1.1 Since When Have We Known of Viruses?

“Poisons” were originally considered as the causative agents of illnesses that we know as viral diseases today. At that time, there were no standard methods to detect pathogenic (disease-causing) organisms such as bacteria and protozoa in the supposed “poisonous materials”. Only animal experiments performed by Louis Pasteur at the end of the nineteenth century, in which no dilution of the poisonous properties was achieved even after several passages, suggested that the disease-causing agent was able to multiply in the organism. Therefore, there was talk of a reproducible “virus” (Latin for “poison” or “slime”) in living organisms, and later also in cells. In St. Petersburg in 1892, Dimitri I. Ivanovski demonstrated that tobacco mosaic disease is caused by an “ultrafilterable” agent, whose size is significantly smaller than that of bacteria: tobacco mosaic virus (bacteria filters have a pore size of...
approximately 0.2 μm, however, most viruses are smaller than 0.1 μm). Soon afterwards, Martinus Willem Beijerinck came to the same conclusion: he developed, for the first time, the notion of a self-replicating, “liquid” agent (*contagium vivum fluidum*). The discovery of foot-and-mouth disease virus by Friedrich Loeffler and Paul Frosch in Greifswald in 1898 was the first evidence of an animal pathogenic virus.

However, it can be retrospectively documented that as long as 3,000 years ago – without knowledge of the nature of the pathogens – practices were implemented which today would be described as vaccinations against viral diseases. In ancient China, India and Egypt, devastating smallpox epidemics must frequently have occurred; Pharaoh Ramses V – as his death mask shows – most likely died of an infection of smallpox virus. As observed at that time, people who had survived the disease were spared from the disease in further epidemics; therefore, they had to have developed some kind of protection caused by the first disease – they were immune. This protective status could also be induced artificially; when dried scabs of smallpox were transmitted to healthy people, they were at least partially protected against smallpox – a measure that we now denominate variolation (the medical term for smallpox is “variola”; ▶ Sect. 19.6). Historical descriptions indicate that smallpox was used as a biological weapon at that time. In the eighteenth century, it was discovered in England and Germany that overcoming milker’s nodule disease, which is triggered by a virus related to smallpox, confers protection against genuine smallpox. Edward Jenner must have been aware of these observations in 1796 when he transmitted swinepox and cowpox material, as a sort of vaccine, initially to his first-born son and later to James Phipps, a young cowherd. Both boys remained healthy following exposure to the human pathogenic smallpox virus by inoculation of smallpox pus; in fact, a protective effect was generated by this first deliberate “virological experiment”.

Knowledge of this vaccination spread very rapidly from England to the European continent and the USA. The term “vaccination” is derived from the Latin *vacca*, which means “cow”. Vaccinations were soon prescribed by law and this led to a gradual reduction of the dreaded disease. In the former German Reich, a first vaccination law was enacted in 1871. However, it still took about 100 years until a human, Ali Maov Maalin, was naturally infected with smallpox (in Somalia) for the last time (in 1977), after the WHO had conducted a worldwide vaccination programme. Today, the disease is considered eradicated.

On a similar basis, i.e., without precise knowledge of the nature of the pathogen, Louis Pasteur developed a vaccine against rabies (▶ Sect. 15.1.5) in Paris in 1885. He transmitted the disease intracerebrally to rabbits in 1882, seeing the causative agent rather in unknown and invisible microbes. As he demonstrated, the pathogen lost its disease-inducing properties by continuous transmission in these animals. In this way, Pasteur achieved the basis for a vaccine virus (*virus fixe*), which, in contrast to the wild-type pathogen (*virus de rue*), was characterized by a constant incubation period. Rubbed and dried spinal cord of rabbits that had been inoculated with the *virus fixe* was no longer infectious, but caused (initially in dogs) protection
against rabies. For the first time, in 1885, Pasteur inoculated a 9-year-old Alsatian boy named Joseph Meister with this material. The boy had been bitten by a rabid dog 2 days before, and finally survived, by virtue of the protective effect induced by the vaccine.

