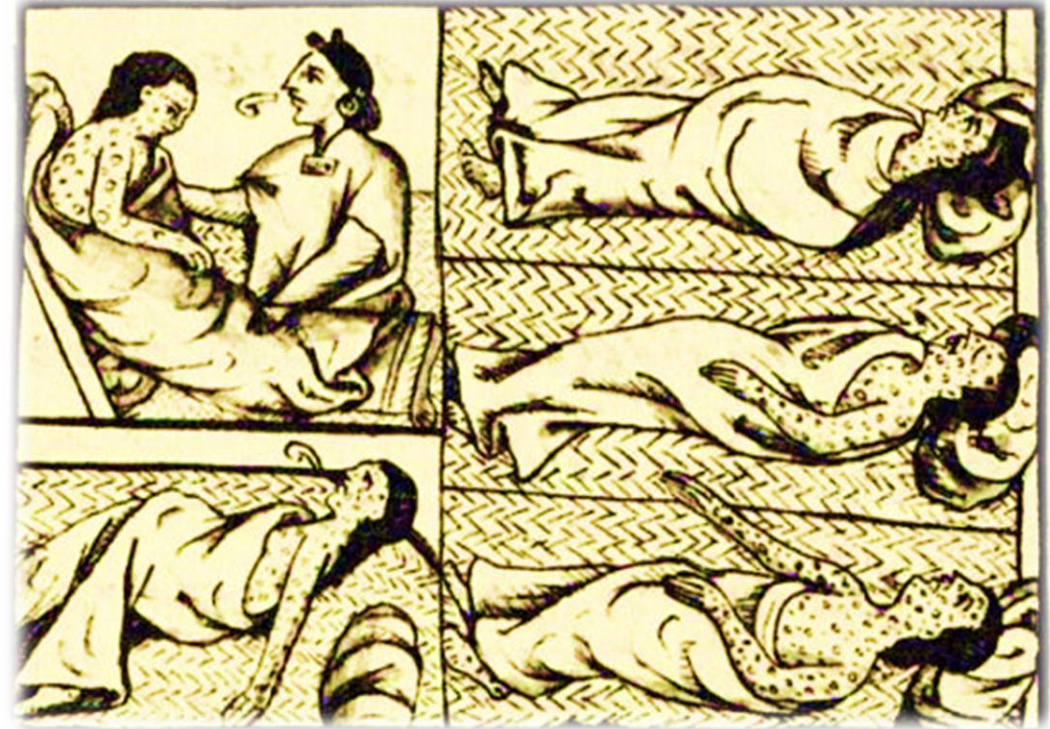
Virus History

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- ❖ **The smallpox virus, which was probably endemic in the Ganges River basin by the fifth century B .C. and subsequently spread to other parts of Asia and Europe, has played an important part in human history.**
 - ❖ **Its introduction into the previously unexposed native populations of Central and South America by colonists in the 16th century led to lethal epidemics.**
 - ❖ **Other viral diseases known in ancient times include mumps and, perhaps, influenza.**

Virus History

THE EARLY YEARS

- ❖ Choosing a precise beginning for the history of the science of virology is somewhat arbitrary, in part because several illnesses that now are known to result from virus infections had been recognized for thousands of years without any knowledge of viruses.
- ❖ Regardless, there is some justification for beginning 1,000 years ago with smallpox.
- ❖ During that time empirically based measure was adopted to control the disease which was variolation. Uninfected individuals were inoculated with materials from the scabs of individuals who survived smallpox infection.

