

**Unit 2: Lesson 4 – Vaccine History and Research****Vaccinated: One Man’s Quest to Defeat the World’s Deadliest Diseases****Chapter 8: Blood**

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*“We had a process that would destroy all life forms.”*

-Maurice Hilleman

Excerpt from pp. 115-126

A few years before HIV first entered the United States, Maurice Hilleman began working on a new vaccine—not for HIV, which was still unknown, but for hepatitis. Because of the method he chose for making it, fear of AIDS would soon spread to fear of Hilleman’s vaccine. For almost two hundred years, researchers had used cells from monkey, chickens, mice, rabbits, and duck to make their vaccine. Hilleman was about to break new ground. He would be the first (and last) to use human blood to make a vaccine. He didn’t know until later that the blood was heavily contaminated with HIV.

Several viruses infect the liver, but by far the most common, the most severe, and the most feared is hepatitis B virus, which infects one third of the world’s population, about two billion people. Most people infected with hepatitis B virus recover completely. But not everyone recovers. Some people die of an overwhelming infection in a matter of weeks. Others have a persistent infection: one million people in the United States and more than three hundred million people in the world are chronically infected with hepatitis B virus. And most of them don’t know it. Victims of chronic hepatitis B are at high risk for two possible fates: dying of cirrhosis, a progressive destruction of the liver, or dying of liver cancer. Hepatitis B virus is the third most common known cause of cancer in the world. The sun, which causes skin cancer, is the first; cigarette smoking, which causes lung cancer, is the second.

Before Maurice Hilleman could make his hepatitis B vaccine, he had to capture the virus. When Hilleman had wanted to make vaccines against measles, mumps, or rubella, he simply swabbed the throats of children with those diseases. Unfortunately, hepatitis B virus is barely detectable in saliva. Blood, on the other hand, contains extraordinarily large quantities of the virus—about five hundred million infectious particles per teaspoon. But blood from people infected with hepatitis B contains more than just virus particles. It contains something that will ultimately lead to the eradication of hepatitis B virus.

Every virus has a different strategy for survival. To avoid provoking an immune response that would destroy them, chickenpox and herpes simplex viruses live silently,

latently, in the nerves. Many people initially recover from infection only to have these viruses re-emerge decades later in the form of shingles or herpes blisters. Influenza virus outsmarts the immune system by constantly changing one of its surface proteins, the hemagglutinin. People make antibodies to the hemagglutinins of influenza viruses one year, only to find that the antibodies don't completely protect them the following year. So influenza virus continues to thrive. Rabies virus, which lives in saliva, evades the immune system entirely. After entering the body through the bite of an infected animal, it slowly, inexorably travels up the nerves of the arm or leg to the brain, moving from one nerve cell to the next, never entering the bloodstream. Many people infected with rabies virus make rabies antibodies. But by traveling from cell to cell, the virus effectively hides from antibodies in the blood. When rabies virus finally reaches the brain—a process that takes about two months but can take as long as six years—death is inevitable.

HIV is probably the most heinous because it infects one particular group of cells: T cells, which are important in directing the immune system. When T cells are destroyed, the immune system is disabled. Worse, HIV evolves rapidly during infection; people make antibodies to the virus only to find that different HIV viruses have taken the place of the old ones.

Hepatitis B virus has a strategy for survival that is different from that of any other known virus. In order for hepatitis B virus to infect the liver, it must first bind to liver cells via a protein that sits on the surface of the virus. People make antibodies, against the viral surface protein to prevent the virus from attaching. If the virus can't bind to liver cells, it can't infect them. But hepatitis B virus fights back by making far more viral surface protein than it needs to make new virus particles, hoping that this excess surface protein will soak up antibodies from the blood and allow free virus to attach to liver cells. Hepatitis B virus is so committed to this method of survival that people infected with the virus have about five hundred quadrillion (500,000,000,000,000) particles of viral surface protein circulating in their bodies during infection. But hepatitis B virus's strategy of overproducing surface protein would eventually prove to be its Achilles' heel.

To make his hepatitis B vaccine, Hilleman followed a trail blazed by Baruch Blumberg, a researcher working at the Fox Chase Cancer Center in northwest Philadelphia. Blumberg, wasn't a virologist, an immunologist, or an infectious disease specialist. He was a geneticist. For the longest time, while studying hepatitis B surface protein, he didn't have the faintest idea of what he was looking at.