1.2 What Technical Advances Have Contributed to the Development of Modern Virology?

Because of their small size, viruses remained occult to humans for long time. The resolution of the light microscope, which was constructed by Ernst Abbé around 1900, was not sufficiently high to visualize these pathogens; this was only possible with the electron microscope, which was developed by Helmut and Ernst Ruska in 1940. With its aid, the structure of a virus was solved for the first time; that of tobacco mosaic virus. Even obtaining (indirect) evidence of such minute agents, which are not cultivable on artificial media, was impossible before the development of bacteria-proof ultrafilters. They finally allowed the existence of many viruses to be evinced: Walter Reed described yellow fever virus as the first human pathogenic virus in 1900, followed by rabbit myxoma virus and rabies virus in 1903; avian leukaemia virus was discovered by Vilhelm Ellermann and Oluf Bang in 1908, Karl Landsteiner and Emil Popper found poliovirus in 1909 and Peyton Rous discovered Rous sarcoma virus in 1911, which is named after him and represents the first virus associated with the induction of cancer diseases (in this case in the connective tissue of poultry), a notion that had already been suspected by the French bacteriologist Amédée Borrel in 1903.

Even bacteria can be infected by ultrafilterable and transmissible agents, as discovered by Frederik Twort and Felix d’Herelle in 1916 and 1917. They especially noticed the striking ability of these agents to lyse bacteria and, therefore, called them bacteriophages – according to the Greek word *phagein*, which means “to eat”. The exploration of the nature of bacteriophages has provided virology with important findings and impulses both in methodological and in conceptual terms. Many of the steps that characterize a viral infection were first discovered in experiments with bacterial viruses: such processes include attachment and penetration, the reproduction-cycle-dependent regulation of gene expression that results in early and late synthesized proteins, and lysogeny, which is associated with the existence of prophages.

1.2.1 Animal Experiments Have Provided Important Insights into the Pathogenesis of Viral Diseases

The study of viruses and their attributes was particularly difficult because they, in contrast to bacteria, could not be propagated in artificial culture media.
However, it could be ascertained that some of the pathogens isolated from diseased people were transmissible to animals, in which they were able to reproduce. For example, human herpes simplex virus was transmitted from human skin blisters to the cornea of rabbits by Wilhelm Grütter in Marburg in 1911. The extraordinary susceptibility of ferrets allowed the isolation of influenza A virus by Christopher Andrews, Wilson Smith and Patrik Laidlaw from pharyngonasal fluid of a sick person for the first time in 1933. Animal experiments also provided many insights into the pathogenesis of viral infections from another point of view. Richard E. Shope discovered rabbit papillomavirus in 1935, and thus the first tumour virus, which – as was later shown – contains a DNA genome. He suspected that such a virus could exist in a latent form as a provirus in the organism. In addition, the discovery that skin cancer can develop from benign skin papillomas is attributed to him. Hence, malignant tumours develop in two or more steps – nowadays a universally accepted notion. Shope further observed that the incidence of cancer differs in different rabbit breeds, and thus genetic traits of the host also influence the development of cancer.

In the framework of animal experiments, Erich Traub made an important observation while studying the virus of lymphocytic choriomeningitis in Princeton in 1935: when pregnant mice were infected with the virus, the virus was transferred to the embryos; mother animals became sick from meningitis, and produced protective antibodies in the further course of the disease. By contrast, the newborn mice remained healthy, but secreted large quantities of the virus for life without developing a specific immune response against the pathogen. This discovery was the first example of an immune tolerance induced by a virus, but the general significance of this phenomenon was not recognized, and the now popular term was not coined (▶ Sect. 16.1.5). Later, lymphocytic choriomeningitis was shown to be an immunologically related disease. The restriction of cytotoxic T lymphocytes by certain genetically determined types of MHC proteins was demonstrated for the first time in this model by Rolf M. Zinkernagel und Peter C. Doherty in 1974. The above-mentioned experiments of Traub evidenced also for the first time the intrauterine transmission of a virus. This raised the question of similar ways of infection in humans. In fact, after a severe rubella epidemic in Australia in 1941, Sir Norman Gregg observed embryopathies when pregnant women were affected by the infection. As demonstrated later, these malformations were the result of intrauterine transmission of rubella virus.

