A Report

The Unpredictable Payoffs of Basic Research

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THE UNPREDICTABLE PAYOFFS OF BASIC RESEARCH

by Maya Pines

How an Australian aborigine and the curiosity of a geneticist led to the discovery of hepatitis B virus and the cleaning up of blood banks, saving thousands of lives every year.

How this led to the discovery of non-A, non-B hepatitis. How it led to a vaccine against hepatitis B, which may also protect against primary cancer of the liver.

How this may lead to.....

INTRODUCTION

The primary mission of the National Institute of General Medical Sciences (NIGMS), a unit of the National Institutes of Health, is to fund basic research in areas that underlie all medical investigation. Discoveries in cell and molecular biology or genetics, for instance, can be applied to fighting a wide variety of diseases.

The link between basic research and medical advances is not always clear. The case history that follows is designed to illustrate the processes by which basic discoveries are made and become applied to medical problems. It was chosen because the story of hepatitis B--from basic discovery of a suspicious antigen to the ultimate prevention of the disease--is almost complete, and the research involved is still bearing fruit. The events described here are so recent that the scientists who played key roles in them are still active in the field and have contributed their own accounts to this story.

The symptoms come on rapidly, with fever, chills, fatigue, nausea, and abdominal pain, followed, in many cases, by yellowing of the skin--the classic signs of acute hepatitis, inflammation of the liver.

Hepatitis strikes close to half a million Americans every year. It can be incapacitating; sometimes it is fatal. It has been known since antiquity. Yet until 1963, researchers were greatly frustrated by this disease. There was no cure for it, no prevention, and no way of studying it effectively, since no trace of the viruses which were presumed to cause hepatitis could be found.

As often happens in medicine, the discovery that revolutionized the study of hepatitis came from an entirely unexpected quarter. It did not grow out of "targeted" research on hepatitis, but out of research on more fundamental questions about susceptibility to disease--such questions as: Why do some persons who are exposed to infection succumb to disease, while others, in the same environment, remain in good health? Why do some patients recover rapidly, while others die?

Baruch S. Blumberg, a medical researcher with an interest in human genetics, had been pursuing such basic studies off and on for thirteen years, when in 1963 a drop of blood from an Australian aborigine caught his attention. No other blood sample had ever reacted in the same way to tests he conducted at the National Institutes of Health in Bethesda, Md. Doggedly, he followed this lead through many twists and turns. Although at first it led him to some blind alleys, within three years it brought him to the discovery of the hepatitis B virus--the key to understanding various forms of hepatitis. His discovery opened up many different lines of research and led to an experimental vaccine against hepatitis B, which may yet prove to be the world's first vaccine against a human cancer.

Along the way, Blumberg won a Nobel Prize. As he made clear in his Nobel Prize address in 1976, however, "At the outset we had no set views on where this path might lead...I could not have planned the investigation at its beginning to find the cause of hepatitis B."

The Australia Antigen

Hepatitis was the furthest thing from Blumberg's mind, in fact, when he made the observation which led him on this zigzag trail. He was looking for new "polymorphisms"--genetic variants which are maintained over generations, probably because they give the bearers some selective advantage. About 120 different polymorphisms have been discovered so far, including the well-known ABO blood groups and the Rh factor. But these are only the tip of the iceberg, for it has been estimated that many thousands of polymorphisms exist in humans.

Blumberg reasoned that his best chance of finding such variants in human blood would be among relatively isolated populations, and the more exotic the better. So while at Oxford, England, he studied the blood of Basques and Nigerians, identifying several inherited differences in their sera (the fluid part of their blood). Later on he focused on Eskimos, Indians and Micronesians, and also carried on a long-term study of Australian aborigines together with an Australian colleague, Robert Kirk, who sent him many samples.

"We wanted to see whether inherited differences in the components of blood were related to differences in susceptibility to disease," he explains. "We assumed that, in due course, such a relation would be found, at least for some of the inherited differences, but first we had to find genetic differences between people."