A stocky, powerful, outgoing native of New York City, Baruch Blumberg got a degree in physics from Union College in Schenectady, New York, before attending the College of Physicians and Surgeons at Columbia University. The single event that changed his life occurred in the early 1950s between his third and fourth years of medical school.

“Harold Brown, our professor of parasitology,” recalled Blumberg, “arranged for me to spend several months at Moengo, an isolated mining town accessible only by river, in the swamp and high bush country of northern Suriname [in South America].” Moengo was a melting pot inhabited by Javanese, Africans, and Chinese, as well as Hindus from India and Jews from Brazil. Blumberg found that people with different backgrounds had different susceptibilities to certain infections.

One infection common in Suriname was elephantiasis, caused by *Wuchereria bancrofti*, a tiny worm that blocks the flow of lymphatic fluid from the legs or genitals, causing massive, disfiguring swelling. Legs become coarse and thick, and scrotums become so swollen that victims have to carry them around in wheelbarrows.

*Wuchereria bancrofti* causes severe elephantiasis in some people, but mild or no disease in others. Blumberg found that susceptibility to diseases like elephantiasis could be directly linked to ancestry. He reasoned that people with different susceptibilities to a particular disease make proteins that served the same function—for example, to counteract the disease—but that these proteins were slightly different in their size or shape. They were thus known as *polymorphisms*, for “many forms.” Researchers had already found several protein polymorphisms. For example, they found that people have different proteins—A, B, and O—on the surface of their red blood cells. Blood group protein differences are important. If a person with type A blood receives type B blood, that person will make antibodies to the type B protein that destroy the transfused cells. The reaction can be massive and fatal. This is why doctors determine a patient’s blood type before transfusion.

Blumberg’s hypothesis that disease susceptibility is genetic is probably best shown by the origin and function of one specific type of hemoglobin, called hemoglobin S. Hemoglobin, a protein found inside red blood cells, also has several different forms. Fetuses and newborn babies have hemoglobin type F; most children and adults have hemoglobin type A; and some people, mostly of African descent, have hemoglobin type S. These three different hemoglobin proteins have the same function—to carry oxygen from the lungs to the rest of the body—but they are clearly different in size and shape. It isn’t a coincidence that hemoglobin S is found mainly in people from Africa. People with hemoglobin S are better able to resist malaria—a parasite common in Africa—than are those with hemoglobin A. When the malaria parasites enter red blood cells, hemoglobin S eventually causes cells to change shape, making it more difficult for the parasites to survive. Unfortunately, some hemoglobin S-containing red blood cells, which look like tiny sickles, have difficulty passing through small blood vessels. The genetic adaptation to malaria infection is called sickle cell disease.

Looking for protein polymorphisms, Blumberg examined blood from people who had received at least twenty-five blood transfusions. He reasoned that people receiving many blood transfusions would be more likely to have antibodies to proteins different from their own. In 1963 Blumberg found that the blood from a man with hemophilia in New

York City contained antibodies to a protein found in the blood from someone halfway across the world, an Australian Aborigine. He called the protein in the Aborigine's blood Australia antigen. (An antigen is a protein that evokes an immune response.) Blumberg found that Australia antigen was very rare in the United States—only one of every thousand people has it—but that it was quite common in tropical and Asian countries.

At this point, Blumberg didn't know what he had stumbled upon. Two years later, in 1965, Blumberg found to his surprise that Australia antigen was common in people with leukemia. He thought that the protein was either a marker for leukemia or part of a virus that caused leukemia. By 1967 he had found that Australia antigen, in addition to its presence in people with leukemia, was often present in the blood of Americans with Down syndrome. Again he thought that because children with Down syndrome were at higher risk for leukemia, Australia antigen was a marker for leukemia. But children with Down syndrome were more likely to have Australia antigen in their blood because they were more likely to have been infected with hepatitis B virus, the result of living in places like Willowbrook. Blumberg still hadn't realized that he had discovered a protein that was part of hepatitis B virus.