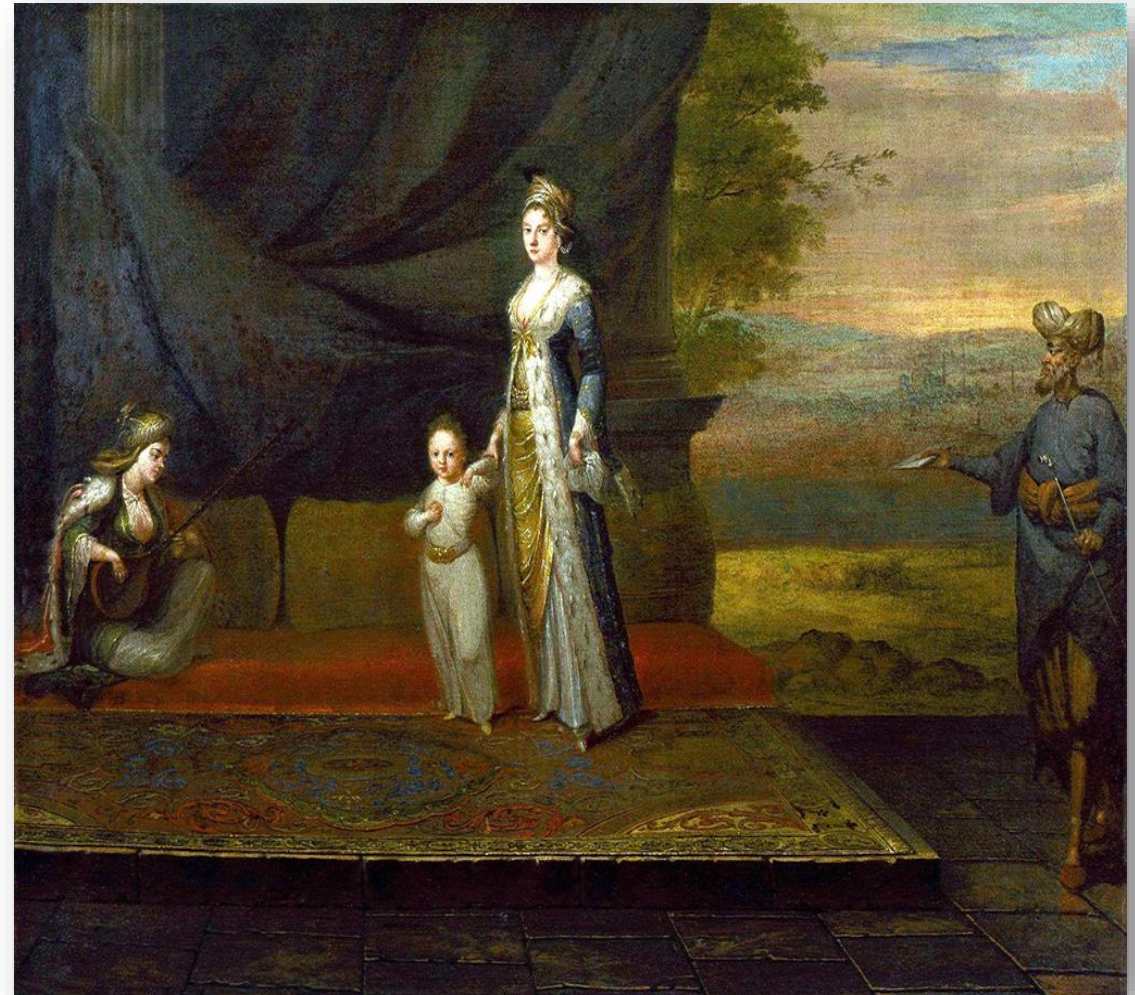


500-year-old drawing depicts Nahua Native Americans suffering from smallpox.

Virus History

The year 1715

- ❖ Lady Mary Wortley Montague, the wife of the British ambassador to Turkey, had her children undergo variolation.
- ❖ Smallpox in a dried-out lesions is partially inactivated by that person's immune response as well by the drying itself.
- ❖ During this time, variolation was based on the observation that smallpox survivors were resistant to subsequent episodes of infection.