In 1960 Blumberg was working in the geographic medicine and genetics section of the National Institute of Arthritis and Metabolic Diseases at NIH. Together with an associate, Anthony Allison, from the National Institute for Medical Research, London, he decided to give his research a new twist by studying the blood of patients who had received a large number of transfusions. On the theory that blood serum contains many polymorphic proteins, the researchers thought that some of the proteins in the blood which these patients had received would differ from the proteins which they had inherited. And any time that a body is challenged with a foreign substance--a virus, a bacterium, a chemical, or a different kind of blood cell or protein--it responds by manufacturing antibodies against the foreign substance. Such antibodies are extremely specific: they bind precisely to the substance, or antigen, which stimulated their production, making it easier for the body to destroy this antigen. Blumberg and Allison hypothesized that people who had received at least 25 transfusions because of various blood diseases were particularly likely to have developed antibodies against some serum proteins in the donors' blood.

To test this hypothesis, the researchers used a technique of agar gel diffusion which had been developed by Orjan Ouchterlony of the Gothenburg University, Sweden, to detect antigen-antibody binding. They coated a glass slide with agar, a gel, and placed some serum from a patient who had received many transfusions in a well in the center of the slide. The serum diffused slowly through the agar gel. So did samples of six normal persons' sera, which were placed in six surrounding wells. If any components of the normal sera reacted with antibodies from the central sample, a line of white deposit called precipitate would develop where the two diffusing serum samples met.

This actually happened on the fourteenth try, with blood serum from a man in Wisconsin who had had many transfusions to treat his anemia. His serum contained an antibody against certain lipoproteins--compounds containing lipids (fats) and proteins--in the other serum samples, and formed a line of precipitate when exposed to them. This antibody's ability to recognize certain lipoprotein variants rapidly became useful to people doing genetic and, in a few cases, legal studies.

Encouraged by this success, Blumberg continued to look for unusual antibodies in the sera of people who had received large numbers of transfusions, "on the principle that this approach had resulted in one significant discovery and that a further search would lead to other interesting findings," he explained.

Meanwhile, at the NIH Blood Bank, Harvey J. Alter, a hematologist, had been using similar techniques for a different reason: he wanted to find out why certain patients developed fever, chills or rashes after blood transfusions. He thought these people might be suffering from reactions against certain serum proteins in the donated blood. When he learned that Blumberg, too, was looking for antibodies in the blood of patients who had received many transfusions, he went to see him and they decided to collaborate.

Methodically, they tested each serum sample from a frequently transfused patient against panels of sera from normal people of widely varied origins, taken from Blumberg's collection. If a patient's serum showed any reaction at all, it generally reacted with more than half (and up to 90 percent) of the 24 sera in these panels. In 1963, as Blumberg and Alter were studying the blood of a hemophilia patient, a line appeared in reaction to only one of the sera on the panel—and that serum came from an Australian aborigine.

"At that point we had an antigen, but we didn't know what it meant," recalls Alter. "We decided to see whether it existed anywhere else. We knew the hemophilia patient's antibody could detect this antigen, and we began to screen many different populations."

The researchers tested the hemophiliac's serum against thousands of serum samples over several months. Among normal American blood donors, they found, only one in 1,000 had the new antigen, but among patients with leukemia, one in 10 had it, and this was also true for people who had received many blood transfusions because of thalassemia, a hereditary disease which produces severe anemia.

Blumberg, Alter and an associate, Sam Visnich, soon wrote up their observations for the Journal of the American Medical Association in a paper entitled "A 'New' Antigen in Leukemia Sera." They postulated that the "Australia antigen"--named in honor of the aborigine's homeland--was linked to leukemia either as a predisposing factor, or as a result of the disease, or through some virus which might be the cause of leukemia. They considered studying the Australia antigen under an electron microscope to see if it looked like a virus, but did not do so at that time.

Blumberg left NIH to join the Institute for Cancer Research at the Fox Chase Center in Philadelphia, and Alter went to Seattle to do his second year of residency in medicine.

