

## Introduction

---

HEPATITIS B virus (HBV) is one of the most common viruses in the world. Hundreds of millions of people have been infected with it—perhaps half of the world’s population—and it ranks as one of the top ten killers of people among the bacteria, protozoans, viruses, parasites, and other infectious agents that plague humankind. The most characteristic clinical sign of hepatitis is the vivid yellow color—jaundice—it imparts to the whites of the eyes and, often, the entire body. Yellow jaundice is the hallmark of the disease and is often the clinical finding that draws attention to the malady, particularly if it occurs in epidemic form. Fortunately, most cases of hepatitis are acute and self-limited, but many progress to a chronic form that can be deadly.

About 1.5 million people worldwide die each year as a consequence of HBV infection. These include about a million people with primary cancer of the liver, one of the most common and deadly cancers known, a large percentage of which are caused by HBV. Currently, over 350 million people are chronically infected with HBV. HBV kills as many, if not more, people than the human immunodeficiency virus (HIV), the deadly causative virus of AIDS.

The presentation of such grim figures as these usually precedes a prediction of even more awful events. But that is not the case for HBV. Life—and death—are full of surprises, and while it may be tempting fate to be too optimistic, it appears likely that within the next few decades this virus will be effectively controlled. It is even possible that it will be eradicated.

Although the diseases associated with yellow jaundice have been recognized since antiquity, the history of research on HBV is not long. The beginning of the “modern” period can be dated to the interval between the two world wars. By the mid-1960s, owing to the efforts of a dedicated and gifted cadre of scientists, there emerged a significant understanding of the clinical and epidemiological nature of the disease, a recognition that it was caused by a “filterable agent”<sup>1</sup>—a virus—and that there were at least two such viruses. In the mid-1960s my colleagues and I in Philadelphia began studies on a material we found in the serum of an Australian, a material that we referred to as “Australia antigen”; by 1967 we had found that it was part of the hepatitis B virus, and we introduced a useful diagnostic method for the virus that, in a relatively short time, essentially eliminated posttransfusion hepatitis due to HBV. In 1969, we invented a vaccine that, in its further development by the pharmaceutical industry, proved to be effective and safe.

Our early work stimulated a worldwide interest in the scientific community, and research in the field proliferated. Today a great deal is known about the virus; effective methods for detection and prevention are available; and there are even reasonably good treatments, along with an expectation that these may improve considerably in the future. As a consequence of the widespread application of the vaccine and other prevention programs, there has been, in several places, a striking decrease in the number of new HBV infections. In parts of Asia, where the vaccine programs were introduced more than ten years ago, the prevalence of carriers with HBV has dropped from about 15 percent to about 1 percent, and, in the impacted vaccinated group, the incidence of cancer of the liver (most of which is caused by chronic HBV infection) has decreased two-thirds from its previous level. If these results are confirmed, then HBV vaccine is the first “cancer vaccine.”

Basic research is often *Shandean*, a term coined in the novel *Tristram Shandy* (1759–67) by the Irish-born English writer Laurence

<sup>1</sup> The term used for an infectious agent that was known to be smaller than bacteria, and that would pass through a filter too fine to allow the passage of bacteria.

Sterne (1713–68).<sup>2</sup> In this comic novel, any trace of narrative order is subordinated to the free associations generated by the narrator and his characters. Events ramble from one apparent irrelevancy to another, but a strange sense of order nevertheless emerges. The novel also offers an interesting exploration of the quality of time: the description of an event takes far longer than the event itself. For example, the author tells of his own conception but gets so embroiled in the tale of his parents' ineptitude in initiating the process that it takes him three volumes to get himself born. Accounts of scientific research are often presented in a non-Shandean form suggesting that the process was planned in advance to follow a logical and ordered sequence from a body of known knowledge to a target that had been defined at the initiation of the project. A timetable appears to have been set, and landmarks on the way to the final goal established to monitor progress. Some scientific projects—particularly applied science with a definable goal—do follow this path, but many do not, especially problems in basic science whose objective is to find the explanation of a natural phenomenon. Science proceeds from one uncertainty to another, serially validating each sufficiently that the next step can be undertaken.