Virus History

The year 1798

- 🦠 **Edward Jenner**, English country doctor, made a major leap forward in preventing smallpox.
- 🦠 **Jenner** observed that milkmaids, were “resistant” to smallpox.
- 🦠 **Jenner** inoculated a child, **James Phipps**, with extract from a cowpox lesion and then demonstrated that young Phipps was resistant to a subsequent challenge with smallpox.



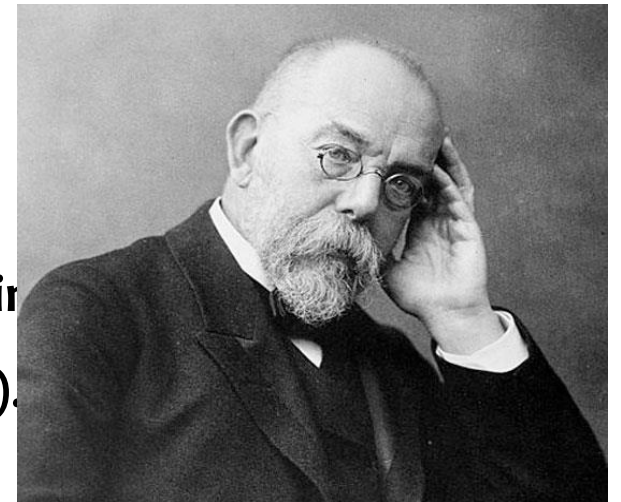
Virus History

The year 1867

- ✿ **Louis Pasteur**, French biologist, microbiologist and chemist, proposed that microorganisms might produce different kinds of diseases.
- ✿ Aseptic techniques that **Lister** then introduced dramatically reduced infections during surgery.
- ✿ Robert Koch created a series of four generalized principles linking specific microorganisms to specific diseases (**Koch's postulates**).



Louis Pasteur: 1822-1895



Robert Koch: 1843-1910

Virus History

The year 1885

- 🦠 **Louis Pasteur**, developed the second human vaccine which was against rabies.
- 🦠 He attenuated the virus by serial passage of the rabies agent in rabbits.
- 🦠 **Pasteur** coined the word “vaccination” based on the Latin word for cow (vacca) in recognition of **Jenner’s** contribution.



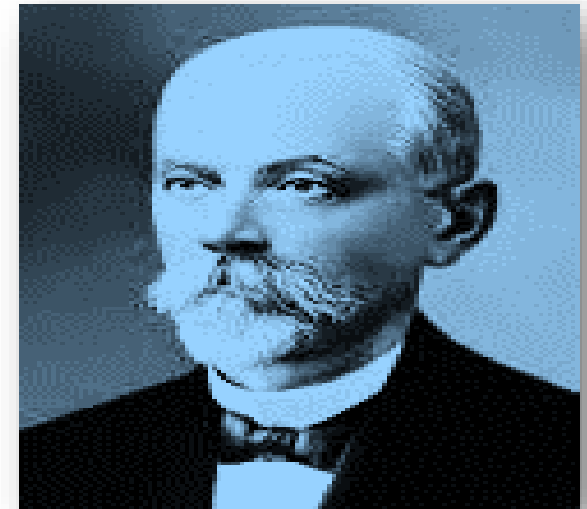
Virus History

The year 1887

- 🦠 **Dmitry Ivanovsky**, a Russian scientist repeated the work of German **Adolf Mayer** to identify the causative agent of tobacco mosaic disease.
- 🦠 Both found that the sap of diseased plants transmit the disease to healthy plants.
- 🦠 However, **Ivanovsky** went an important step further, He found that the infectious agent could actually pass through the so called Chamberland Filters.
- 🦠 Both were unable to satisfy an important components of **Koch's** postulates “**that is the cultivation of a single species of microorganisms in pure culture**”.



