

A microscopic image of cells, likely showing a virus. The cells are stained in various colors, including green, yellow, orange, and pink. The virus is a small, dark, spherical particle with a distinct outer shell and a lighter inner core, located in the upper right quadrant of the image. The background is dark, making the stained cells and the virus stand out.

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M.D.

VIRUS
HUNTING
AIDS, CANCER,
& THE
HUMAN RETROVIRUS:

A STORY OF SCIENTIFIC DISCOVERY

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Prologue

In marshy places little animals multiply, which the eye cannot see but they . . . enter the body through mouth and nose and may cause grave disease.

—Marcus Varro

The Roman writer who made this observation over two thousand years ago was, I imagine, the first person to make a connection between disease and what centuries later we came to call microbes. Though we now know that microbes have been linked with human biology for as long as we have been on earth, it was almost two millennia after Varro's astute guess that scientists had their first glimpse of these organisms and began to record their activity.

Far-reaching scientific advances inevitably await major technological breakthroughs, and it wasn't until 1677 that the Dutchman Anton van Leeuwenhoek perfected a lens powerful enough to allow us our first look into the world of microbes. Though Leeuwenhoek's lens-grinding techniques opened this new world to human investigation, neither he nor any of the many scientists of his time who used his lenses to study microbes made the connection to human disease. A century later, the Italian scientist Lazzaro Spallanzani demonstrated

that microbes reproduce themselves and that it is their growth that causes meat to decay. Yet even he did not suggest that they might be involved in human disease.

That was left to an amateur Italian scientist named Augustino Bassi (whom Barry Wood, the eminent infectious disease expert, called the founder of medical microbiology). Bassi first identified a microbe (in this case, a fungus) as the cause of a certain disease of silkworms and then offered the startling proposition that smallpox, cholera, and other human diseases are also caused by microbes. Around 1839, the German physician Johann Schönlein linked a human disease (of the skin) to a microbe (also a fungus). Soon thereafter, the marvelously analytical thinker Robert Koch of Germany and the passionate, equally brilliant Louis Pasteur of France made major advances that would alter the history of microbiology and, ultimately, of biology itself.

Working separately, Koch and Pasteur (and the schools that arose around them) discovered the microbial causes of the major infectious diseases of their time. In 1865, Pasteur identified in silkworms the first disease caused by a protozoan; in 1876, Koch was the first to convict a specific bacterial agent as the cause of a specific disease—anthrax of sheep, and in 1882, he was the first to describe and isolate the cause of a human *bacterial* disease—tuberculosis. From 1875 to 1895, Koch established his famous postulates for identifying causal agents of disease. He and the German school found bacterial causes for many other diseases. During the same twenty-year span, Pasteur discovered the principles of the vaccine.

The discovery of viruses soon followed. The plant virus known as tobacco mosaic virus was the first to be found—by the Russian biologist Ivanovsky in 1892 and, independently and with more accompanying insight, by Beijerinck in Holland in 1899. In 1898, the German bacteriologist Friedrich Löffler identified the first animal virus, the foot-and-mouth viral disease of cattle. The United States made its historical entry into microbiology in 1900, when the army surgeon Walter Reed and his group, by establishing the cause of yellow fever, were the first to discover a disease-causing virus in humans.

This was the romantic era of biomedical science. The personal courage of these scientists and their persistence in the face of almost continual frustration and disappointment benefited from an increased understanding of and reliance upon the scientific method. In time their efforts, though often excessively zealous and relying upon

human experimentation far riskier than anything we would allow today, led to the elucidation of the microbial causes and modes of transmission of many of the known infectious diseases.

The age of empirical antimicrobial therapy followed Paul Ehrlich's discovery in 1909 of his "magic bullet," Salvarsan, to attack the syphilis spirochete.* These discoveries and treatment breakthroughs fueled the imagination of science writers, novelists, and screenwriters, as well as providing the raw material for the classic work of popular science writing of that time—Paul de Kruif's *Microbe Hunters* (1926). For decades to come, this book would inspire many young readers to follow a career in science.

While de Kruif was writing about the romantic age of biomedical discovery, he probably knew little—if anything—of two pioneering experiments that would in time help refine our notions of infectious disease. These experiments, ignored by most scientists, were the first to suggest that certain animal cancers appeared to be communicable.

The first of these experiments was conducted at the turn of the century by two Danish researchers, Oluf Bang and Vilhelm Ellerman, who found that filtered extracts of chicken leukemic cells inoculated into other chickens reproduced leukemia. The culprit in the extract was not isolated at the time, but its ability, whatever it was, to move through certain filters suggested that it was smaller than the smallest bacteria then known—in other words, it was probably in the category of viruses.