Eventually a virologist named Alfred Prince, working at a transfusion center in New York City, figured it out. In the early 1960s, Prince took blood from people before and after they received transfusions. In 1968, he found a patient who had hepatitis. Early samples of the patient's blood didn't contain Blumberg's Australia antigen, but later samples did. Prince concluded that "[Australia] antigen is located on a virus particle and the virus particle is etiologically related to some or all cases of serum hepatitis [soon to be called hepatitis B virus]." Prince was the first person to realize that Australia antigen was part of hepatitis B virus. Ten years later, in 1976, Baruch Blumberg won the Nobel Prize in medicine for discovering Australia antigen. His acceptance speech mentioned Alfred Prince briefly, parenthetically, and unfairly: "The Australia antigen association was also confirmed in 1968 by Dr. Alberto Vierucci, who had worked in our laboratory, and [that of] Dr. Alfred M. Prince."

Now that researchers knew that Australia antigen was a protein made by hepatitis B virus, they could begin to investigate the possibility of using it to make a vaccine. Saul Krugman, the infectious diseases specialist who had fed hepatitis virus to mentally retarded children at Willowbrook, performed the controversial experiment.

Krugman was born in the Bronx, the son of Russian immigrants. His family later moved to Paterson, New Jersey, near the home of Krugman's first cousin Albert Sabin. In high school, Krugman was a lively, outgoing member of the debate team, the drama club, and the student council. After high school, he attended Ohio State University until he could no longer afford it, dropping out after his junior year. He worked for a year, finally graduating from the University of Richmond and later the Medical College of Virginia. Two years later, during the Second World War, he served as a flight surgeon in the South Pacific, earning a Bronze Star. When the war ended, Krugman returned to New

York and took a position at the Willard Parker Hospital as an extern (an intern without salary). From this lowly rank he made a steady climb, eventually becoming a professor of pediatrics at the New York University School of Medicine and chairman of the department of pediatrics. Krugman was a latecomer to academic medicine. He didn't publish his first scientific paper until he was thirty-nine years old. Nevertheless, by the end of his career he had published two hundred and fifty more papers and was the coauthor of a leading textbook in infectious diseases, now in its eleventh edition. Krugman's colleagues remember him as honest, thoughtful, hardworking, and highly ethical: a wonderful father, mentor, and friend. But his hepatitis B experiments, although they paved the way toward prevention of the disease, later caused many in the media and the public to see him as a monster.

Knowing the work of Blumberg and Prince, Krugman took blood from a patient with hepatitis B virus infection, let it clot, took the serum, and injected it into the veins of twenty-five mentally retarded children, again at Willowbrook. He wanted to see whether serum from people with hepatitis contained hepatitis virus. Not surprisingly, it did. Twenty-four of the twenty-five patients became sick as the virus attacked their livers. Krugman concluded that "this study indicated that serum was highly infectious for susceptible individuals." One of the children sickened by the injection of live dangerous hepatitis B virus was still infected five years later, likely eventually to have either cirrhosis or liver cancer.

Now that Krugman had found an infectious serum that made children sick, he wanted to see if he could use it to protect them. So he took the infectious serum, diluted it in water, and heated it for one minute. Krugman hoped that by heating serum just below the boiling point he would kill hepatitis B virus but leave Australia antigen— hepatitis B surface protein—intact. He gave some children one dose of the vaccine and others two. Krugman then injected these children with untreated infectious serum, knowing that if the vaccine didn't work, virtually all would be infected with hepatitis B virus. The vaccine worked, protecting all of the children given two doses and half of the children given one dose. "It was a very, very exciting time," remembered Krugman. "But I really wasn't trying to develop a vaccine. Actually, all we did in our little laboratory, our little kitchen, so to speak, was [to] boil hepatitis B serum and water."

A local politician soon tempered Krugman's excitement. On January 10, 1967, Seymour Thaler, a New York state senator, took the floor of the senate chambers in Albany. Thaler said that "he had searched his soul and conscience" and that "the medical profession has presumed to act as God over the health and lives of the medically indigent." "I have the documentary proof," he said. "I have undergone a terrible inner conflict on whether to bring to the attention of the public that thousands of patients are being used daily as medical guinea pigs." Jack Hammond, director of Willowbrook, stood up to disagree: "We're not using the youngsters because they are mentally retarded, but because hepatitis is a particular problem at Willowbrook. We have the consent of the parents of every child enrolled in the program." New York State medical

officials supported Hammond, pointing out that because of Saul Krugman, hepatitis had been virtually eliminated from the school. Thaler wasn't impressed. He introduced a bill banning medical research on children. Although the bill died in deliberation, the effect of the bill and its publicity on Saul Krugman didn't. "That business with Senator Thaler was very difficult," recalled Krugman. "It happened when he ran for reelection. Politicians have to get publicity, so he invited the press to join him when he went to Willowbrook School and held a press conference and [made accusations] completely, of course, out of context. It was difficult."

