Baruch Blumberg (1925-2011) and the discovery of the Hepatitis B virus, diagnostic methods for detection, and vaccine

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Abstract

Baruch Blumberg's research was designed to gain a better understanding of the role of human genetic polymorphisms in relation to inherited susceptibility to disease. This led to the discovery of the hepatitis B virus, diagnostic methods for viral detection and a vaccine. The vaccination program has prevented the death of millions from primary liver cancer. It was the first widely used vaccine against cancer. For his work with the hepatitis B virus, Blumberg was honored in 1976 by the award of the Nobel Prize in Medicine or Physiology.

Introduction

Baruch Blumberg's (1925-2011) research was initially designed to gain a better understanding of the role of human genetic polymorphisms in relation to inherited susceptibility to disease. Blumberg: "At the onset, there was no obvious practical application of this project. However, building on a large body of research on hepatitis over the preceding decades, these studies resulted in the discovery of the hepatitis B virus (HBV), diagnostic methods for viral detection, and a vaccine. These applications have had a major impact on worldwide medical and public health problems…Hepatitis B vaccination is one of the largest worldwide disease-prevention programs. It has decreased the spread of HBV, particularly in China and East Asia. It has significantly decreased morbidity from liver disease and prevented the death of millions. HBV vaccination appears to prevent primary cancer of the liver; it is the first widely used preventative cancer vaccine." For his work with HBV, Dr. Blumberg was honored in 1976 by the award of the Nobel Prize in Medicine or Physiology. Blumberg had an association with Ben-Gurion University of the Negev for several years, see Figures 1 and 2 [1, 2].

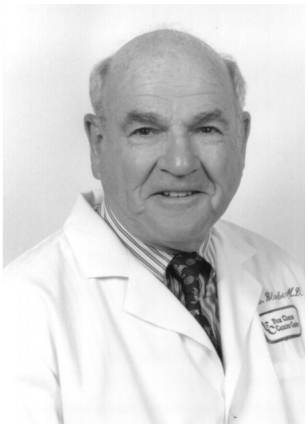

Figure 1. Baruch Blumberg. Photograph courtesy of B. Blumberg.

Bob Weintraub was born in Brooklyn, New York and made aliyah in 1975 to Beer Sheva, where he remained. He earned the PhD in Physical Chemistry from MIT and the Diploma in Library Science from the Hebrew University of Jerusalem. He held positions in scientific and technical librarianship in industry, hospital and academic institutions. He is now retired. He has an interest in the history of chemistry.

Figure 2. Baruch Blumberg delivering the Zlotowski Annual Lecture at the Ben-Gurion University of the Negev on May 9, 2010, entitled, "Strategies of Human Disease Control-The Hepatitis B Programs." In the lecture, attended by the author, Dr. Blumberg showed that the hepatitis-B vaccine program up until that time had prevented an estimated 29 million deaths from liver cancer. Photograph courtesy of Dani Machlis/Ben-Gurion University of the Negev.

Baruch Blumberg

Baruch S. Blumberg was born in Brooklyn, New York, in 1925, into a Jewish family. He earned his undergraduate degree in physics at Union College in New York State. Following war service in the Navy, he earned his medical degree in 1951 from the Columbia University College of Physicians and Surgeons. In 1957, he earned his DPhil from Oxford University in biochemistry for his work on hyaluronic acid. Blumberg accepted a position at the National Institutes of Health in Bethesda, Maryland and in 1964 moved to the Institute for Cancer Research in Philadelphia, now called the Fox Chase Cancer Center. He remained there except for extended periods away in England, California, and elsewhere [1–4].

Genetic polymorphism

Genetic polymorphism (inherited biochemical and immunologic variation in human populations) is a concept introduced by the lepidopterist and professor of ecological genetics E. B. Ford of the Department of Zoology at Oxford. He defined it as the occurrence together in the same habitat of two or more (inherited) discontinuous forms of a species in such proportions that the rarest of them cannot be maintained merely by recurrent mutation. Blumberg, in recalling his time at Oxford: "It began to dawn on me that the study of human polymorphisms would provide a conceptual framework for the investigation of inherited human variation and its connections with disease and survival, and that the gel method of electrophoresis could be a main technique for identifying the variation…Our grand plan was to track the distribution of the polymorphic traits in populations living under very different environmental conditions, where the health risks would vary greatly. We expected that different disease risks would have generated different selection pressures, and that the frequency of the genes determining the polymorphisms would vary. Also, we would be more likely to find previously undiscovered associations between disease and polymorphisms…It was during the course of our study of human polymorphisms that we, unexpectedly, discovered the hepatitis B virus." [3]

Blumberg: "The blood cell antigens were an example of inherited differences in susceptibility to disease. If an individual had inherited a particular combination of antigens, he or she would be susceptible to transfusion reactions if transfused with blood containing different antigens; if transfused with the same antigens, the person was protected against a transfusion reaction. The ABO red blood cell antigens were among the first of the systems of inherited common biochemical traits, called polymorphisms, studied by scientists…

The original concept of polymorphism implied that there are survival benefits conferred by some combinations of alleles that other combinations do not provide, and that there is heterozygote advantage. However, it has been difficult to demonstrate advantage for many polymorphic traits. It is possible that polymorphisms are selectively neutral and occur as a consequence of chance. In many instances the selective advantage of a single polymorphic system taken by itself may be too small to detect. But if a given polymorphism is considered along with other polymorphic traits and with environmental factors with which they could interact, selective advantage may be detected.