A few years later, in 1911, Peyton Rous in New York isolated a microbe from a chicken with a sarcoma, a cancer of muscle tissue. He, too, showed that this agent could reproduce its disease when injected into another chicken.

At the time these experiments were being conducted and for several decades thereafter, no one, not even the researchers themselves, knew that these experiments were the first to study the effects on animals of a class of infectious agent that would play a profound role in infectious disease of the late twentieth century. These pioneering

*The magic bullet was also given the name "606," from its number in Ehrlich's sequence of experiments. (The popular 1940 movie *Dr. Ehrlich's Magic Bullet*, starring Edward G. Robinson, told the story of Paul Ehrlich's work.) When Salvarsan proved too toxic to humans, Ehrlich developed Neosalvarsan, still toxic to the spirochete but less so to humans. It remained the standard treatment for syphilis until penicillin was brought into clinical use.

cancer researchers had found an RNA tumor virus—that is, a virus with RNA as its genome and a distinctive way of reproducing itself once inside a cell, giving it the capability to cause serious disease in both animals and (as my laboratory was the first to show) humans. Not until the beginning of the 1950s, however, were scientists able to distinguish RNA viruses from DNA viruses. And not until the 1960s, and especially after 1970 when the RNA tumor virus was more fully characterized and renamed a retrovirus, did scientists reexamine these early-century pioneering experiments and begin to realize their significance. By the end of the century RNA tumor viruses, or retroviruses, would be recognized as one of the most important agents of infectious microbial disease in humans.

Prior to that reexamination and, to some extent, well after it, the prevailing views, held not without some scientific basis, had been that viruses did not cause cancers in humans and that RNA tumor viruses did not even exist in humans. After all, there was the indisputable fact that for decades scientists had looked for evidence of RNA tumor viruses in humans, to no avail. As late as the 1970s, the majority of scientists working with animal retroviruses in the laboratory simply had no interest in studying any role they might have in human disease, using them primarily as useful tools in basic molecular biological research.

In 1970, two scientists, working independently of each other, changed the nature of the debate about RNA tumor viruses by showing that in the process of replication, these special RNA viruses had the help of a unique enzyme that they alone, among all the RNA viruses, carried. With this enzyme, RNA tumor viruses went through an intermediate stage that converted their viral RNA to DNA, giving them the unique quality among the RNA viruses of being able to insert their own genome into the genome of cells.

This enzyme, reverse transcriptase, in effect gave these viruses permanent access to a variety of cell mechanisms, which they put to use for their own replication and often to a cell's detriment. As important, in time, that cell would go through its own normal process of division. When it did, it would then pass on to daughter cells the viral genes with which it had been infected. Thus infection by a retrovirus was virtually lifelong in the organism.

The two discoverers of this enzyme, Howard Temin and David Baltimore, won the Nobel Prize for their work in 1975. The signifi-

cance of their finding was immense both because it gave us new insight into how RNA tumor viruses reproduce themselves and because it provided an immediate explanation for how a class of RNA virus could permanently alter the DNA of cells and thus produce a cancer. Even more important, the discovery of reverse transcriptase overturned what was then known as the "central dogma" of modern cellular biology: namely, that DNA codes for itself or RNA and that RNA codes for protein, but that the reverse—from RNA to DNA—did not occur. The general name for these viruses was changed from RNA tumor viruses to retroviruses—an apt change, as we would soon learn that retroviruses can cause not only tumors but other diseases as well.

In 1970, while all of this new thinking about RNA tumor viruses and cancers was coming together, I was a young scientist looking for a new approach to the study of cancer. While the discovery of how retroviruses replicate had its most immediate impact on the "central dogma," for me it presented a practical laboratory breakthrough—one that might, in time, allow me to reopen the question of whether retroviruses could cause cancers in humans. I was interested in the question primarily as a cancer researcher (at just about this time, veterinarians were finding additional evidence of retroviruses causing animal cancers). But, in time, I came to realize that if some forms of cancer were caused by a retrovirus, they might be communicable, even though these viruses acted so slowly that it could take years for them to produce the disease. And if at least some forms of cancer were communicable, what about a number of other serious chronic diseases about whose cause we had no idea? The full spectrum of communicable disease might have been too narrowly defined.