Saul Krugman's studies at Willowbrook showed that there were two different types of hepatitis virus (A and B) that gamma globulin could prevent disease and that Australia antigen could be used as a vaccine. Humanity clearly benefited from his work. For his efforts, Krugman received many awards, including the John Howland award, the Bristol Award, and the Lasker Award. He was also elected to the National Academy of Sciences, one of the greatest honors that a scientist can receive from his peers. And he received a special citation from parents at Willowbrook for having helped their children. But in 1972, when Krugman received an award from the American College of Physicians in Philadelphia, he needed a police escort to protect him from nearly two hundred people who came to denounce him. Protesters, sickened that he had injected retarded children with a dangerous virus, would follow Saul Krugman for the rest of his life.

Krugman knew that his experiment at Willowbrook was only the first step. "I don't like to call it a vaccine," he said, "because it really wasn't a vaccine. Our finding was serendipitous. It demonstrated that a vaccine might indeed be developed. What was needed then was for the vaccine manufacturers, with their highly sophisticated technology, to follow up our lead." Blumberg had found Australia antigen. Prince had shown that Australia antigen was hepatitis B surface protein. And Krugman has shown that antibodies to the surface protein protected children against hepatitis B virus infections. "Now all the bells were ringing," recalled Hilleman. "Because all a vaccinologist needs is an antigen. I had to find out [first] whether or not blood from hepatitis B virus carriers had enough Australia antigen [for commercial use] and, second, whether that blood could remain safe."

In the late 1970s, to get enough hepatitis B surface protein for his vaccine, Hilleman sought out homosexual men and drug users, groups at the highest risk of hepatitis B infection. (Many of these people lived in flophouses, stairwells, doorways, and fire escapes in the Bowery, one of the New York City's most notorious neighborhoods.) Then he began a seemingly impossible task. Hilleman took blood loaded with hepatitis B surface protein, live dangerous hepatitis B virus, large quantities of other blood proteins and—unknown to Hilleman at the time—HIV, and purified it so that only hepatitis B surface protein remained. He had no previous studies to guide him, no precedent for this kind of work.

Initially Hilleman decided, as had Krugman before him, to heat the blood. "The program went off in two different directions," re-called Hilleman, "one of which I called Klink's Clunk. Klink was an engineer here at Merck. I told him I wanted him to build a Clunk. And that would be a continuous flow system into which we would put highly purified hepatitis B plasma, and we would pass it through a pipe with hot water, then past an ultraviolet light, and [then] into a pool of formaldehyde. That damn thing was so technical because we had to have constant flow: if we were going to put it into hot oil, everything had to be [processed very quickly]. But Klink's Clunk really hadn't significantly materialized before we developed a chemical process."

Klink's Clunk failed, so it was on to plan B. Hilleman decided to use three different chemicals to treat the blood. He started with pepsin, an enzyme that breaks down proteins. Hilleman hoped to destroy blood proteins, such as gamma globulin, that were present in large quantities, but he didn't want to destroy the hepatitis B surface protein. It worked. "For some reason pepsin didn't destroy [Australia] antigen," recalled Hilleman; "in fact the stuff that came out was almost totally pure." Hilleman found that pepsin reduced the number of infectious hepatitis B virus particles in blood one hundred-thousandfold. But he knew that such a reduction might not be enough to destroy every last virus particle. So he added a second step: urea. A product of protein metabolism, urea is present in large quantities in the urine of mammals (hence its name). Like pepsin, concentrated urea also destroys proteins. Hilleman used urea because it destroyed prions, a particular group of proteins that might also be present in human blood and that were dangerous to humans.

In the mid-1950s a researcher named Carleton Gadjusek traveled to New Guinea to study kuru, a disease characterized by a slow but relentless descent into dementia. Gadjusek found that the disease occurred mostly in cannibals who ate human brains. At first, Gadjusek and others thought that the disease was either genetic or caused by a virus. But neither theory was correct. Kuru was caused by unusual proteins called proteinaceous infectious particles, or prions. Mad cow disease, caused by eating meat contaminated with infected brains or spinal cords, is also caused by prions. And Creutzfeldt-Jakob disease, a similar ailment, although not caused by eating contaminated meat, is also caused by prions. When Hilleman made his hepatitis B vaccine, he was afraid that blood might be contaminated with prions. "I'll tell you one thing that really worried me at the time, and that was Creutzfeldt-Jakob," recalled Hilleman. "This disease was known to be infectious. It had been shown, quite uniquely, that urea would destroy [prions]. We used [urea] and had a pretty good reason to believe that there would be no problem."

