To Catch a Virus
To Catch a Virus

John Booss, MD, and Marilyn J. August, PhD
Cover image: Specter of death waiting over Panama (U. J. Keppler, 1904). Cover illustration for Puck, a political satire and humor magazine. (See Figure 1 in chapter 1.) (Courtesy of Beinecke Rare Book and Manuscript Library, Yale University.)

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In tribute to Gueh-Djen (Edith) Hsiung, PhD, who is remembered for her pioneering contributions to the field of diagnostic virology, for training and inspiring generations of diagnostic virologists with her passion for virology, and for her social grace and generosity. (Courtesy of Zhe Zhao.)
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FOREWORD

This book traces the growth of diagnostic virology from its beginnings over a century ago to the present: the scientific discoveries, the blind alleys, the missteps, the epidemics that gave urgency to the quest, the technological advances, and the unique individuals whose commitment and hard work were the keys to progress.

The idea for this book first arose at a memorial service for Dr. Gueh-Djen (Edith) Hsiung, a leader in clinical and diagnostic virology who died in 2006 and in whose laboratory the authors and I had all trained. To us, Edith Hsiung embodied the enthusiasm, dedication, and perseverance of an older generation who, sadly, had died or were dying and whose stories were being lost. John Booss, to his great credit, has been the driving force behind this project, traveling the country to research historical archives and interview key people. He was fortunate to enlist Marilyn August, a diagnostic expert and science writer who is a key contributor to this important endeavor. Although a diagnostic virologist myself, I knew little of the history of the field and thus have learned a tremendous amount reading the material they have unearthed and presented in this fascinating book.

When I first entered Dr. Hsiung’s laboratory in 1979, virus isolation involved inoculating litters of newborn mice or embryo-nated hens’ eggs, or preparing cell cultures by harvesting rabbit kidneys and chicken and guinea pig embryos—i.e., working with a virtual menagerie—as well as recovering discarded human foreskins from the obstetrics ward. Time to result was slow, and it was often said that the patient was dead or better by the time the result was received. Over the intervening years, diagnostic advances have
transformed the field by allowing accurate results in a clinically useful time frame. Today, with molecular methods and rapid diagnostic tests, most results are reported within minutes to hours to 1 to 2 days. Providing sophisticated molecular tests that require minimal skill is now a reality.

With these advances have come new challenges. As tests become more sensitive, low levels of clinically irrelevant or nonviable viruses may be detected and can be misleading to clinicians. Similarly, interpreting the clinical relevance of multiple viral pathogens in the same sample is problematic. Furthermore, with numerous commercial virus detection kits now becoming available, laboratories can find it hard to decide which technologies to invest in. As diagnostic virology enters a new phase in the clinical mainstream, it is highly fitting and fortunate that this book is available to mark the first century of progress and to recount the many stories and contributions that have led us to where we are today.

Marie Louise Landry, MD
Yale University School of Medicine
**PREFACE**

With a nod to *To Catch a Thief*, Alfred Hitchcock’s 1955 classic mystery film, this book tells the story of the ways in which viruses are captured and identified. It is a chronicle of discovery and diagnosis, a history of diagnostic virology. It begins with yellow fever, the first human disease shown to be viral in nature. That happened in Cuba at the turn of the 20th century, when Walter Reed and the Yellow Fever Commission demonstrated that the disease was transmitted by mosquitoes. They then showed that the agent passed through a filter designed to hold back bacteria, a defining characteristic of viruses. The chronicle has continued through more than a century of historical developments, epidemics, and discoveries, coming into the 21st century with AIDS and human immunodeficiency virus (HIV) and looking into the future.

Diagnostic virology sits astride the confluence of dynamic developments in science, public health struggles with epidemics and emerging diseases, and the intensive medical care of individual patients. Virology as a science was built on the emergence of germ theory and on the developments of cell technology. Most recently, it has made unprecedented advances based on the dizzying progress of molecular biology. During the time covered by this book, terrifying epidemics have made their appearance. The influenza epidemic of 1918 to 1919 is estimated to have killed 25 to 50 million people worldwide, more than all the military casualties of World War I combined. Yet it was not until 1933 that the influenza virus was finally captured and identified in an unusual host, the ferret. The global pandemic of AIDS, which revealed itself in 1981, had by 2008 killed over 25 million
people. It became the driver of molecular diagnostic techniques. In so doing, it dramatically amplified the paradigm of diagnostic virology from making a diagnosis, often after the fact, to prompt diagnosis and active disease management of individual patients.