"Had we actually done the electron microscopic studies then, we might have advanced research by at least four years," muses Alter, who is now back at the NIH Blood Bank as chief of the immunology section. "But there were so many lines of research to follow—you couldn't follow them all!" In his opinion, Blumberg deserves credit precisely for "pursuing and pursuing that single finding about the Australia antigen for years, when it could have been dropped at any point."

In Philadelphia, Blumberg came up with the idea that people who had an inherited susceptibility to developing leukemia would also be more likely to have the Australia antigen. Since children with Down's syndrome (mongolism) run a particularly high risk of developing leukemia, he began to test the blood of Down's syndrome patients in a large institution in New Jersey. It turned out that a large proportion—about 30 percent—of these patients did have the Australia antigen. This was a much higher frequency than among other mentally retarded patients in the same institution, and the result seemed to support his hypothesis. A second test of this hypothesis, in a large institution in Pennsylvania, confirmed his results.

However, when Blumberg tested the same hypothesis a third time, among children with Down's syndrome who lived at home with their parents, he did not find any trace of the antigen in their blood. Because of this result, the hypothesis had to be rejected.

Some scientists suggested that the findings of this third study, done on children who lived at home, cancelled out those of the first two studies—and that the net result was zero. But Blumberg viewed all these findings as the raw material for a new hypothesis. Since people who live in institutions are much more likely to become infected by various agents than people who live at home, he hypothesized that (1) the Australia antigen is associated with an infectious agent, and (2) because of a genetic abnormality, people with Down's syndrome are more likely than other mentally retarded patients to become infected with this agent when exposed to it.

Therefore, he began to study some of the factors associated with Down's syndrome which might make these people more susceptible to infection. (As has been learned in recent years, several defects in these persons' immune systems are involved.)

In the midst of these studies, Blumberg and his colleagues at the Institute for Cancer Research, W. Thomas London and Alton I. Sutnick, heard some intriguing news. A 12-year-old boy with Down's syndrome who had had no trace of the Australia antigen in his serum when he was first examined in the state institution suddenly showed signs of this antigen in his blood a few months later. Until then, the presence or absence of Australia antigen had seemed to be a permanent characteristic, much like a genetic trait. Yet there was young James Blair, who apparently had just developed this "new" protein in his blood. Since many proteins are produced in the liver, the researchers did a series of liver chemistry tests on him. To their suprise, they found that James had contracted a form of hepatitis.

At this point it became crucial to test the hypothesis that Au (the Australia antigen) was associated with hepatitis. By the end of 1966, Blumberg had not only found such an association, but had also raised the possibility that Au might be the cause of the disease. Then a technician who had been working on Au in his lab, Barbara Werner, began to feel ill. Being fully aware of the relationship between Au and hepatitis, she tested her own serum for the presence of Au--and found it positive. She subsequently developed hepatitis, and recovered. "This was the first case of viral hepatitis diagnosed by the Au test," Blumberg recalls.

The original paper on hepatitis by Blumberg and his colleagues did not receive wide acceptance. There had been too many erroneous claims about hepatitis viruses by other scientists who thought they had found the cause of the disease and had been proved wrong. A second paper, in which the group extended its findings, was initially rejected for publication on the grounds that it proposed another "candidate virus" for hepatitis, and that there were already many of these. Nevertheless, the association between Au and hepatitis was soon confirmed by a Japanese scientist, Kazuo Okochi, and others, particularly by Alfred Prince of the New York Blood Center.

Unlike Blumberg, Prince is a virologist. He had been interested in hepatitis for about twenty years. While doing his military service in Japan in the early 1960's, he had looked for evidence of a hepatitis virus in the livers of soldiers who had contracted the disease, which is prevalent in the Far East. Although he had actually found some evidence of antigens that might be related to an infectious virus, nobody followed up on in his discovery. It was a time of great discouragement among researchers on hepatitis.

Cleaning Up the Blood Banks

The fact that hepatitis can be contagious had been obvious for centuries. Wars breed epidemics of hepatitis, and so do crowded conditions. Until the middle 1940's, however, doctors could not distinguish between different kinds of hepatitis. At that time, a series of international studies with human volunteers demonstrated that "infectious hepatitis" (now known as hepatitis A) was caused by a virus. The disease was transmitted by contaminated food or water, or by direct person-to-person contact, and had an incubation period of two to six weeks.