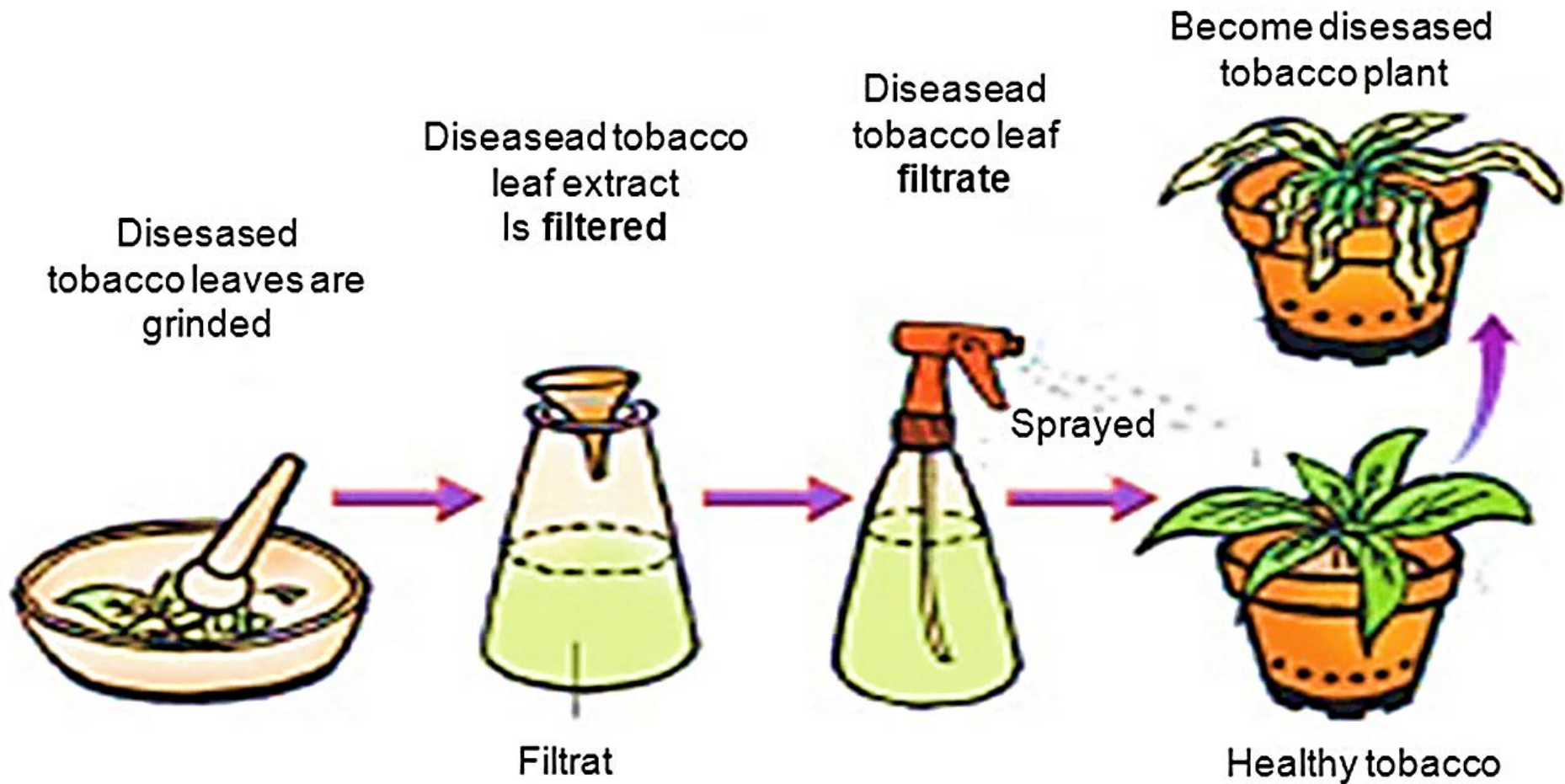
Adolf Mayer: 1843 –1942



Dmitry Ivanovsky :1864 -1920

Virus History

Dmitri Ivanovsky (1892)



Virus History

- 🦠 The influence of Koch's postulates was so strong that Ivanosky did not want to that he might actually have seen evidence for a previously unknown kind of microorganism.
- 🦠 Perhaps the causative agent was a bacterium and the filters were defective, or perhaps the causative agent was a toxin, a non-reproducing poisonous substance produced by an organism.