History and commerce have had a critical hand in the advances in virological diagnosis. The first agent identified as a virus, tobacco mosaic virus, was investigated because of the threat to a commercial crop. The date of that discovery, 1892, is usually identified as the start of virology. The second virus was identified in 1899, foot-and-mouth disease virus. Similar to tobacco mosaic virus, it was examined because of a commercial threat to farm animals and cattle. Wars, too, have driven developments in virology. The demonstration of yellow fever virus had been initiated by the need of the Army to protect soldiers in Cuba in the aftermath of the Spanish-American War. Another first, the establishment of the first viral and rickettsial diagnostic lab, was a response to the incipient World War II (WWII). The Army established the lab at the Walter Reed Army Medical Center in January 1941 in Washington, DC. That is the date on which independent diagnostic virology labs, in contrast to labs devoted primarily to research, can be said to have begun.

The president during WWII, Franklin Delano Roosevelt (FDR), whose ringing words in declaring war stirred the nation, had fought both a personal and national battle against polio. It was his National Foundation for Infantile Paralysis, with Basil O’Connor, that underwrote the development of the Salk polio vaccine. In doing so, John Enders, Thomas Weller, and Frederick Robbins developed tissue culture to grow, isolate, and enumerate viruses. It gave the means to capture and identify viruses directly without having to resort to assays in animals or embryonated hens’ eggs. This was the turning point, after which discoveries in human virology and the development of diagnostic virology simply exploded. These events and other crucial developments are recounted, along with vignettes of the personalities who propelled the capacity to catch and identify viruses.

Most chapters are built around specific viral diseases, such as yellow fever in the first chapter, to demonstrate the development of a technology. In the second chapter, polio, rabies, and influenza are described to show the use of animals and embryonated chicken eggs to isolate and identify viruses. Smallpox is described in the third chapter to demonstrate that the body’s immune system, like
the brain, has memory. Immunological memory provides protection from reinfection and allows the measurement of antibodies to identify a virus. Jennerian vaccination, inducing immunity, was the basis of the remarkable smallpox global eradication project. Some viral infections, like smallpox virus, rabies virus, and the herpes family of viruses, leave footprints called inclusion bodies. The detective work to recognize those footprints, the development of Rudolf Ludwig Virchow’s concepts of cellular pathology, and the beginnings of electron microscopy (EM) are unraveled in chapter 4.

Chapter 5 details the events leading up to the development of tissue culture, including FDR’s polio. Chapter 6 describes the virtual torrent of viruses captured and identified by the development of tissue culture for virus isolation and identification. At the National Institutes of Health in Bethesda, MD, the Laboratory of Infectious Diseases was a hotbed of viral discovery and disease investigation. Led by Robert J. Huebner, investigators such as Wallace Rowe, Robert Chanock, and Albert Kapikian made discovery after discovery linking viruses to illness or, conversely, showing them to be non-pathogenic passengers. The role of diagnostic virology labs at the state level, at the Communicable Diseases Center, and in university hospitals exploded from the latter 1950s onward. These laboratories defined individual patients’ illnesses, often after the acute phase had passed. They also alerted the country to the appearance of epidemics such as influenza.

The final three chapters trace developments which brought diagnostic virology into active patient management. Chapter 7 describes the clinical application of EM and of fluorescent-antibody staining. EM came into its own with several advances, notably negative staining developed by Sydney Brenner and Robert Horne, allowing the detailed description of virus architecture. Viral gastroenteritis is used as the exemplar of disease in which EM played a defining role. Fluorescent-antibody staining, developed though the imagination and tenacity of Albert Hewlett Coons, allowed “taillights” to be put on molecules. That is, the technique would allow the identification of an offending virus. This methodology was applied by Phillip S. Gardner and Joyce McQuillin in pioneering efforts at Newcastle-upon-Tyne in the United Kingdom. They aimed to provide clinicians with a “rapid viral diagnosis,” particularly of acute respiratory disease in infants and children, within 24 hours.
Chapter 8 describes the evolution of our understanding of viral hepatitis and how innovative immunological techniques, developed by both serendipity and ingenuity, led to the identification of some of the culprits. In the case of radioimmunoassay (RIA), Rosalyn Yalow and Solomon Berson originally developed the highly sensitive and accurate technique to measure human insulin and other endocrine molecules. When applied to viral diseases, it allowed the screening of the blood supply for hepatitis viruses. Less complicated and non-radioactive assays, such as the enzyme-linked immunosorbent assay (ELISA) and the enzyme immunoassay (EIA), soon followed. They transformed many aspects of biology, including the diagnostic process in virology.

The final chapter, chapter 9, examines where we are today in diagnosing and managing viral diseases, and where we are going. It tracks HIV, AIDS, and the application of molecular methods for discovery and control. The syndrome first appeared in 1981 as a virtually inevitable death sentence, but that characterization was transformed by the use of an antiviral “cocktail,” including a protease inhibitor, in 1996. Its current status is as a managed chronic disease in those individuals fortunate to have access to molecular viral diagnostic assays and a wide spectrum of specifically targeted antiviral drugs. Tragically, that fortunate group represents only a small portion of the global population infected with HIV.