Another form of hepatitis was also recognized: "serum hepatitis" (now known as hepatitis B). This, too, was thought to be caused by a virus, but it was believed to be generally noncontagious, except through injection of contaminated blood. For example, large numbers of persons who were inoculated with vaccine against yellow fever developed hepatitis four months after the injections; this was later traced to some human blood serum which had been incorporated in the culture medium during the production of the vaccine. This form of hepatitis had a longer incubation period than the other—two to six months—and was more severe.

Unfortunately, it seemed impossible to isolate--and thus study--the infectious agents which appeared to be responsible for these diseases. Try as they might, researchers could not make these agents grow consistently anywhere--not in laboratory cell cultures, nor in guinea pigs, hens' eggs, hamsters, rabbits, mice, rats, canaries, pigeons, dogs, cats, horses, sheep, and not even in such nonhuman primates as baboons, chimps, marmosets or monkeys. As all these efforts ended in frustration, scientific journals lost interest in the virus research.

Nevertheless, Prince continued to work on hepatitis when he returned to New York. There he met Blumberg, who told him about the Australia antigen. In late 1966, the two men decided to work together to see whether the Australia antigen was part of a virus. The collaboration soon broke up, but Prince started an experiment which was to confirm the association between Au and hepatitis.

Knowing that at least one in ten patients who received blood transfusions would come down with hepatitis, Prince wanted to show that the antigen appeared in their blood during the incubation period of the disease, before they had any symptoms of illness: this is how it happens in most viral diseases. The New York Blood Center, where he worked, was a perfect place to follow up patients who received transfusions.

Under a grant from the National Heart, Lung, and Blood Institute of NIH, Prince began taking blood samples from certain patients at regular, two-week intervals and storing them in a freezer for future use. Finally, in 1968, he heard that one patient whose blood he had collected had developed clear symptoms of hepatitis. Rushing to the freezer, he took out the man's blood samples and tested them. He was thrilled to find that the Australia antigen had appeared in the patient's blood weeks before the illness. This confirmed that Au was involved in the development of hepatitis B.

Meanwhile in Tokyo, Okochi reported preliminary evidence that Au could be transmitted through blood transfusions. Blumberg at once embarked on a controlled study of the effects of blood transfusions from donors whose blood contained the Australia antigen. He wished to determine whether such blood was more likely to transmit hepatitis than blood which did not have the antigen. But in the middle of the experiment, he got word from Okochi that the answer had to be yes. Okochi actually visited Blumberg's lab in Philadelphia in 1969 and showed him the data he had gathered from a similar study in Japan. Blumberg found these data so convincing that he immediately stopped his own study for ethical reasons.

"Before Okochi's data had become available, it was a moral necessity to determine the consequences of transfusing blood containing Australia antigen; and it had to be done in a controlled and convincing manner, since major changes in blood transfusion practice were consequent on the findings," Blumberg explained in his Nobel Prize address. But "as soon as the conclusions of Okochi's well-controlled studies were known to us, it became untenable to administer donor blood containing Australia antigen." The blood was too dangerous.

From then on, would-be donors whose blood was found to contain the antigen were excluded from some of Philadelphia's blood banks, as well as from the NIH Blood Bank. Other blood banks throughout the U.S. rapidly followed suit. This dramatically slashed the rate of post-transfusion hepatitis B among patients.

Until the late 1960's, one out of three patients who received many blood transfusions at NIH and other hospitals developed hepatitis. The risk was particularly high when the blood came from paid donors, many of whom were infected with hepatitis B. As the use of blood from volunteer donors increased and the use of tests for the Australia antigen became universal, millions of persons around the world were spared the risk of contracting hepatitis B. It has been estimated that this produces savings of about half a billion dollars a year in the U.S. alone.

Zeroing In on The Hepatitis Virus

Clearly, blood that harbored the Australia antigen could transmit hepatitis. But was the Australia antigen a virus?