In 1947, coxsackievirus was discovered after transmission of virus-containing stool extracts into newborn mice (Coxsackie is a small town in the US state of New York). Later in New York, Ludwik Gross isolated murine leukaemia virus from blood cells. Besides the importance for tumour virus research, these observations aroused interest in the question concerning the basis of the high susceptibility of newborn animals to viral infections, and suggested investigations on the innate resistance of an organism to infections as well as the time and the causes of its formation.
1.2.2 Cell Culture Systems Are an Indispensable Basis for Virus Research

Laborious and time-consuming experiments were initially the only way to prove the existence of viruses: therefore, there simpler methods were sought. One way involved the observation of so-called inclusion bodies in virus-infected tissues, which were soon judged as an indication for proliferation of the pathogen; as we now know, inclusion bodies are the accumulation of viral proteins and particles in the cytoplasm or the nucleus. The first inclusion bodies were discovered by Dimitri I. Ivanovski; at the same time, Guiseppe Guarnieri discovered similar deposits in cells infected with smallpox virus, then in 1903, Adelchi Negri found inclusion bodies in ganglion cells of rabid animals, which were later named after him. Thus, there were at least simple dye detection methods for some viral diseases. However, virus culture methods became available later.

In the 1930s, it was found that embryonated chicken eggs are appropriate for the propagation of some viral species. Between 1918 and 1920, a pandemic emerging viral disease, Spanish flu, claimed more than 20 million lives, i.e., more than in the First World War. After cultivation of the virus responsible in embryonated chicken eggs in 1933, their haemagglutinating properties were discovered in 1941 (i.e., their ability to agglutinate red blood cells), thereby laying the basis for the development of haemagglutination tests to detect viruses. Another important step in the history of modern virology was the development of the first ultracentrifuges, which became available at about the same time. They made possible the sedimentation and concentration of the minute virus particles. However, the breakthrough in the elucidation of the pathogenetic mechanism of influenza viruses was only possible by the development of molecular biological techniques that allowed the investigation of the genetic material of this pathogen, which exists in the form of single-stranded RNA. Its sequencing revealed the genetic reasons for the previously not understood ability of influenza viruses to change their antigenic properties at periodic intervals (▶ Sect. 16.3.5).

However, it was particularly the donation-funded research of poliomyelitis (▶ Sect. 14.1.5) which provided crucial new insights. Retrospectively, it represents the actual transition to molecular biological research of viral infections. The strong increase in the incidence of polio and the number of deaths – a result of enhanced hygiene standards and the shift of infection rates into later years of life – brought about in the USA the establishment of the National Polio Foundation by Franklin D. Roosevelt, himself a victim of this disease, in the early 1930s. With the funds raised, a major research programme was initiated whose coronation was the discovery of the cytopathic effect by John F. Enders, Thomas H. Weller and Frederik C. Robbins in 1949.

In 1928, Hugh B. and Mary C. Maitland had already introduced the method of tissue culture, in which the cells of small tissue pieces were cultivated in serum-containing liquid media and infected with viruses. Successful viral replication was then demonstrated in animal experiments or by detecting the presence of inclusion bodies. When antibiotics became available in the 1940s, it was then possible to
largely prevent bacterial contaminations in cultures, which led to much simpler handling in this method. Polioviruses were cultivated in embryonic human cells of fixed kidney tissue fragments, and thereby cellular alterations were easily identifiable. This diagnostically valuable cytopathic effect drove the development of virology forwards. It was the basis for the plaque test that was developed by Renato Dulbecco and Marguerite Vogt in 1952, which rendered possible, for the first time, the quantitative determination of the number of infectious particles in cell culture. The capability to cultivate polioviruses under controlled conditions in vitro was the basis for the development of the two polio vaccines: the inactivated vaccine developed by Jonas E. Salk and the live vaccine with attenuated, i.e., weakened polioviruses, developed by Albert B. Sabin. Both vaccines are still in use today. Later, vaccines against measles, rubella and mumps were also produced following the principle applied by Sabin.