Hilleman wasn't finished. He wanted to add one more chemical to destroy any contaminating viruses. So he picked the one that had been used successfully by Jonas Salk to kill polio virus: formaldehyde. Polio virus, like hepatitis B virus, was difficult to destroy, but formaldehyde readily destroyed both.

Now Hilleman had his method: he would treat human blood with a combination of pepsin, urea, and formaldehyde. He knew that each of these treatments caused a one hundred-thousandfold decrease in hepatitis B virus; the combination of the three caused a quadrillionfold (1,000,000,000,000,000) decrease. Hilleman didn't know whether his method would destroy all other contaminating viruses, so he carefully tested representatives of every virus known: viruses similar or identical to rabies, polio, influenza, measles, mumps, smallpox, herpes, and the common cold. These viruses cause infections of the brain, spinal cord, liver, lungs, nose, throat, and intestines. Hilleman's chemical treatments completely destroyed every one of them. "[I thought] that if we could show that each step could kill surrogate viruses," recalled Hilleman, "a whole bunch of different viruses, then we had a process in which viruses would be deader than dead. A process that would destroy all life forms."

As it turned out, hepatitis B surface protein was quite hardy. While the combination of chemical treatments destroyed other proteins in blood like gamma globulin, the hepatitis surface protein remained intact. Hilleman used a series of filtration steps to further purify his vaccine. In the end, Hilleman's blood-derived hepatitis B vaccine was virtually 100 percent pure hepatitis B surface protein—a technical miracle. But the road to a final product wasn't easy. "This was a precedent," recalled Hilleman, "and it really took a lot of god-damned-guts to take Merck down that trail. You can imagine the progress that we made. It was just about a damned zero data base [to start]. Shall we drop it this week, or should we wait another week? We were walking around in the dark or in the mud. This was one big gamble, I'm telling you."

In the late 1970s Hilleman didn't test his chemical inactivation method to determine whether it killed HIV because HIV hadn't been discovered yet. Harvey Alter, a microbiologist who worked with Baruch Blumberg, remembered that "Hilleman was very careful about making the vaccine. He inactivated it in many more ways than were absolutely necessary. As it turned out, it was a great thing because then AIDS came along and scared everybody to death about taking vaccines. But he had done all the right things to kill the AIDS virus, even if he didn't know it was in there."

Hilleman had to convince people that a vaccine made from the blood of intravenous drug users and homosexual men was safe. "You can go ahead and [take a protein]," he said, "and you can purify it, and you think you have a way of inactivating it, but you're still pretty much in the area of faith. You still don't know the potency, the safety, or the efficacy." Hilleman had trouble getting permission from the FDA to test his new product. Then he ran headlong into the same man who had tried to torpedo Stanley Plotkin's rubella vaccine, Albert Sabin, a respected virologist whose opinions continued to influence researchers and regulators. "We had to get [permission from the FDA], and we had trouble," recalled Hilleman. "What do you think happened? Sabin hears about it, says that [our] vaccine will not be used in any human being. Sabin said that if there was a lawsuit, he would go to court to testify against us. He would sue Krugman [his first cousin] if there were any problems with the studies. My feeling was, 'Screw you, Albert.'"



We went to see John Seal [at the NIH]. He advised us against using our [blood-derived] vaccine. He said, 'You know Albert says he's going to go public.' We had futzed around for about one year. I told Saul [Krugman] that I couldn't wait any longer, that I was going to go ahead and put this into people."