Electron micrographs soon revealed that the sera of people with the Australia antigen contained three different kinds of particles. There were innumerable small, spherical particles, about 20 nanometers (millionths of a millimeter) in diameter. There were sausage-shaped particles of the same diameter, but much longer. And there were some much larger, more complex particles, with a diameter of about 42 nanometers and an inner core of about 26 nanometers, first observed by D. S. Dane of the Middlesex Hospital in London in 1970. These more complex particles, now known as "Dane particles," represent the whole virus and are the only ones that are infectious. Each Dane particle has a surface coat made up of Australia antigen (now termed hepatitis B surface antigen). Its inner core consists of a different protein, hepatitis B core antigen, as well as a molecule of double- and single-stranded DNA. By contrast, the two smaller particles are devoid of DNA and consist entirely of hepatitis B surface antigen.

A person who has been infected with the hepatitis B virus may have an acute illness and recover completely. In this case, surface antigens will appear in the blood for a while but will eventually disappear, to be replaced by antibodies against this antigen—a sign that the person is protected against further infection with this particular virus.

If, on the other hand, a person who has been infected with the virus fails to produce any antibodies against the surface antigen, continues to harbor surface antigens, and also has a high concentration of antibodies against the core, this means the person has become a chronic "carrier" of hepatitis B.

Although it used to be believed that hepatitis B is not generally contagious, except through blood transfusions, by the late 1960's it had become evident that the virus spreads in many ways. It can be spread by saliva, by semen, and perhaps through insect bites. There have even been reports of its spreading by means of computer cards--presumably, through a cut in the skin. In addition to such "horizontal" transmission, the virus can be transmitted "vertically," from mother to child.

This creates a major public-health problem, for it has been estimated that there are 1 million carriers of hepatitis B in the U.S., and nearly 200 million carriers of hepatitis B around the world. Some of these carriers are infectious. Others (perhaps the majority) are not. It is not yet possible to tell one kind from the other precisely, though a new marker, the "e" antigen, seems to correlate with infectivity.

"We are building a population of hepatitis carriers," declares Maurice Hilleman, a virologist who is senior vice-president of Merck, Sharp & Dohme Research Laboratories and has been involved in the development of several vaccines. The hepatitis B virus is transmitted with particular frequency among male homosexuals; drug abusers who share hypodermic needles; health-care workers and patients in kidney-dialysis clinics; institutionalized mental patients, many of whom are now being integrated into society; the families of Vietnam veterans; and immigrants from Vietnam, Cambodia or Africa. Recently dentists were warned that they should take precautions against infection when filling the teeth of Indochinese refugees who have not been tested for the disease.

People who carry the hepatitis B virus are usually not aware of it. Yet some of them eventually develop chronic active hepatitis. Some of the people with chronic active hepatitis develop cirrhosis of the liver, though most do not. And some of the people with cirrhosis of the liver develop a rapidly fatal cancer--primary cancer of the liver--which, though rare in the U.S., is one of the most common cancers in the world.

Hepatitis B and Cancer

Primary liver cancer attacks five or six times as many men as women. It is particularly prevalent in China, other parts of Asia, and most of Africa. About one million persons die from it every year.

As early as the 1950's, investigators in West Africa had suspected an association between this cancer and hepatitis, but there was no way to prove it--or even to test the hypothesis. The Australia antigen made studies possible. Tests for the presence of this antigen (and therefore of the hepatitis B virus) soon showed that such a link did exist.

Since then, researchers have found many independent lines of evidence which support the hypothesis that persistent infection with hepatitis B virus is necessary for the development of most cases of cancer of the liver. For

example, the cancer occurs most frequently in parts of the world where there are many carriers of hepatitis B. Victims of primary liver cancer have hepatitis B surface antigen and antibodies to the core of the virus in their blood far more frequently than do people who are free of the cancer. Most of the cases of primary liver cancer occur in people who already have cirrhosis of the liver and/or chronic hepatitis. And a prospective study at the Tokyo Women's Medical College, begun in 1973, showed that patients with cirrhosis of the liver who carried hepatitis B surface antigen at the time of their admission to the hospital were four times more likely to develop liver cancer than patients with cirrhosis who did not carry the antigen and whose liver damage had other causes, such as alcoholism.

