The History of Virology

Those who cannot remember the past are condemned to repeat it.

George Santayana

1796: Edward Jenner used cowpox to **vaccinate** against smallpox. Although Jenner is commonly given the credit for vaccination, **variolation**, the practice of deliberately infecting people with smallpox to protect them from the worst type of the disease, had been practiced in China at least 2000 years previously. In 1774, a farmer named Benjamin Jesty had vaccinated his wife and two sons with cowpox taken from the udder of an infected cow and had written about his experience (see 1979). Jenner was the first person to deliberately vaccinate against any infectious disease (i.e., to use a preparation containing an antigenic molecule or mixture of such molecules designed to elicit an immune response).

1885: Louis Pasteur experimented with rabies vaccination, using the term *virus* (Latin for poison) to describe the agent. Although Pasteur did not discriminate between viruses and other infectious agents, he originated the terms *virus* and *vaccination* (in honor of Jenner) and developed the scientific basis for Jenner's experimental approach to vaccination.

1886: John Buist (a Scottish pathologist) stained lymph from skin lesions of a smallpox patient and saw "elementary bodies," which he thought were the spores of micrococci. These were in fact smallpox virus particles, just large enough to see with the light microscope.

1892: Dmiti Iwanowski described the first "filterable" infectious agent—Tobacco mosaic virus (TMV)—smaller than any known bacteria. Iwanowski was the first person to discriminate between viruses and other infectious agents, although he was not fully aware of the significance of this finding.

1898: Martinus Beijerinick extended Iwanowski's work with TMV and formed the first clear concept of the virus *contagium vivum fluidum*—soluble living germ. Beijerinick confirmed and extended Iwanowski's work and was the person who developed the concept of the virus as a distinct entity.

Freidrich Loeffler and Paul Frosch demonstrated that foot-and-mouth disease is caused by such filterable agents. Loeffler and Frosch were the first to prove that viruses could infect animals as well as plants.

1900: Walter Reed demonstrated that yellow fever is spread by mosquitoes. Although Reed did not dwell on the nature of the yellow fever agent, he and his coworkers were the first to show that viruses could be spread by insect vectors such as mosquitoes.

1908: Karl Landsteiner and Erwin Popper proved that poliomyelitis is caused by a virus. Landsteiner and Popper were the first to prove that viruses could infect humans as well as animals.

1911: Francis Peyton Rous demonstrated that a virus (Rous sarcoma virus) can cause cancer in chickens (Nobel Prize, 1966; see 1981). Rous was the first person to show that a virus could cause cancer.

1915: Frederick Twort discovered viruses infecting bacteria.

1917: Felix d'Herelle independently discovered viruses of bacteria and coined the term **bacteriophage**. The discovery of bacteriophages provided an invaluable opportunity to study virus replication at a time prior to the development of tissue culture when the only way to study viruses was by infecting whole organisms.

1935: Wendell Stanley crystallized TMV and showed that it remained infectious (Nobel Prize, 1946). Stanley's work was the first step toward describing the molecular structure of any virus and helped to further illuminate the nature of viruses.

1938: Max Theiler developed a live attenuated vaccine against yellow fever (Nobel Prize, 1951). Theiler's vaccine was so safe and effective that it is still in use today! This work saved millions of lives and set the model for the production of many subsequent vaccines.

1939: Emory Ellis and Max Delbruck established the concept of the one-step virus growth cycle essential to the understanding of virus replication (Nobel Prize, 1969). This work laid the basis for the understanding of virus replication—that virus particles do not grow but are instead assembled from preformed components.

1940: Helmuth Ruska used an electron microscope to take the first pictures of virus particles. Along with other physical studies of viruses, direct visualization of **virions** was an important advance in understanding virus structure.

1941: George Hirst demonstrated that influenza virus agglutinates red blood cells. This was the first rapid, quantitative method of measuring eukaryotic viruses. Now viruses could be counted!

1945: Salvador Luria and Alfred Hershey demonstrated that **bacteriophages** mutate (Nobel Prize, 1969). This work proved that similar genetic mechanisms operate in viruses as in cellular organisms and laid the basis for the understanding of antigenic variation in viruses.