The molecular foundation for these developments started with the demonstration of DNA as the basis of heredity by Oswald Avery in the 1940s. The demonstration of the double helix by James D. Watson and Francis Crick, using X-ray crystallographic data of Rosalind Franklin, allowed the cracking of the genetic code and the molecular biological revolution which followed. Another key development was the demonstration of the enzyme reverse transcriptase, which transmits genetic information from RNA to DNA and facilitated the discovery of HIV. In another crucial development, exquisitely sensitive detection and quantitation assays were produced. They are based on nucleic acid amplification principles developed for PCR by Kary Mullis. PCR and other molecular techniques such as nucleic acid sequencing allow the measurement of the amount of HIV in plasma, i.e., “viral load,” and the determination of mutations of the virus, facilitating management of antiviral therapy.
The final section of chapter 9 takes a look into the future of viral diagnosis, which even now is becoming highly transformed. Molecular diagnostics have been streamlined so that the many individual steps of nucleic acid extraction, amplification, measurement, and reporting are done in closed systems in “real time.” Hence, the highly trained diagnostic virology specialists of the tissue culture era are being replaced by computer-savvy technologists. In the opinion of a number of experienced diagnostic virologists, the diagnostic virology lab as we have known it is becoming a thing of the past. Many of its functions are being and will be transferred to “point-of-care” locations such as clinics and other medical and public health locations. The process of viral discovery will make use of high-throughput nucleic acid sequencing and information comparisons in large databases. These will be fundamentally important to identifying new viruses or old viruses in “new clothes” that will emerge to attack, frighten, and baffle.

We have sought illustrations from the general social context to illustrate perceptions of viral infections. Several other types of figures have also been chosen to support the text. In addition to photographic portraits of key historical figures, diagrams of diagnostic procedures and micrographs of virus-infected cells have been selected as examples of the kinds of work that diagnostic virologists have performed.

We hope that the book will appeal to a large audience, one concerned about the broader issues that our society faces. This audience includes the many types of professionals whose scientific interests have led them to work with viral diseases. There have always been a fascination, curiosity, and fear of viral epidemics that threaten the lives of individuals and the fabric of society. This was true for the yellow fever outbreak in 1793 in Philadelphia, as it was in the 1980s when AIDS first made its mysterious entrance, and as it is in the constant fear of a newly lethal influenza pandemic. Those emotions find some release in many popular films and books. It is to this broad audience that the book is directed, to demonstrate how science and technology have advanced to confront the virological threats to our well-being.

John Booss
Marilyn J. August
ABOUT THE AUTHORS

John Booss is Professor Emeritus of Neurology and Laboratory Medicine at the Yale University School of Medicine. For twelve years he was the National Program Director of Neurology for the U.S. Department of Veterans Affairs. Following residency in neurology, he trained in virology with G.-D. Hsiung, to whom this book is dedicated, and subsequently worked with E. F. Wheelock in viral immunology. He studied experimental models of viral infection of the brain, modulation of immune functions by murine cytomegalovirus, and T cells in multiple sclerosis with Margaret M. Esiri in Oxford and studied the host response to xenogenic brain cell transplantation with C. Jacque in Paris. Dr. Booss’ clinical interests have focused on viral encephalitis, multiple sclerosis, and the neurology of HIV/AIDS. He and Professor Esiri are coauthors of *Viral Encephalitis in Humans*, published by the ASM Press in 2003. (Republised with permission from the American Academy of Neurology Institute.)

Marilyn J. August was trained as a clinical virologist and microbiologist, completing her undergraduate work in microbiology at the University of Massachusetts, Amherst, and her PhD in virology with an emphasis on electron microscopy at Columbia University, College of Physicians and Surgeons. With training in both microbiology and virology, she became a postdoctoral fellow with G.-D. Hsiung at Yale University School of Medicine, which launched her career in clinical, diagnostic virology. Her professional activities progressed with positions as director of hospital and clinical diagnostic virology, microbiology, and infectious serology laboratories in southern California. Accepting a new challenge and returning to her roots in virology, Dr. August moved to the biotechnology industry in northern California and joined Aviron (now MedImmune/AstraZeneca) as director of the clinical testing laboratory, overseeing clinical trials testing to support pivotal studies that contributed to the approval of a live, intranasal influenza vaccine that was first licensed in 2003. Dr. August’s recent professional activities include consulting as a scientist and freelance medical writer-editor between wonderful trips, hiking adventures, and activities as a Let’s Look at Art docent for the San Jose Museum of Art. (Photo by Laurie Naiman.)
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