Along with many other scientists, all of us working independent of one another, I decided to try to find out if retroviruses could indeed cause cancer in humans. To do this it would be necessary to find at least one retrovirus that caused at least one cancer in at least some humans.

Our search for the first cancer-causing retrovirus in humans would take place at a time when many scientists believed that the great age of medical microbiology had passed. At least some medical schools in the United States had already replaced their medical microbiology departments with "pure" molecular biology departments. Not sur-

prisingly, in at least some quarters the idea was being floated that serious global pandemics were a thing of the past, and some textbooks of the time suggested that global epidemics of microbial disease were not possible unless the microbe that caused the disease could be easily transmitted—for example, by fomites in a sneeze or cough, or orally, by contamination of food or other ingested matter. Thus, the work I embarked on was largely at the periphery of what were seen as the important questions for modern molecular biology.

Virus Hunting is the story of this work, which led to the discovery of the first cancer-causing retrovirus in humans (work completed by 1980), the discovery of a second shortly thereafter (by 1982), and the surprise discovery (in late 1983 to early 1984) that the causative agent in the most terrifying epidemic disease of the twentieth century—the disease we now call AIDS—is also a retrovirus, but a new kind.

Part I, “Some History Behind the Story,” sets the stage as I saw it. In chapter 1, I recount both my boyhood and youth and look at the individuals who shaped my special interest in biomedical research. In chapter 2, I discuss the origins of the National Institutes of Health, the peerless but now increasingly troubled government institution that is home to the largest gathering of biomedical scientists in the world. Chapter 3 is a scientific introduction to microbes.

Part II, “The Discovery of Cancer-Causing Retroviruses in Humans,” opens with the crucial early work on animal retroviruses (chapter 4). Chapters 5 through 7 pick up the story with the often exhilarating but surely thorny success of the Laboratory of Tumor Cell Biology, our lab at NIH, in finding two human retroviruses, finally demonstrating that there is such a thing as a human retrovirus and a cancer virus.

Part III, “The Discovery of a Third Human Retrovirus: The AIDS Virus,” covers the heady and explosive years when investigators in France and my co-workers and I identified the third known human retrovirus as the cause of AIDS. The tail end of this period—while we cultured the virus and developed the all-important blood test that could identify HIV-infected individuals and HIV-contaminated blood—was also the time when I began to be embroiled in the controversies that plague me to this day. The personal and professional strands of my life would become inextricably entwined, leaving me vulnerable to harmful misimpressions that were disseminated in some parts of the public press.

"A Scientist's Look at the Science and Politics of AIDS," which makes up the final section of the book, lays out the reasonable as well as the fanciful interpretations offered for the rapid spread of AIDS and answers the thirteen questions I have been asked most frequently about AIDS (chapter 12), follows the destructive path of this disease through an infected individual (chapter 13), explains the link to Kaposi's sarcoma (chapter 14), and presents the irrefutable evidence that HIV causes AIDS (chapter 15). Finally, in chapter 16, I discuss the medical and social possibilities for fighting the disease and some such efforts already under way, including the first steps toward the development of a vaccine.

All during this period I was head of the Laboratory of Tumor Cell Biology at the National Cancer Institute of the National Institutes of Health. The story reflects my memory and perceptions of how our work there proceeded. But it has been enriched by the recollections of many of my colleagues at the lab, whom I have quoted in certain chapters.

I suppose the book will turn out to have its share of both the virtues and the flaws found in most first-person accounts of dramatic or controversial periods in human history. But *Virus Hunting* is not my story alone. It is the story of many dedicated scientists—members of our own lab, contract collaborative workers, outside collaborators—who, through painstaking, sometimes dangerous work, isolated and characterized the first, second, and third human retroviruses and thereby made possible an understanding of the mechanism by which they cause disease at the cellular level in humans. Complicating our AIDS work was an acrimonious controversy involving legal, moral, ethical, and societal questions that soon spilled over into the world of scientific research and threatened to poison relationships between scientists, as well as between the research community and the general public.

My main intent in telling this story has been to portray the scientific process as it goes on in our time and to describe the process of discovery in biomedical research in at least one laboratory. As such, it is a story of how modern-day scientists, often collaborating and sometimes competing (even within one lab), dream, work, stumble, fall, recover, and dream again, of how the rhythms of nature and the cyclical pattern of success and failure that characterizes most human endeavors also influenced our search for understanding. I hope to

convey a little about our lives, more about our work, and most about our thinking.