1949: John Enders, Thomas Weller, and Frederick Robbins were able to grow poliovirus *in vitro* using human tissue culture (Nobel Prize, 1954). This development led to the isolation of many new viruses in tissue culture.

1950: André Lwoff, Louis Siminovitch, and Niels Kjeldgaard discovered **lysogenic** bacteriophage in *Bacillus megaterium* irradiated with ultraviolet light and coined the term **prophage** (Nobel Prize, 1965). Although the concept of lysogeny had been around since the 1920s, this work clarified the existence of **temperate** and **virulent bacteriophages** and led to subsequent studies concerning the control of gene expression in prokaryotes, resulting ultimately in the operon hypothesis of Jacob and Monod.

1952: Renato Dulbecco showed that animal viruses can form plaques in a similar way as **bacteriophages** (Nobel Prize, 1975). Dulbecco's work allowed rapid quantitation of animal viruses using assays that had only previously been possible with bacteriophages.

Alfred Hershey and Martha Chase demonstrated that DNA was the genetic material of a **bacteriophage**. Although the initial evidence for DNA as the molecular basis of genetic inheritance was discovered using a bacteriophage, this principle of course applies to all cellular organisms (although not all viruses!).

1957: Heinz Fraenkel-Conrat and R.C. Williams showed that when mixtures of purified TMV RNA and coat protein were incubated together virus particles formed spontaneously. The discovery that virus particles could form spontaneously from purified subunits without any extraneous information indicated that the particle was in the free energy minimum state and was therefore the favored structure of the components. This stability is an important feature of virus particles.

Alick Isaacs and Jean Lindemann discovered interferons. Although the initial hopes for interferons as broad-spectrum antiviral agents equivalent to antibiotics have faded, interferons were the first cytokines to be studied in detail.

Carleton Gajdusek proposed that a slow virus is responsible for the **prion** disease kuru (Nobel Prize, 1976; see 1982). Gajdusek showed that the course of kuru is similar to that of scrapie, that kuru can be transmitted to chimpanzees,and that the agent responsible is an atypical virus.

1961: Sydney Brenner, Francois Jacob, and Matthew Meselson demonstrated that bacteriophage T4 uses host-cell ribosomes to direct virus protein synthesis. This discovery revealed the fundamental molecular mechanism of protein translation.

1963: Baruch Blumberg discovered hepatitis B virus (HBV; Nobel Prize, 1976). Blumberg went on to develop the first vaccine against HBV, considered by some to be the first vaccine against cancer because of the strong association of hepatitis B with liver cancer.

1967: Mark Ptashne isolated and studied the λ repressor protein. Repressor proteins as regulatory molecules were first postulated by Jacob and Monod. Together with Walter Gilbert's work on the *Escherichia coli* Lac repressor protein, Ptashne's work illustrated how repressor proteins are a key element of gene regulation and control the reactions of genes to environmental signals.

Theodor Diener discovered **viroids**, agents of plant disease that have no protein capsid. Viroids are infectious agents consisting of a low-molecular-weight RNA that contains no protein capsid responsible for many plant diseases.

1970: Howard Temin and David Baltimore independently discovered reverse transcriptase in retroviruses (Nobel Prize, 1975). The discovery of reverse transcription established a pathway for genetic information flow from RNA to DNA, refuting the so-called central dogma of molecular biology.

1972: Paul Berg created the first recombinant DNA molecules, circular SV40 DNA genomes containing λ phage genes and the galactose operon of *E. coli* (Nobel prize, 1980). This was the beginning of recombinant DNA technology.

1973: Peter Doherty and Rolf Zinkernagl demonstrated the basis of antigenic recognition by the cellular immune system (Nobel Prize, 1996). The demonstration that lymphocytes recognize both virus antigens and major histocompatibility antigens in order to kill virus-infected cells established the specificity of the cellular immune system.