Gary Saul Morson, professor of Slavic languages at Northwestern University, is a literary commentator and critic, an authority on the great Russian novelists Dostoyevsky and Tolstoy. He has stressed that these authors did not want their characters or themselves restricted in their freedom of action; they desired, rather, that events over time—*Tempics*, as he called it—would determine outcome, and that the end could not be foretold in the beginning. *The Idiot* and several of the other great novels were written as serial pieces for a literary periodical. When writing the first chapters, the authors did not know the ultimate ending. Historic events that were included in the later chapters had not even occurred when the first chapters were written and published. The stories are not neat. An incident

<sup>2</sup> The historian and sociologist of science Robert K. Merton has elaborated on the theme of Shandean narration in his popular book on the origins of the phrase, attributed to Newton, "If I have seen farther, it is by standing on the shoulders of giants." R. K. Merton, *On the Shoulders of Giants: A Shandean Postscript* (New York: Harcourt Brace Jovanovitch, 1985).

recounted early in the novel may not figure in the later narrative, and not all events are incorporated into the final outcome. Similarly, in our story, things don't always pull together, even though an ordered reason was the predominant guide. But the story does have a pattern, and I hope it will emerge in this book. Don't expect *War and Peace*—but you may recognize some of the apparent confusion that permeates that novel.

There is a story told by a historian who for years had tried to interest his bright young daughter in his subject: bringing books home for her to read, telling her stories, and encouraging her to watch educational TV shows designed to stimulate the interest of the young in our collective past. Nothing moved her. Then, the family took a trip to Rome and spent a day wandering about the Forum gazing at the enormous ruined temples, markets, and palaces that bestrew this reserve in the center of the modern city. His daughter roamed the site by herself for most of the day and, in the evening—her imagination fired by all the possibilities suggested by the great ruins—asked her father, in wonderment, “What happened?” Her interest in history began on that day.

What happened with the discovery of the hepatitis B virus? My colleagues and I at Fox Chase Cancer Center in Philadelphia had a role in its discovery and application to medical practice, and I propose to tell you about it. I want to offer readers (both scientists and nonscientists, I hope) an account of the events that we took part in, and also to give some idea of how scientists work day to day. The scientist gets up in the morning, goes to the laboratory, the clinic, the field, and then—what transpires? I believe that there is insufficient knowledge in the general community of the methods and the processes that scientists use. There is a growing body of literature in this genre, much of it excellent, that helps to make our goals, possibilities, and motivations—what drives scientists—more transparent to those who are not scientists. Although science, particularly in America, is generally well received and often well supported, there is still a suspicion of its process and the resultant products. Industrial pollution, environmental degradation, nuclear weapons, biological and chemical warfare, and many other products of technology are seen as the baleful outcome of the scientific endeavor. One

has only to look at the portrayal of scientists in literature and the movies to see the concerns that are conveyed to the public. Mary Shelley's brilliant story of Victor Frankenstein and the Creature he (she) invented and fabricated is a classical tale often retold in print, on the stage, and in the movies. There is a fear in the public mind of creative arrogance, of efforts to mimic natural forms or even to outdo them. This is especially well illustrated in the movie and novel *Jurassic Park*, the Michael Crichton blockbuster. The molecular biologist who is responsible for the recombinant chemistry not only wants to create dinosaurs from the scraps of DNA obtained from an extinct dinosaur's blood found in the gut of an arthropod preserved for centuries in amber, but he strives to improve them. He wants them to grow more rapidly to provide a quick return on the investment of the venture capitalists, and to move more ponderously to fulfill the preconception the public has of dinosaur demeanor. This results in the fearsome outcomes so vividly told and shown.

I hope that the story presented here, along with the many other accounts of scientific research that are now available, will help to acquaint the reader with the process of scientific research and the motivations and generally amiable character of its practitioners.