The year 1898

- 🦠 Dutch microbiologist **Martinus Beijerinck**, who was working with **Mayer** but was unaware of **Ivanovsky's** findings.
- 🦠 He did the same work of **Ivanosky**, however, he went another major step further.



Martinus Beijerinck: 1851 -1931

Virus History

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- ❖ **Beijerinck** demonstrated that dilution of the sap did not affect its ability to cause disease (i.e. **the disease-causing agent was in fact replicating in the plant tissue, thus accounting for its ability to replenish its pathogenic activity**).
 - ❖ The work of **Beijerinck** led to identification of two fundamental properties that are characteristic of this new class of pathogens.
 - ❖ First, they are smaller than bacteria, since they pass through filters that block bacteria.
 - ❖ Second, they require living cells or tissue to support their propagation.
 - ❖ **Beijerinck** termed the submicroscopic agent responsible for tobacco mosaic disease ***contagium vivum fluidum***.

Virus History

The year 1898

🦠 **Loeffler and Frosch** isolated the first virus obtained from animals, the foot-and-mouth

The year 1901

🦠 **Walter Reed** isolated the first virus pathogenic in humans, yellow fever virus.

The year 1911

🦠 **Peyton Rous** found that sarcomas (cancers of connective tissue) in chickens could be transmitted by a virus that is now known as the **Rous sarcoma virus**

The year 1938

🦠 The first electron micrographs of TMV were taken.

🦠 The term “virus,” from the Latin word for poison, came to be used to refer to the agents having the properties described by **Mayer, Ivanovsky, and Beijerinck**.

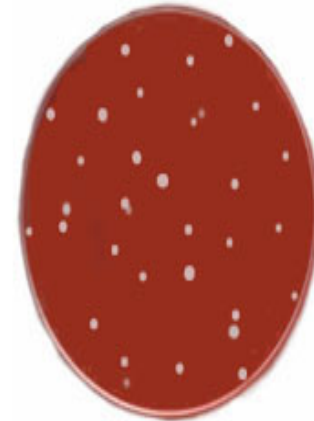
Cell Culture Methods:

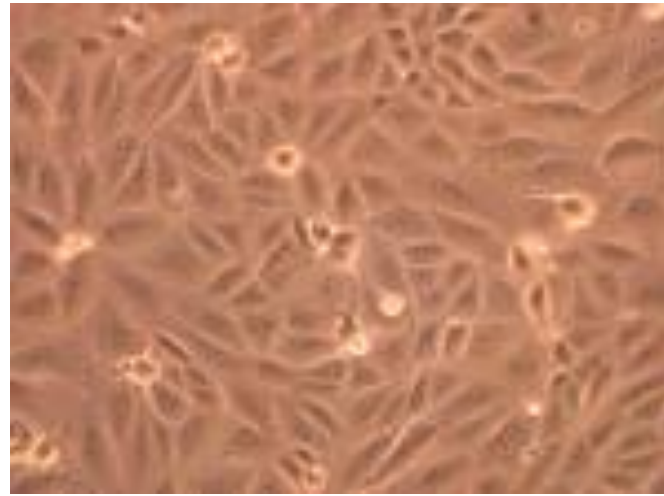
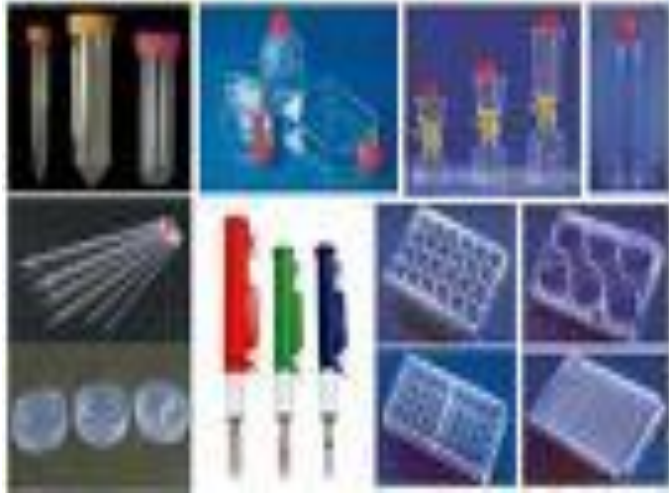