1975: Bernard Moss, Aaron Shatkin, and colleagues showed that messenger RNA contains a specific nucleotide cap at its 5′ end that affects correct processing during translation. These discoveries in reovirus and vaccinia were subsequently found to apply to cellular mRNAs—a fundamental principle.

1976: J. Michael Bishop and Harold Varmus determined that the **oncogene** from Rous sarcoma virus can also be found in the cells of normal animals, including humans (Nobel Prize, 1989). Proto-oncogenes are essential for normal development but can become cancer genes when cellular regulators are damaged or modified (e.g., by virus **transduction**).

1977: Richard Roberts, and independently Phillip Sharp, showed that adenovirus genes are interspersed with noncoding segments that do not specify protein structure (**introns**; Nobel Prize, 1993). The discovery of gene splicing in adenovirus was subsequently found to apply to cellular genes—a fundamental principle.

Frederick Sanger and colleagues determined the complete sequence of all 5375 nucleotides of the bacteriophage ϕX174 **genome** (Nobel Prize, 1980). This was the first complete genome sequence of any organism to be determined.

1979: Smallpox was officially declared to be eradicated by the World Health Organization (WHO). The last naturally occurring case of smallpox was seen in Somalia in 1977. This was the first microbial disease ever to be completely eliminated.

1981: Yorio Hinuma and colleagues isolated human T-cell leukemia virus (HTLV) from patients with adult T-cell leukemia. Although several viruses are associated with human tumors, HTLV was the first unequivocal human cancer virus to be identified.

1982: Stanley Prusiner demonstrated that infectious proteins he called **prions** cause scrapie, a fatal neurodegenerative disease of sheep (Nobel Prize, 1997). This was the most significant advance in developing an understanding of what were previously called slow virus diseases and are now known as transmissible spongiform encepthalopathies (TSEs).

1983: Luc Montaigner and Robert Gallo announced the discovery of human immunodeficiency virus (HIV), the causative agent of AIDS. Within only 2 to 3 years since the start of the AIDS epidemic the agent responsible was identified.

1985: US Department of Agriculture (USDA) granted the first ever license to market a genetically modified organism (GMO)—a virus to vaccinate against swine herpes. The first commercial GMO.

1986: Roger Beachy, Rob Fraley, and colleagues demonstrated that tobacco plants transformed with the gene for the coat protein of TMV are resistant to TMV infection. This work resulted in a better understanding of virus resistance in plants, a major goal of plant breeders for many centuries.

1989: Hepatitis C virus (HCV), the source of most cases of non-A, non-B hepatitis, was definitively identified. This was the first infectious agent to be identified by molecular cloning of the genome rather than by more traditional techniques (see 1994).

1990: First (approved) human gene therapy procedure was carried out on a child with severe combined immune deficiency (SCID), using a retrovirus vector. Although not successful, this was the first attempt to correct human genetic disease.

1993: Nucleotide sequence of the smallpox virus genome was completed (185,578 bp). Initially, it was intended that destruction of remaining laboratory stocks of smallpox virus would be carried out when the complete genome sequence had been determined; however, this decision has now been postponed indefinitely.

1994: Yuan Chang, Patrick Moore, and their collaborators identified human herpesvirus 8 (HHV-8), the causative agent of Kaposi's sarcoma. Using a polymerase chain reaction (PCR)-based technique, representational difference analysis, this novel pathogen was identified.

2001: Twenty-fifth anniversary of the discovery of AIDS. The AIDS pandemic continued to grow; confirmed cases were an underestimate of the true total worldwide.

The complete nucleotide sequence of the human genome was published. About 11% of the human genome is composed of retrovirus-like retrotransposons, compared with only about 2.5% of the genome that encodes unique (nonrepeated) genes!

2003: Number of confirmed cases of people living with HIV/AIDS worldwide reached 46 million, and still the AIDS pandemic continued to grow.

The newly discovered *Mimivirus* became the largest known virus, with a diameter of 400 nm and a genome of 1.2 Mbp.

Severe acute respiratory syndrome (SARS) broke out in China and subsequently spread around the world.

2010: The United Nations Food and Agriculture Organization (FAO) declared rinderpest virus to be globally eradicated.