The story about to be told has a Shandean character, particularly because, at its outset, we did not know we would discover HBV and apply the findings to practical medical and public health purposes. There are roughly three phases to the story that often overlap in time. During my medical school years and clinical house staff training (1947–55) I became impressed with the great variation among individuals and populations of individuals in their response to disease risks. Some became ill and others did not; some responded to treatment well and others poorly; some died and some lived. What were the reasons for these differences? Luck could account for some, but scientific explanations and, therefore, wholesome interventions should also be possible. This period is covered, more or less, in the first two chapters of the book.

The second phase began about 1956 when my colleagues and I started a systematic search for inherited biochemical and immunologic variation ("polymorphisms") in human populations and sought to explain how this inherited variation—"diversity" is the

word that is currently popular—interacted with a sometimes hostile environment. Underlying this program was the notion—in fact, the faith—that in due course we would identify inherited differences in susceptibility and resistance to disease, although at the outset we did not know what the disease would be. This portion of the story is covered in chapters 3 and 4, which also include a digression describing the research on physical biochemistry accomplished during my graduate school period. The third part of the story (chapters 5 to 11) begins in about 1965 when, as a direct consequence of our study of biochemical variation, we discovered the hepatitis B virus and invented the HBV vaccine. We shifted our research and dedicated our energies for the next thirty years to understanding how HBV operates and how this information could be used to prevent and treat the disease. Our research eventually turned back to its conceptual origins—the study of variation—and this is described in chapter 12. Conjectures on the future of research in the field—some not firmly rooted in solid data—are presented in the final chapter.

It would be inaccurate and misleading to give the impression that we had a set goal from day one; we did not. The story line isn't direct, but neither was the research—nor, for that matter, is life in general.

In the years following the identification of HBV, other hepatitis viruses—HAV, HCV, HDV, HEV, HGV—have been identified, and still more are likely to be found. Control of these viruses has also advanced considerably, although, in general, not as far as that of HBV. In the early 1980s, the tragic AIDS epidemic became apparent. HIV and HBV have many features in common. They both can be transmitted in human blood. HIV is a member of a class of viruses that can produce DNA from RNA—they are retroviruses. HBV is also a retrovirus, although in a somewhat different fashion from HIV and other “conventional” retroviruses. The epidemiology and methods of transmission have similarities, and many of the risk groups for HBV are the same as those for HIV. The histories of the two viruses have been intertwined in large part because of these similarities, and their research paths were often parallel. Unfortunately, it has not been possible, so far, to develop a vaccine for HIV, although this may happen in time. Lessons that have been learned

from HBV research have been and will continue to be of help in illuminating the complexities of HIV.

Prevention of a disease has great advantages over treatment; a goal of modern medicine is to keep people healthy and functional and allow them to live out their allotted times disease-free and in reasonable comfort. HBV vaccine is the first widely used vaccine to prevent a common cancer. Other viruses cause, in part or in the main, several uncommon and common cancers. Included among these are cancer of the cervix, cancer of the nasopharynx, certain forms of leukemia and lymphoma, and probably others. If the current HBV vaccination campaign against cancer of the liver continues to be as successful as the initial results have indicated, then it will be an inspiration to scientists to seek other vaccines to prevent other common cancers.

Hepatitis is a very important disease and has attracted outstanding investigators. I will refer to many of them during the course of the account, but I have undertaken to describe our role in the search for the hepatitis virus and its consequences and have not attempted to write a history of the entire research program. I hope that I have not slighted any of my colleagues, and I assure the reader that comprehensive reviews of past and present work are available.<sup>3</sup>

<sup>3</sup> See, for example, the WHO monograph *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, vol. 59, *Hepatitis Viruses* (Lyons: IARC, 1994), and W. Mura-skin, *The War against Hepatitis B: A History of the International Task Force on Hepatitis B Immunization* (Philadelphia: University of Pennsylvania Press, 1995).