Hilleman knew that he would have a tough time convincing people to try his vaccine. So he turned to the one group he was certain would take it—midlevel executives in his own company. "I went to a meeting for marketing, sales, production, and research," recalled Hilleman, "and I headed up the meeting. And I said, 'Look, guys, our next product is going to be a hepatitis B vaccine, but I need to have volunteers.' I said that I could not use lab people because if any of us came down with hepatitis B, that would be the end of the product. I said, 'Here are the consent forms. Just sign these and I'll collect them after the meeting, and then I'll figure out who are the chosen people.' " Hilleman soon found that he hadn't been very persuasive. "There wasn't a damn one of them that sent in the form," he said. At the next meeting Hilleman made it clear that the consent form didn't contain "No" as an option. "I said, 'I need volunteers, damn it. Just decide who among you are going to take this vaccine. Give yourselves a little bit of time to regain your senses.' " Joan Staub, one of those asked to take the vaccine, remembers things differently. "Consent forms? What consent forms?" she asked. "We got that vaccine because we had to get it. If Hilleman told you to do something, you did it." Staub learned months later where the blood had come from and that there was a possibility that it might be contaminated with HIV. "We were scared to death," she recalled. "I thought I was going to die. Maurice pulled us all into one room and had to explain to us over and over again about the inactivation process and that we were going to be OK."

Excerpt from pp 136-140.

Maurice Hilleman's blood-derived hepatitis B vaccine, licensed by the FDA in 1981, was on the market until 1986, but doctors were reluctant to use it. They remained concerned about the source of the blood, unconvinced by the science. "When we brought [the vaccine] onto the market, we had one hell of a time," recalled Hilleman. "The doctors and the nurses did not want to be vaccinated with human blood." Hilleman knew that his method of inactivation killed all known human viruses. But he also knew that asking physicians to understand the science of viral inactivation was asking a lot. "Chemicals are chemicals," he said. "It doesn't matter where the blood comes from. But it took a really enlightened person to understand the story."

Ironically, Hilleman's blood-derived hepatitis B vaccine, made from the most dangerous starting material ever used, was probably the safest, purest vaccine ever made.

But because clinicians in the United States were uncomfortable using a vaccine made from human blood, Hilleman had to find another way to make it. (Although Hilleman's blood-derived hepatitis B vaccine is no longer made by manufacturers in North America

or Europe, it is still made by several companies in Asia.) Fortunately, in the early 1970s, two researchers eating lunch at a delicatessen in Hawaii struck a deal that gave Hilleman the technology he needed to make another hepatitis B vaccine. Its creation would also help to usher in the age of genetic engineering.

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Herbert Boyer and Stanley Cohen started a revolution in biology. Boyer was born in Derry, a dark, industrialized corner of western Pennsylvania best known for its mines, railroads, and quarterbacks; Jim Kelly, Joe Namath, Johnny Unitas, and Joe Montana all played high school football in western Pennsylvania. Boyer also played football as an offensive lineman. But Boyer's football coach was also his science teacher, and his coach's passion for science influenced Boyer more than his passion for football. After high school, Boyer studied biology and chemistry at St. Vincent's College in nearby Latrobe, Pennsylvania, followed by graduate studies at the University of Pittsburgh and postgraduate work at Yale. Then he traveled west, arriving in San Francisco at the height of the 1960s counterculture. With a broad round face, impish smile, thick walrus-like mustache, and a wardrobe of leather vests, blue jeans, and wide, open-collared shirts, Herbert Boyer looked like the rock musician Jerry Garcia from the Grateful Dead. And, like Garcia, he was active in the civil rights movement and vigorous in his protests against the war in Vietnam.

But Boyer had come to California to pursue his love of science, not the counterculture. He took a job as an assistant professor of biochemistry at the University of California in San Francisco. By 1969 *Escherichia coli*, or *E. coli*, a common intestinal bacterium, had caught his attention. Boyer found that *E. coli* made enzymes that neatly and specifically cut DNA. In 1972, while he was in the middle of these studies, Boyer traveled to Honolulu for a scientific meeting. There he met Stanley Cohen, a scientist from Stanford who was also working on bacteria. Cohen had found that some bacteria resisted the killing effects of antibiotics, while others didn't, and that bacteria could transfer this resistance to bacteria living next to them. Then Cohen discovered how they did it. Bacteria carried the genes for antibiotic resistance on small circular pieces of DNA that he named plasmids. Plasmids were promiscuous, easily moving from one bacterial cell to another.

At the Hawaii conference, Boyer and Cohen were each intrigued by the other's work. They decided to meet later that evening. Sitting over corned beef and pastrami sandwiches, they had an idea for how their research could be combined. To test it, they performed an experiment that would generate four hundred product licenses from the FDA, form the basis of fourteen hundred biotechnology companies, and launch an industry with annual revenues of \$40 billion. Cohen took Boyer's DNA-cutting proteins, cut a plasmid DNA that contained one antibiotic-resistance gene, and inserted a gene that resisted a different antibiotic. Then the two researchers repaired the plasmid so that it again formed a circle. Now the plasmid had genes that resisted two antibiotics.