By using the method of cell culture, it was possible to cultivate even yellow fever virus, vaccinia virus and rabies virus in vitro. Wallace P. Rowe isolated adenoviruses from cultures of human tonsil tissue after a long cultivation period in 1953. A further development of viral cultivation in vitro provided the method of co-cultivation, which consists in the addition of indicator cells to the tissue cultures, which indicate viral replication by the occurrence of a cytopathic effect. In this manner, the existence of herpes simplex virus was verified in latently infected human dorsal root ganglia in 1971, whereas direct virus detection was not possible at that time. Until then, it had generally been assumed that in the course of viral infections the pathogen would be eliminated completely from the body by the resulting antibodies. The occurrence of herpes blisters as recurrent disease in people with antibodies – known as herpes immunological paradox – refuted that notion (▶ Sect. 19.5). Ernest W. Goodpasture had previously suggested that the trigeminal ganglia should contain a “latent” form of the virus. After such a virus had been detected by co-cultivation, it was recognized that there are a number of infections with latent or persistent viruses, which – independently of the illness symptoms – are excreted either intermittently (e.g., herpes simplex virus) or permanently (such as Epstein–Barr virus). The primary isolation of human immunodeficiency virus (HIV) 1 was also accomplished by co-cultivation of lymph node biopsy material from an AIDS patient with suitable T lymphocytes.

1.2.3 Modern Molecular Biology Is also a Child of Virus Research

Concurrently with the rather practical benefits from developments in viral cultivation, interest in general biological issues became increasingly important. The crystallization of tobacco mosaic virus from liquid media by Wendell Stanley in California in 1935 stimulated discussions as to whether viruses are dead or living matter. The main question concerned, however, the nature and structure of the genetic material, which was found to be nucleic acid by the
seminal experiments of Oswald T. Avery, Colin McLeod and Maclyn McCarty with pneumococci in 1944. In 1952, Alfred D. Hershey and Martha Chase proved that during bacteriophage T4 infections only DNA, but not the protein shell of the virus, penetrates into the bacterial cell. This demonstrated that nucleic acids are the carrier of genetic information. A few years later, in 1955, Gerhard Schramm and Heinz Fraenkel-Conrat showed independently in tobacco mosaic virus that RNA can also be infectious. Schramm and his colleagues had already described in Germany in 1944 that tobacco mosaic virus is composed of RNA and proteins; however, these findings attracted initially only little attention. The base ratios in DNA molecules \( (A = T \text{ and } C = G) \) that were discovered and developed by Edwin Chargaff enabled James D. Watson and Francis H. Crick, in connection with the Rosalind Franklin’s X-ray structural analysis, to develop their model of the DNA double helix in 1953. In 1958, Matthew Meselson and Franklin W. Stahl demonstrated that DNA is replicated semiconservatively during cell division. These fundamental insights created the way for the elucidation of basic molecular biological processes which are nowadays generally familiar. The now common molecular genetic, biochemical and immunological methods allow the detection of viruses in the organs and the study of their spread in the organism. The function and effect of viral genes can be explored in isolation and in interaction with other viral or cellular components. Today, many viruses can be cultivated in large quantities in vitro in order to resolve their morphology and particle structure as well as to sequence their genetic information. In the case of non-cultivable viruses, modern molecular biological methods are available which make possible the investigation of the pathogens. Virus–cell interactions can be explored, and provide important insights into the mechanisms of viral replication. On the other hand, many of the molecular processes in eukaryotic cells have been elucidated by using viruses as cell research tools. In this way, the process of RNA splicing was originally described in adenoviruses, in which widely separated gene segments are assembled into single messenger RNA molecules after transcription. The fact that DNA is arranged with histone proteins into nucleosome structures within the nucleus was also first discovered in a virus, simian virus 40. In addition, even enhancers were originally described in viruses, i.e., the specific DNA regions that increase the expression of certain genes in a localization- and orientation-independent manner. Several of these viral regulatory elements have been used for alternative purposes: for example, the most frequently used promoter/enhancer sequences to control the expression of heterologous genes in commercially available vectors are derived from cytomegalovirus. This immediate-early promoter/enhancer region actually regulates the expression of early genes of the virus (see ▶ Sect. 19.5). Furthermore, the transfer of nucleic acid sequences and foreign genes by viral transduction, e.g., using vector systems based on the functions of adenoviruses or retroviruses, is today an indispensable constituent of molecular and cell biology, and has essentially contributed to the development of gene therapy procedures.
1.3 What Is the Importance of the Henle–Koch Postulates?

