Viruses exact an enormous toll on the human population and are the single most important cause of infectious disease morbidity and mortality worldwide.This process of discovery has continued with growing momentum to the present, with recently identified skin cancer–associated Merkel cell polyomavirus,2 novel Old World arenaviruses causing fatal disease,3, 4 bat–related respiratory coronavirus5 and reoviruses,6, 7 and novel swine– and avian–origin influenza viruses8, 9 counted among the most recent entries in the catalog of human disease–causing viruses.Nucleic acid–based strategies are now used routinely in the diagnosis of infections caused by enteroviruses, hepatitis B virus (HBV), hepatitis C virus (HCV), herpesviruses, human immunodeficiency virus (HIV), and, with increasing frequency, respiratory and enteric viral pathogens.The pioneering experiments of Avery, MacLeod, and McCarty12 on the transformation of pneumococci established DNA as the genetic material and set the stage for corroborating experiments by Hershey and Chase using bacteriophages.13 In the late 1940s, Enders and colleagues14 cultivated poliovirus in tissue culture.Careful clinical observations enabled the identification of many viral illnesses and allowed several viral diseases to be differentiated (e.g., smallpox vs. chickenpox and measles vs. rubella).In the 1940s, Delbruck, Luria, and others10, 11 used bacteriophages as models to establish many basic principles of microbial genetics and molecular biology and identified key steps in viral replication.This accomplishment led to the development of both formalin–inactivated (Salk)15 and live–attenuated (Sabin)16 vaccines for polio and ushered in the modern era of experimental and clinical virology.These observations were quickly followed by the discovery of yellow fever virus and the seminal research on the pathogenesis of yellow fever by Walter Reed and the U. S. Army Yellow Fever Commission.1 By the end of the 1930s, tumor viruses, bacteriophages, influenza virus, mumps virus, and many arthropod–borne viruses had been identified.Techniques to detect viral genomes, such as the polymerase chain reaction (PCR) and its derivatives, have proven superior to conventional serologic assays and culture techniques for the diagnosis of many viral diseases.Furthermore, these powerful new techniques are leading to breakthroughs in foundational problems in viral pathogenesis, such as the nature of virus–cell interactions that produce disease, immunoprotective and immunopathologic host responses to infection, and viral and host determinants of contagion.Nucleotide sequences of entire genomes of most human viruses are known, and functional domains of many viral structural and enzymatic proteins have been defined.Furthermore, rapid developments in mass spectrometry and nucleotide sequencing technology are permitting the application of these tools to highly sensitive and specific virus detection in clinical specimens.Finally, the work of Pasteur ushered in the systematic use of laboratory animals for studies of the pathogenesis of infectious diseases, including those caused by viruses.Progress in an understanding of disease at the level of cells and tissues, exemplified by the pioneering work of Virchow, allowed the pathology of many viral diseases to be defined.Improved understanding of these aspects of viral infection will facilitate new approaches to the prevention, diagnosis, and treatment of viral diseases.Ivanovsky and Beijerinck identified tobacco mosaic virus, and Loeffler and Frosch discovered foot–and–mouth disease virus.This information is being applied to the development of new strategies to diagnose viral illnesses and design effective antiviral therapies.Strategies now exist whereby specific .mutations or even entire genes can be inserted into the genomes of many viruses