Cohen reinserted this new plasmid into a bacterium and found that they had created a new bacterium that could now resist killing by both antibiotics. Boyer and Cohen reasoned that any gene, even human genes, could be inserted into bacterial plasmids. Every time these genetically engineered bacteria reproduced and made their own proteins, they would also be making human proteins; bacteria could become tiny factories that mass-produced a wide variety of human products. The new field of research launched by Boyer and Cohen was called recombinant DNA technology, or genetic engineering.

The value of this invention wasn't lost on a venture capitalist named Robert Swanson, who called Boyer and asked to meet him in a San Francisco bar. There, the twenty-nine-year-old Swanson and forty-year-old Boyer drank beer and discussed the commercial value of synthesizing human proteins in a laboratory. On paper napkins, they sketched out plans for the first biotechnology company based on genetic engineering. Boyer named it Genentech, a contraction of *genetic engineering technology*. When Genentech went public in 1980, the stock had the most dramatic escalation in the history of Wall Street, raising more than \$38 million in capital and making multimillionaires of its founders. Later that year, Boyer's picture was on the cover of Time magazine under the heading "Shaping Life in the Lab: The Boom in Genetic Engineering." Genentech's first product was human insulin. No longer did insulin have to be purified from the pancreas of cows and pigs; it could be made by bacteria in a laboratory. Later Genentech made proteins that helped children grow, broke down clots in the arteries of heart attack victims, and helped people with hemophilia clot their blood. Without having to rely on human blood to supply the clotting factors they needed, people with hemophilia were no longer at risk for HIV from blood transfusions.

But Boyer's and Cohen's studies also precipitated fears among scientists and the public that genetic engineering was an invasion of humanity into the realm of God. A Time magazine cover in the 1980s titled "Tinkering with Life" showed a DNA molecule surrounded by several white-coated scientists with hammers and rulers. At the head of the DNA was a fanged snake.

Merck scientists realized that Boyer's and Cohen's discovery could be used to make a hepatitis B vaccine without using human blood. They recruited a molecular biologist working at the University of California in San Francisco, William Rutter. Using Boyer's DNA-cutting enzyme, Rutter removed the surface protein gene from the virus and inserted it into one of Stanley Cohen's bacterial plasmids. When the bacteria reproduced, they made large quantities of hepatitis B surface protein. But Rutter and Merck found, much to their dismay, that the surface protein made by the bacteria didn't induce an immune response in animals. So they decided to try something else, soliciting the help of Ben Hall at the University of Washington. Hall used common baker's yeast instead of bacteria. Hilleman found that the hepatitis B surface protein made in yeast

induced protective antibodies in chimps and, later, in people, so he used this system to make the next hepatitis B vaccine.

On July 23, 1986, the FDA licensed Merck's yeast-derived recombinant hepatitis B vaccine. The vaccine is still used today.

By the late 1980s, the hepatitis B vaccine had been used by less than 1 percent of the world's population. But between 1990 and 2000, hepatitis B vaccine usage increased to 30 percent. By 2003, more than 150 countries used the vaccine, and the impact has been dramatic. In Taiwan, hepatitis B vaccine has caused a 99 percent decrease in the incidence of liver cancer. In the United States, the incidence of hepatitis B virus infections in children and teenagers has decreased by 95 percent. Furthermore, because hepatitis B virus infects fewer people, the hepatitis B vaccine has dramatically increased the number of potential liver donors. "Hilleman's heroic role in controlling the hepatitis B virus scourge ranks as one of the most outstanding contributions to human health of the twentieth century or any century," recalls Thomas Starzl, a pioneer of liver transplantation. "From my parochial point of view, Maurice removed one of the most important obstacles to the field of organ transplantation."

Hilleman ranked the hepatitis B vaccine as his company's greatest single achievement: "We made the world's first hepatitis vaccine, the world's first anticancer vaccine, the world's first recombinant vaccine, and the world's first vaccine made from a single protein." If the worldwide use of hepatitis B vaccine continues, chronic infection with the virus will be virtually eliminated, and in thirty to forty years, so will consequent cirrhosis and liver cancer.