The study of the epidemiology and pathogenesis of infectious diseases raises the fundamental question of how can it be proved that an illness is caused by infection with a bacterium or a virus. Robert Koch derived four postulates from his work with anthrax bacteria between 1882 and 1890, which his teacher Jacob Henle had previously developed as a hypothesis from the study of so-called miasma and contagions, i.e., the animate or inanimate disease and infection agents:

1. A pathogen must be detected in all cases of a certain disease, but it must be absent in healthy organisms.
2. The pathogen must be cultivable on culture media or in suitable cell cultures in the form of pure cultures.
3. Healthy animals must develop the same disease after inoculation of the pathogen.
4. The causative agent must be reisolated from the infected animals.

Koch noted that the postulates do not comply in all cases. He acknowledged that there are healthy and long-term carriers and that a normal flora of facultative pathogenic bacteria exists. In the realm of virology, not all pathogens comply with these postulates. Positive examples are measles virus (▶ Sect. 15.3.5), human poxviruses (▶ Sect. 19.6.5), canine and feline paroviruses (▶ Sect. 20.1.6) and classical swine fever virus (▶ Sect. 14.5.7). With regard to viral diseases, Charles River proposed modifications of the postulates in 1937. The exceptions concern preferentially latent or persistent viral infections and the fact that tissue and organ damage or tumour formation cannot always be reproduced as consequences of infection.

Taken from epidemiology, the “Evans postulates” are a worthy supplement (▶ Table 11.1). They show the aetiological importance of a pathogen for a clinical picture if, among others, the pathogen is significantly more frequent in an exposed group and the disease in this population is commoner than in a non-exposed group. Similarly, an immune response should be detectable in the affected collectives. The Evans postulates are valuable particularly for multifactorial infectious diseases, such as canine kennel cough and porcine circovirus infection (▶ Sect. 20.2.6).

The further development of virological and immunochemical detection methods in recent years has allowed the use of additional criteria for the causal relationship between a virus and a disease. These include the detection of a specific humoral or cellular immune response against the pathogen, i.e., IgM or IgG antibodies and specific stimulatable lymphocytes, and the detection of viral proteins, enzyme activities, DNA or RNA by in vitro and in situ methods. The specific detection of viral nucleic acids in tissues is especially important for the aetiological correlation between persistent viral infections and cancer. The fulfilment of Koch’s postulates or their modifications is still essential for the development of aetiological relationships between the pathogen and the host.
1.4 What Is the Interrelationship Between Virus Research, Cancer Research, Neurobiology and Immunology?

1.4.1 Viruses are Able to Transform Cells and Cause Cancer

As early as in 1911, it was demonstrated that Rous sarcoma virus can cause cancer. In 1959, Margarete Vogt and Renato Dulbecco observed the transformation from benign to malignant cells after infection with murine polyomavirus in vitro. After animals had been inoculated, these cells generated tumours. Shortly afterwards, it was also discovered that Rous sarcoma virus can transform cells in vitro. Thus, tumour virus research became a driving force of virology. It has enriched the realm of cancer research with decisive impulses both in conceptual and in methodological terms. Experiments with the oncogenic polyomavirus also showed that its dissemination within mouse populations can be followed by serological methods. This aroused the hope that it would be possible to reduce cancer development to viral agents and to study its nature using the classical methods of epidemiology such as virus isolation and antibody detection. In particular, the study of oncogenic retroviruses in animal systems provided seminal insights into the molecular processes that lead to carcinogenesis (▶ Sect. 18.1). By investigating oncogenic retroviruses in 1970, Howard Temin and David Baltimore discovered reverse transcriptase – an enzyme that transcribes the single-stranded RNA of retroviruses into double-stranded DNA. After integration of the viral genetic information into the genome of the host, these viruses lose their individual existence. A few years earlier, Temin had described that an inhibitor of DNA synthesis prevents replication of Rous sarcoma virus, which should not be the case in a typical RNA virus. The integration of a viral genome, which is then present as a provirus, has been associated with tumour development. This event interrupts the continuity of the genome of the cell, as cellular and viral genes can be amplified and destroyed, or their expression can be activated by recombination with viral promoters.