Cell culture began early this century with **whole organ cultures**, then progressed to methods involving individual cells, either **primary cell cultures** (somatic cells from an experimental animal or taken from a human patient which can be maintained for a short period in culture) or **immortalized cell lines**, which given appropriate conditions, continue to grow in culture indefinitely.

In 1949, **Enders** & his colleagues were able to propagate poliovirus in primary human cell cultures.

Renato Dulbecco in 1952 was the first to accurately quantify animal viruses using a **plaque assay** - dilutions of the virus are used to infect a cultured cell monolayer, which is then covered with soft agar to restrict diffusion of the virus, resulting in localized cell killing & the appearance of plaques after the monolayer is stained. Counting the number of plaques directly determines the number of infectious virus particles applied to the plate.

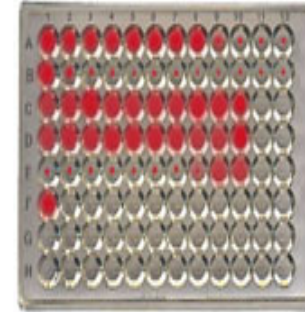




Serological and Immunological Methods

In 1941 **Hirst** observed haemagglutination of red blood cells by influenza virus. This proved to be an important tool not only in the study of influenza, but also with several other groups of viruses, e.g. rubella virus.

[ONLINE EXPERIMENT: Influenza Haemagglutination](#)



In the 1960s & subsequent years, many improved detection methods for viruses were developed, for example:

- Complement fixation tests
- Radioimmunoassays
- Immunofluorescence (direct detection of virus antigens in infected cells or tissue)
- Enzyme Linked Immunosorbent Assays ([ELISAs](#))
- Radioimmune precipitation
- Western blot assays

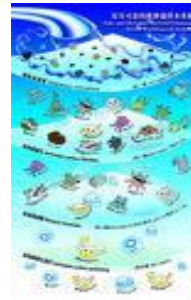
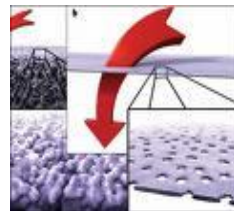


Ultrastructural Studies

These can be considered under three areas:

- Physical methods
- Chemical methods
- Electron microscopy

Physical measurements of virus particles began with the earliest determinations of their size by **filtration** through colloidal membranes with various pore sizes in the 1930s. Experiments of this sort led to the first (rather inaccurate) estimates of the size of virus particles.



The accuracy of these was improved by studies of the **sedimentation properties** of viruses in ultracentrifuges in the 1960s.



Rotor

Ultracentrifuge



**Spectrophotometric
Determination of Virus
N.A & Proteins**

The physical properties of viruses can also be determined by **spectroscopy**, using both ultra-violet light to examine the nucleic acid content of the particle & visible light to determine its light-scattering properties.

1931: Ernst Ruska constructed the first electron microscope. Electron microscopes overcome the fundamental limitation of light microscopes from the virologist's point of view, i.e. the inability to resolve individual virus particles due to physical constraints caused by the wavelength of visible light illumination. During subsequent years, techniques were developed which allowed the direct examination of viruses at magnifications of over 100,000X.