Others have taken it upon themselves to write about our lab's work, particularly our role in AIDS. Some of this writing and reporting has been adversarial, on occasion outrageously so. To a large extent I have been the victim of nothing more sinister than my own unguarded frankness in talking to the press. I have learned to be more careful. But, more important, in the continuing dialogue that must take place between scientists and the public, I and other scientists have come to believe that the popular press is not always a disinterested medium for such communication. Indeed, this is one of the reasons I wrote this book.

But the subject of this book is scientific research, not public controversy about science or the role of the media vis-à-vis scientists and the public. I do discuss at the appropriate points how my lab interacted with others and what I did and said and thought both within the lab and in my dealings with other scientists. But these are my own recollections, not my response to those who have chosen to put their own spin on these events. I did not write this book to answer critics or to lament my being chosen as one of the objects of so much of the anger incidental to the suffering caused by AIDS.

That larger story needs to be told, and I hope it will be one day; but I am not the person to tell it. Properly told, it will become part of a much longer and complex story, one that takes into account, among other things, the nature of scientific discovery during a public health emergency; the role of advocacy journalism in a free society; what limits ought to be established on the ability of reporters to tie up the work of public employees through endless interrogatories submitted under the Freedom of Information statutes; the changing rules of biomedical science in the closing decades of the twentieth century; the nature of leadership at the public research institutes and what happens to science in the absence of such leadership; and the nature of competition between scientists and between scientific institutes.

Anyone attempting to write this story would also have to place it in the context of a broad questioning of the role of the scientist's right to pursue knowledge as scientists have traditionally pursued it—largely according to the rules that have been formulated by other scientists, with little input from the media, the government, or even the public.

In this context, it is relevant that during the 1980s a variety of biomedical research people and institutions found themselves and their work being questioned. This same period saw a new wave of suits brought against personal attending physicians. For the first time in memory, animal rights activists started to use force in their attempts to demand changes in research involving live animals. Research requiring the use of fetal embryo tissue suddenly became entwined in the abortion issue, the most controversial political issue of our day. The courts were asked to decide whether tissue from a leukemic patient belonged to the patient or to the researcher who had made scientific use of it. Two Nobel Prize winners were publicly accused by one of their postdoctoral Fellows of not giving him enough credit for the work for which they were recognized. The challenge by AIDS activists to the Federal Drug Administration's clinical trial rules for the testing of new drugs has been described as nothing less than a frontal assault on the power of the FDA to regulate which drugs should be offered to the general public.

Even the staid scientific journals found themselves in the hot seat: the long-standing rule that publication of findings in scientific journals will not be allowed if the findings have previously been released to the general public has caused new public debate about whether the benefits of this rule outweigh the possible dangers of delaying transmission of information of life-or-death importance to the public.

As for those of us in AIDS research, few scientists working in this area have not at one time or another found themselves criticized, shouted at, shouted down, ridiculed, or harassed. The motives of scientists working for the government-supported NIH seemed to be automatically suspect during this period, when it seemed to many that AIDS was not receiving the priority it deserved in medical research funding from the Reagan administration, something that had never happened to us in the more than fifteen years we spent working solely in cancer research.

I have tried in these pages not to shy away from discussing politics when politics entered the lab, as on the occasion of the French government's suit on behalf of the Pasteur Institute for a share of the patent money for the AIDS blood test. I have also tried to discuss openly and fairly those ways in which scientific competition can impede (though I think this happens rarely) and, much more often, aid scientific discovery. But I have attempted in such discussions to keep my purpose clear: not to inflame old passions or to one-up the others, but to make

my own contributions to a greater understanding of all that was, and remains, involved in such discussions.

Perhaps I should also say that this is not a book about AIDS as an illness. None of us has been insulated from the personal tragedy of seeing friends, relatives, colleagues, and acquaintances snatched in the prime of life by the ruthless disease called AIDS. But in my work on the AIDS retrovirus in the laboratory, I do not confront the individual victims of a dreadful disease. I deal with knowledge, with the science of retroviral disease. There are no patients in a research laboratory, no pain, no suffering, no disease, no death. Instead there are cells, viruses, and molecules; and the questions are scientific—not moral, not political, not even humanistic. Those looking here for a dramatic and emotional retelling of the international human tragedy that is AIDS must look elsewhere.

But science has a major role to play in the AIDS drama, and in my view, it is the most important one. And because individuals, with all the strengths and weaknesses that make us human, are critical to the success or failure of any endeavor, there should be a place for a scientist's discussion of the science involved in the solution of biomedical scientific problems, particularly one who has been involved in this area of research throughout the history of the disease.

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