As mentioned above, Shope had already described that carcinomas arise from papillomas by a two-stage or multistage process. The development of cervical carcinoma caused by human papillomaviruses and that of primary liver cancer caused by hepatitis C virus or hepatitis B virus are similar. Even Epstein–Barr virus exerts its tumorigenic effect in a complex way: the viral DNA is detectable in nasopharyngeal carcinoma tumour cells and in various lymphomas (African Burkitt’s lymphoma). The cells are infected and immortalized, but do not produce infectious virus particles. Furthermore, chromosomal translocations are found in B-cell lymphomas (▶ Sect. 19.5). However, malignant transformation develops in a multistep process by interaction with other factors, such as malaria, which contributes to a chronic stimulation of cells.

Research on the molecular processes that occur in infections with papillomaviruses, hepatitis B virus and retroviruses has led to the development of vaccines which induce protection against the respective viral infection and are capable of preventing the development of cancer as a long-term consequence.
The vaccination strategy in Southeast Asia that was initiated and promoted by the WHO 25 years ago has led to a significant decrease of primary liver carcinoma, which is caused by hepatitis B virus infections (▶ Sect. 19.1). In veterinary medicine, vaccines against feline leukaemia virus have proved that cats are protected against infections by this exogenous retrovirus and that tumour formation can be prevented (▶ Sect. 18.1). The detailed investigation of the molecular biology and pathogenesis of human papillomavirus infections by the research group of Harald zur Hausen at the German Cancer Research Center (DKFZ) paved the way for the development of appropriate vaccines. These have been available for several years and protect against infections with the highly oncogenic papillomaviruses: they prevent the possible development of cervical carcinoma – one of the commonest cancers in women (▶ Chap. 10, ▶ Sect. 19.3). In September 2008, Harald zur Hausen was awarded the Nobel Prize in Physiology or Medicine for his work concerning the role of papillomaviruses in cervical cancer.

### 1.4.2 Central Nervous System Disorders Emerge as Late Sequelae of Slow Viral Infections

The term “slow virus infections” was initially coined by Bjoern Sigurdsson for maedi disease of sheep in Iceland in 1954. Maedi–visna virus causes respiratory symptoms in a slow and progressive disease after very long incubation and latency periods. Maedi–visna virus thus became a model for a range of pathogens that cause diseases with a similar protracted course (▶ Sect. 18.1.6).

The exploration of its pathogenesis revealed that most slow virus infections are caused by pathogens which are usually associated with other diseases. Slow virus infections principally affect the central nervous system and are caused, for example, by measles virus and JC polyomavirus. Subacute sclerosing panencephalitis is probably caused by mutations in measles virus genes, which lead to the emergence of defective virus particles (▶ Sect. 15.3.5). In progressive multifocal leucoencephalopathy, which is triggered by JC polyomavirus, the virus seemingly enters the brain very early and persists there for a long time before the disease breaks out as a result of damage to the immune system (e.g., by infection with HIV; ▶ Sect. 19.2.5). Infections with HIV can also be considered as a slow virus disease. Similarly, prion diseases also progress along the lines of a slow virus infection, but they are caused by non-viral pathogens and have a fundamentally different pathogenesis (▶ Chap. 21).

### 1.4.3 Interferons Stimulate the Immune Defence Against Viral Infections

Working on yellow fever virus, M. Hoskins, G.M. Findlay and F. MacCallum discovered the phenomenon of interference in 1935: if an avirulent virus was
injected into an experimental animal, the animal was protected from the consequences of infection by a virulent strain when it was applied within the next 24 h, i.e., before the onset of an immune response. In 1957, Alick Isaacs and Jean Lindenmann showed that interferon is responsible for the interference effect. It is species-specific, inducible and belongs to a group of substances that are known as cytokines today. Interferons play an important role in the primary, non-specific defence against viral infections and in stimulating the immune system. The observation that antiviral interferon preparations also have tumour-inhibiting effects was surprising. Generally, cytokines are synthesized when a suitable inducer binds as a ligand to its receptor on the cell membrane, thus triggering specific signal transduction processes in the cell (▶ Chap. 8).