Other studies in Taiwan and Japan followed up apparently healthy chronic carriers of the hepatitis B virus and compared them with matched groups of people who were not carriers, for periods of up to four years. Of the three cases of primary liver cancer that occurred among 18,000 middle-aged employees of the Japan National Railway in the Tokyo district during this period, all developed in people who were carriers. Of the 34 cases of liver cancer in the more extensive and longer study performed in Taiwan by Palmer Beasley, of the University of Washington, all but one developed among chronic carriers.

In addition, the liver cells of patients with primary liver cancer nearly always show the presence of hepatitis B viral DNA integrated into the cell's chromosomes.

The Hepatitis B Vaccine

One way to protect against hepatitis and liver cancer would be to vaccinate people against hepatitis B. But hepatitis B is so different from most other viruses that a very unorthodox vaccine is required. While other vaccines are made from live or killed viruses that are grown in tissue culture, the hepatitis B virus will not grow in artificial media. Nor can it be tested in the usual experimental animals, since it will not infect them.

In 1969, Irving Millman of the Institute for Cancer Research and Blumberg thought of a novel approach: using the blood of human carriers as a source of antigen. Shortly afterwards, Saul Krugman of the New York University School of Medicine, who had been studying the natural history of hepatitis for fifteen years, made a happy discovery. Krugman had collected hundreds of blood samples from patients at various stages of hepatitis in an institution for the mentally retarded, where exposure to the disease was nearly unavoidable. His earlier research had provided definitive evidence that there were at least two distinct forms of hepatitis. Now he wanted to find out how the hepatitis B virus could be inactivated.

He took some serum that he knew was infectious, diluted it, boiled it one minute, and injected it into new patients at the institution, who had not yet been exposed to hepatitis. This treatment of the virus inactivated it almost completely, and none of the patients showed signs of hepatitis. The happy suprise was that a large proportion of the patients who had received the boiled serum were thereby protected from subsequent infection with hepatitis B. This demonstrated that a vaccine was feasible.

At that point, Merck, Sharp & Dohme became interested in developing a pure and safe vaccine against hepatitis B. Its raw material is blood taken from carriers of the virus—the very same people who are now rejected as donors by regular blood banks. At NIH, Robert H. Purcell and John L. Gerin developed a similar vaccine.

After working on the measles, mumps, rubella, influenza and meningitis vaccines, Maurice Hilleman calls the hepatitis B vaccine "the most technologically complicated vaccine I've ever dealt with." Since only one of the three particles associated with hepatitis B is infectious (the large Dane particle, which contains DNA), the vaccine is made by "harvesting" the smaller particles, which can stimulate the production of antibodies but cannot pass on the infection. As Hilleman points out, however, "one cannot totally separate the particles of surface antigen from the whole virus--and just one molecule of the virus could cause the disease." Therefore, even after the small particles have been purified to the highest possible degree, they must still be treated with chemicals so as to kill any remaining viruses. And even then, each lot must be tested to make sure it is really safe. Fortunately, NIH researchers recently found a way to transmit hepatitis B to chimpanzees, and Merck now tests each new batch of vaccine on four chimpanzees before releasing it.

The first major trials of the hepatitis B vaccine began in 1978, with several groups of volunteers who were at particularly high risk of developing the disease: male homosexuals in six American cities, and patients and staffs of kidney-dialysis centers. The studies were conducted in double-blind fashion, so that neither the scientists nor the volunteers knew who received the vaccine and who received a placebo (an inactive substance). In 1980, Dr. Wolf Szmuness of the New York Blood Center announced that the New York trial had been highly successful: 96% of the 549 young men who were vaccinated showed high levels of antibody to hepatitis B surface antigen, and not one of these men developed the disease during the first 18 months of follow-up. By contrast, 52 of the 534 men who received a placebo came down with hepatitis B during the same time.

Outside of the U.S., the vaccine is being tried in babies as young as three months of age, in the hope that this will prevent them from becoming carriers of hepatitis B.