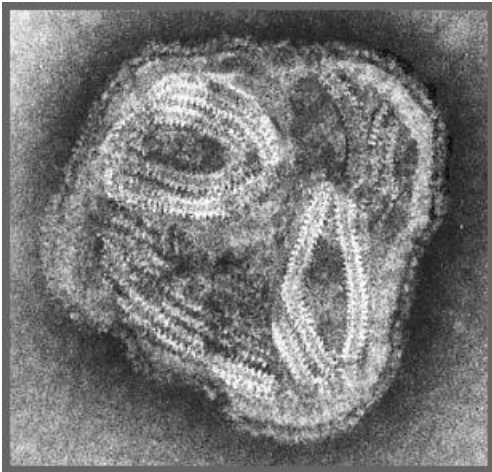
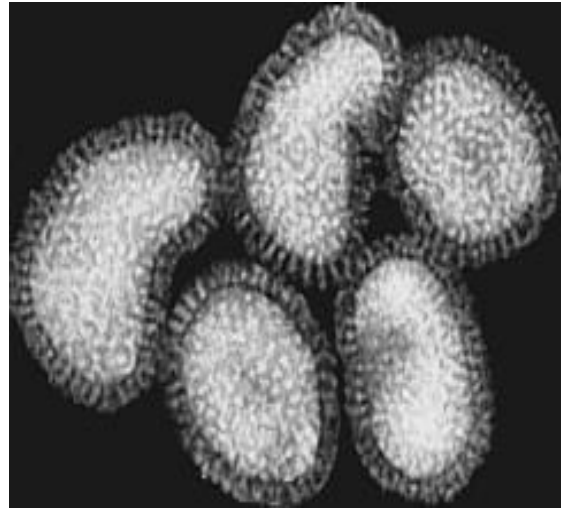
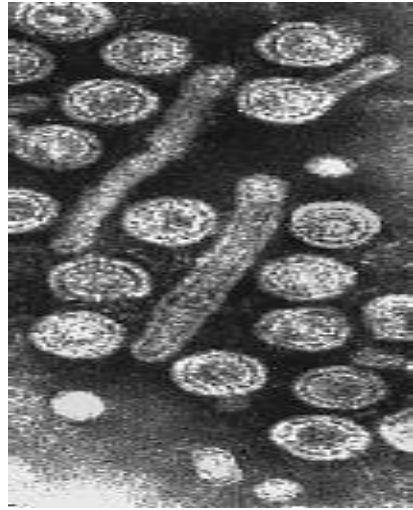
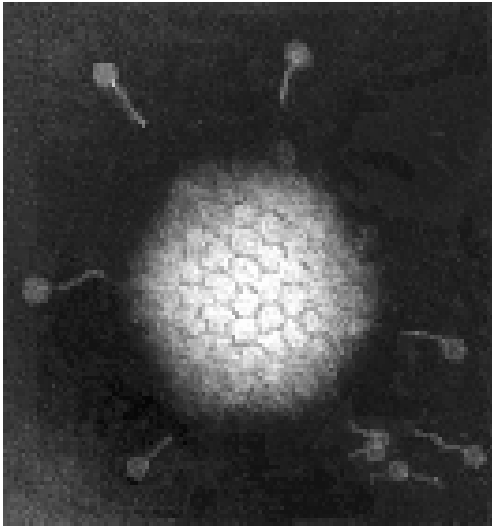
There are two fundamental types of electron microscope, the transmission type (TEM) & scanning electron microscopes (SEM).

Although beautiful images with the appearance of three dimensions are produced by the SEM, for practical investigations of virus structure, the higher magnifications achievable with the TEM have proved to be of most value.