1.5 What Strategies Underlie the Development of Antiviral Chemotherapeutic Agents?

Attempts have been made to develop antiviral chemotherapeutic agents since about 1960. In retrospect, this search can be divided into three stages: the first successful experiments for therapy of a viral infection were performed by Josef Wollensak and Herbert E. Kaufman around 1960 in herpetic keratitis. They used substances that inhibit viral replication in vitro and were known from experimental cancer therapy. However, the selectivity of these substances, i.e., their ability to selectively influence viral and not cellular processes, was only slight because of the high cytotoxicity of the compounds. After the discovery of virus-coded enzymes such as thymidine kinases, DNA polymerases and proteases, it was possible to address the development of specific inhibitors. Antiviral drugs such as amantadine against influenza A virus (▶ Sect. 16.3) and adenine arabinoside and acyclovir (acycloguanosine) against herpes simplex virus (▶ Sect. 19.5) were found by targeted empiricism, i.e., by attempting to find a compound that selectively influences viral reproduction among many compounds with similar effects. The achievement of Gertrude Elion and her staff to use acyclovir as a systemically applicable and selective antiviral drug in herpes encephalitis was an important milestone in chemotherapeutic research. She was awarded the Nobel Prize in Physiology or Medicine in 1988 for her work. After the development of DNA sequencing techniques, the experimental chemotherapy of viral infections entered its third stage. Virus-encoded enzymes were discovered such as the retroviral protease and neuraminidase of influenza viruses, and it was possible to build structural models of enzymes by comparison with proteins of similar functions and known three-dimensional structures. This allows one to identify potential active centres and to develop compounds, also known as “designer” drugs, which accommodate within the active centres and inhibit the viral enzymes. That means deviating from purely empirical research, and is a first step towards a more rational development of antiviral compounds (▶ Chap. 9).
1.6 What Challenges Must Modern Virology Face in the Future?

Molecular virology has achieved significant successes in recent decades: Many infectious diseases can be prevented through the use of modern vaccines or have been completely eradicated (▶ Chap. 10). This ultimately made possible the global elimination of infectious agents such as smallpox virus. Poliovirus, which causes poliomyelitis, is no longer found on some continents, and is currently confined to fewer than ten countries worldwide. In cases in which no preventive vaccination is possible today, e.g., against HIV and some herpesviruses such as cytomegalovirus and herpes simplex virus, a large number of antiviral drugs are available. Although these drugs do not provide a cure, they substantially allow the control of symptoms. These successes might tempt one to assume that virus research has become unnecessary. The assessment of the epidemiological situation by the WHO and the many sensationalistic headlines in newspapers and the media with which we are repeatedly confronted imply the opposite. Because of their frequent and high rates of mutation, viruses are subject to continuous change and development: viruses are permanently compelled to cope with the infected organism and its immune defence systems, always trying to undermine and circumvent them. In particular, viruses that persist in the organism are capable of evading the host immune defence systems by very skilful strategies. The worldwide increase in travel leads not only to contact with new human pathogens, but also to their rapid dissemination. This is demonstrated, for example, by SARS virus infections (▶ Sect. 14.8), the pandemic with the new influenza A virus variant (Mexican flu, “swine flu”) and the threatening potential with regard to humans of new highly pathogenic influenza viruses (► Sect. 16.3). New and novel viral diseases which have their origin in the animal kingdom (zoonoses) are also expected owing to increased environmental changes and their serious consequences. Outbreaks of infection with Ebola virus, Nipah virus and Hendra virus are examples. Deforestation of rainforests has led to a change in living conditions for bats, which then infect horses and pigs and, via these intermediate hosts, also humans. Birds carried West Nile virus from Africa to North America, and avian flu virus H5N1 was transported from Asia to Europe by migratory birds. The AIDS pandemic that was induced by human immunodeficiency viruses was originally the result of a zoonotic transmission from monkeys to humans, followed by efficient further dissemination within the human population.

The threat from both new and already well-known viral infections will not decrease because of reduced vaccination, particularly in industrialized countries; therefore, scientists who conduct research in the field of molecular virology will continue to have an ample sphere of activity.

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