A possibly more economical and safer form of hepatitis B vaccine may soon be on the way. As a result of recent advances in recombinant-DNA technology, scientists can now insert fragments of hepatitis B virus DNA into bacteria or

yeast cells and make these micro-organisms produce hepatitis B surface antigens. This means that bacterial or yeast factories may be used to manufacture large quantities of hepatitis B vaccine at low cost. This method would be more efficient than a process which begins with infected blood, and would also eliminate any possibility of contamination with infectious particles.

The Discovery of Non-A, Non-B Hepatitis

The discovery of hepatitis B virus made it possible to do research on hepatitis A virus without confusing it with hepatitis B.

In 1973, a decade after Blumberg discovered antigens linked to hepatitis B, Stephen M. Feinstone, who was working in Robert H. Purcell's laboratory at the National Institute of Allergy and Infectious Diseases (NIAID), found viruslike particles in the stool of volunteers who had been experimentally infected with hepatitis A and were in the acute stage of the disease.

In the meantime, there had been major improvements in the tests for hepatitis B. The agar gel diffusion test with which Blumberg had found the Australia antigen was simple and inexpensive, but quite insensitive and slow—it took between 24 and 48 hours to produce an answer. By 1972, rapid tests became available, particularly the radioimmunoassay, which Solomon A. Berson and Rosalyn Yalow had developed as part of their research on peptide hormones at the Bronx Veterans Hospital in New York—and for which she won the Nobel Prize in Medicine in 1977. It proved not only rapid, but 100 to 200 times more sensitive than previous tests.

"Using this assay, we can pick up nearly all carriers of the hepatitis B virus," declares Harvey Alter, of the NIH Blood Bank.

Nevertheless, a number of transfused patients continued to develop hepatitis. Before the radioimmunassay, it seemed likely that the fault lay in the tests, which were not sensitive enough to detect all carriers of hepatitis B. But now it became clear that some other factor must be responsible for at least some of the cases. Some scientists assumed that the guilty virus was hepatitis A; others began to suspect a different cause.

As soon as the NIAID's researchers had identified the hepatitis A virus, they tested 22 patients who had come down with non-B hepatitis after receiving blood transfusions. They were facinated to find that not one case was due to hepatitis A.

"This showed that a fairly large population of patients suffered from hepatitis that was neither A nor B," points out Purcell. He refuses to call this illness "hepatitis C," however, since there is evidence that more than one virus may be responsible for it, and he does not want to repeat the kind of confusion that existed between A and B.

The study of "non-A, non-B hepatitis," as it was dubbed, is now one of the hottest areas of biological research. Three separate groups at NIH are working on it. They realize that non-A, non-B hepatitis presents a serious health hazard, for although its symptoms are generally mild, up to 40 to 50 percent of the persons who contract this illness after a blood transfusion go on to develop chronic hepatitis--far more than the 2 to 4 percent who develop chronic hepatitis after infection with hepatitis B. Eventually, one or more vaccines against non-A, non-B hepatitis may be developed.

Giving "Chance" A Chance

No one can tell where the long and intricate chain of discoveries begun by Baruch Blumberg's interest in a drop of aborigine blood will lead. It has already uncovered three different types of hepatitis virus, cleaned up the world's blood banks (and thus made serious operations infinitely safer), produced a vaccine against hepatitis B which may also be a vaccine against liver cancer, and turned up several clues to how cancer develops. The next links in this chain will appear after yet another burst of work by people with varying interests of their own, and after some puzzling zigzags. This may seem like an erratic process, but it is the way basic research is done.

Much depends on having a critical mass of information in a given field, so that a spark can ignite it. Blumberg's finding of the Australia antigen, for instance, came at just the right time. Thanks to earlier researchers, much information about hepatitis was available, and thousands of samples of sera from hepatitis patients had been collected, making it relatively easy to identify the mysterious antigen. Other basic research had produced the technical tools which Blumberg used, including the agar gel diffusion technique and electron microscopy. Although the scientists who had been doing targeted research on hepatitis were stymied in their search for a hepatitis virus until Blumberg supplied the essential clue, his finding fell on prepared ground.