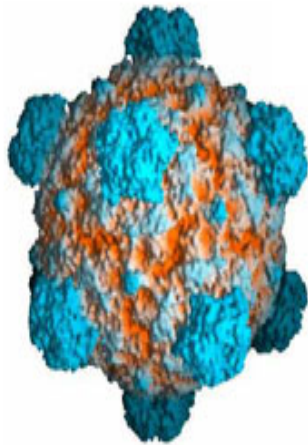
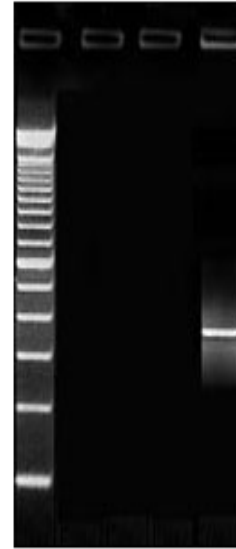


Two fundamental types of information can be obtained by electron microscopy of viruses:

- the absolute number of virus particles present in any preparation (total count)
- the appearance / structure of the particles



Electrophoresis of intact virus particles has yielded some limited information, but electrophoretic analysis of individual virion proteins by gel electrophoresis, & particularly also of nucleic acid genomes, has been far more valuable.



However, by far the most important method for the elucidation of virus structures has been the study of **X-ray diffraction** by crystalline forms of purified virus (**crystallography**). This technique permits determination of the structure of virions at an atomic level. The complete structures of many viruses, representative of many of the major groups, have now been determined at a resolution of a few angstroms. This has advanced our understanding of the functions of the viral particle considerably.



Table 1.2 Some milestones in virology research

Discovery	Date	Scientists	Nobel prize awarded
Smallpox vaccine	1798	Edward Jenner	
Rabies vaccine	1885	Louis Pasteur	
Filterable viruses:			
Tobacco mosaic virus	1892	Dimitrii Ivanovski	
	1898	Martinus Beijerinck	
Foot-and-mouth disease (cattle)	1898	Friedrich Loeffler and Paul Frosch	
Yellow fever (humans: transmitted by mosquitoes)	1900	Carlos Finlay and Walter Reed	
Discovery of Rous Sarcoma virus	1911	Peyton Rous	1966
Discovery of bacteriophages and the plaque assay	1915	Frederick Twort	
	1917	Felix d'Herelle	
Vaccine against yellow fever	1930s	Max Theiler	1951
Crystallization of tobacco mosaic virus	1935	Wendell Stanley and John Northrup	1946
Studies with bacteriophages	1940s	Max Delbruck and Salvador Luria	1969
Growth of poliovirus in cultured cells	1949	John Enders, Frederick Robbins, and Thomas Weller	1954
Bacteriophage lambda and lysogeny	1950s	Andre Lwoff	1965
Bacteriophage genes are DNA	1952	Alfred Hershey and Martha Chase	1969
Discovery of interferon	1957	Alick Isaacs and Jean Lindenmann	
Poliovirus vaccines:			
killed	1955	Jonas Salk	
live	1960	Albert Sabin	
Studies on polyomavirus: a tumor virus	1960s	Renato Dulbecco	1975
Kuru is caused by an infectious agent	1965	D. Carleton Gajdusek	1976
Discovery of hepatitis B virus	1968	Baruch Blumberg	1976
Reverse transcriptase in retroviruses	1971	Howard Temin and David Baltimore	1975
Virus vectors and genetic engineering	1970s	Paul Berg	1980
Cellular oncogene is part of a retrovirus genome	1976	Michael Bishop and Harold Varmus	1989
RNA splicing in adenovirus	1977	Phillip Sharp and Richard Roberts	1993
Prions: infectious proteins	1975–1990	Stanley Prusiner	1997
Human papillomaviruses cause cervical cancer	1972–1984	Harald zur Hausen	2008
Discovery of AIDS virus (HIV-1)	1983	Luc Montagnier and Françoise Barré-Sinoussi	2008



Thank
You