Much also depends on the quirks, previous experience, curiosity and doggedness of the individual researcher. While it is often said that science advances through a series of lucky accidents, far more than chance or "serendipity" is usually involved in such findings.

The term "serendipity" was coined by Horace Walpole in 1754 after he read a fairy tale about "The Three Princes of Serendip" (Serendip was the ancient name of Ceylon). "As their highnesses traveled," Walpole wrote, "they were always making discoveries, by accident or sagacity, of things which they were not in quest of."

In 1945, the physiologist Walter Cannon popularized the word "serendipity" in an essay on the role of chance or accident in research and discovery.

Since then, it has been interpreted to mean that scientists simply stumble onto their discoveries through no effort of their own--thus leaving out the important part played by what the scientists bring to their chance observations, and what they make of them. As Louis Pasteur said, "Chance favors only the prepared mind."

Blumberg made his chance discovery while pursuing basic research in a field of his choice. Many other discoveries which have provided the key to the prevention or cure of specific diseases have resulted from basic research in unrelated fields. For example, nearly half of the key scientific articles which led to "the top ten clinical advances in cardiovascular-pulmonary medicine and surgery between 1945 and 1975" dealt with topics that were unrelated to either heart or lung disease, according to Julius H. Comroe of the University of California, San Francisco, and Robert D. Dripps, of the University of Pennsylvania.

"Basic reseach is done to find out how things work in nature; it is essentially a search for mechanisms," notes Lewis Thomas, president of the Memorial Sloan-Kettering Cancer Center in New York. When a basic researcher is imaginative enough and deals with a subject in which enough knowledge has been accumulated, he can propel a whole field of science forward by a quantum jump. Then medicine can sometimes move from ineffective and expensive "half-way technologies," as Lewis Thomas calls them, to effective and inexpensive ones. For example, the iron lung, which was used to allow victims of polio to breathe, could be replaced by the polio vaccine, which effectively prevents the disease.

"All of today's medical advances draw on capital from a bank of undifferentiated information produced by basic research--and this bank needs constant replenishment," Thomas declares. "We are still profoundly ignorant about nature. . . We will solve the problems of heart disease, cancer, stroke, arthritis, schizophrenia, senile dementia, and all the rest, if we can just keep learning."

THE THREE TYPES Of VIRAL HEPATITIS KNOWN TO DATE

	Hepatitis A	Hepatitis B	Non-A Non-B Hepatitis
Previous name:	Infectious hepatitis.	Serum hepatitis.	
How spread:	Through contamination of food, water, clothing, toys, eating utensils, etc., by feces.	Via blood transfusion, hypodermic needles, tears, saliva, semen.	Similar to hepatitis B.
Incubation period:	2-6 weeks.	2-6 months.	1-6 months.
Long-term effects:	No lasting liver damage; complete recovery. No cancer risk.	5-10% of patients become carriers, some of whom can transmit hepatitis B to others. 40% of carriers develop chronic liver disease. Hepatitis B has also been linked to primary liver cancer.	40%-50% of patients show evidence of chronic liver disease and are presumably carriers; risk of liver cancer unknown.
Description of virus:	Diameter of 27 nanometers; no outer envelope.	An infectious core, 26 nanometers in diameter, containing DNA and hepatitis B core antigen, surrounded by an envelope of non-infectious hepatitis B surface antigen (formerly known as Australia antigen).	Unknown.
Prevalence of infection:	In the developing nations, nearly everyone is infected with hepatitis A at birth. In the U.S., 80% of the population over the age of 40 carries antibodies to it, evidence of previous exposure to the virus; however, few young adults or children have such antibodies, probably because of improvements in hygiene and public health.	On the average, only 7-10% of the U.S. population has been infected with hepatitis B; fewer than .5% are carriers of the virus. By contrast, 60-80% of the population in Southeast Asia and Africa has been infected with hepatitis B, and 6-10% are carriers of the virus. Certain groups in the U.S., such as male homosexuals or workers in kidney dialysis clinics, have an infection rate of up to 70%.	Unknown.

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