Independent of the question of selection, the polymorphic systems provided an excellent mechanism for studying biochemical and immunologic variation among individuals and among human populations." [3]

Hepatitis B Virus

In 1963, Blumberg and his colleagues observed a reaction between an antigen from sera of an Australian with an antibody from sera of a New York hemophilia patient. The sera of hemophilia patients who have received many transfusions was often used in experiments as they are exposed to sera from many donors and are likely to become infected with blood-borne agents or to develop antibodies against serum proteins.

"I'm often asked why we were testing sera from Australian aborigines. The answer derives from our overriding interest in human inherited variation—polymorphisms. Our long-term goal in studying what at that time was an esoteric field in human population genetics was to find relations between these polymorphisms and differences in susceptibility to disease. We knew that the frequency of polymorphic alleles varies greatly from population to population and from country to country. In looking for a new polymorphism without any knowledge of the population distribution of the alleles, we reckoned that we could increase the probability of success by randomizing the populations used in the screens of the transfused sera from different populations, and the screen in which the new antiserum was found included, not exactly by chance, Australian aborigines. " [3]

The serum of the hemophiliac was then tested against thousands of serum samples. Observations started to point to the hypothesis that the Australia antigen (later known as the hepatitis B surface antigen, designated as HBsAg) was a part of the hepatitis virus. The antigen was being observed in many samples from patients with hepatitis, among other indications. Tom London and Irving Millman made the important observation that when the highly purified fraction of the Australia antigen was used in injection experiments with vervet monkeys the infection did not occur, but if less purified material was used, the vervet became infected. This lead to the understanding that the purification process separated the infectious particle (still unobserved) that could cause the disease from the noninfectious particles (that were observed in the electron microscope). Blumberg: "Oddly, most of the important applications of the research on HBV were realized before there was a significant understanding of the virus's molecular details." [3]

Hospital post-transfusion hepatitis used to be a major complication of surgery. By 1967, a test was devised for the presence of the Australia antigen which indicated the presence of hepatitis B in occult carriers and also could be used to diagnose patients with hepatitis B. By the mid 1970's, post-transfusion HBV had virtually disappeared in countries where compulsory testing had been instituted. Later, in the 1980's, hepatitis C virus was discovered and a method of testing for it was worked out. Other hepatitis viruses have since been discovered, D, E, and G, but they present a much lesser clinical problem than that of the B and C viruses. It has been estimated that the annual saving resulting from the prevention of post-transfusion hepatitis amounts to about half a billion dollars in the United States.

Invention of the vaccine

Blumberg: "In 1968 we were informed by the Federal government, who provided most of the funds for our work, that they would like to see applications of the basic research they had funded for many years. It occurred to us that the existence of the carrier state provided an unusual method for the production of a vaccine. We presumed that the very large amounts of HBsAg present in the blood could be separated from any infectious particles and used as an antigen for eliciting the production of antibodies. The antibodies in turn would protect against infection with the virus. Irving Millman and I applied separation techniques for isolating and purifying the surface antigen and proposed using this material as a vaccine. To our knowledge, this was a unique approach to the production of a vaccine; that is, obtaining the immunizing antigen directly from the blood of human carriers of the virus. In October, 1969, acting on behalf of ICR [Institute for Cancer Research] we filed an application for a patent for the production of a vaccine. This patent [USP 3,636,191] was subsequently (January, 1972) granted in the United States and other countries." [4]

Primary hepatocellular carcinoma

HBV is transmitted by transfusion, sexually, from mother to child at birth, and by contaminated needles. The association of chronic liver disease with cancer of the liver had been recognized since the 1950's, but it took the identification of the HBV to enable the interconnection to be made between HBV, cancer of the liver, and chronic liver disease. Blumberg's group first proposed this connection in 1969, two years after their first publication on HBV. "Primary hepatocellular carcinoma (HCC) is a cancer that originates in the liver. The cancer process may start in the liver cells for a susceptible person at a very young age; the affected cells initially divide and reproduce themselves very slowly…The slow growth proceeds over many decades, unknown to the host and without any symptoms." HCC usually occurs in people who already have liver disease, typically due to HBV or HCV. When symptoms finally do appear, often several decades after HBV infection, the patient generally dies within 6-20 months. The five-year relative survival rate is 18 percent." [4–6]

Manufacture of the Vaccine

Blumberg: "It took some time before the concept was accepted by virologists and vaccine manufacturers who were more accustomed to dealing with vaccines produced by attenuation of viruses, or the use of killed viruses produced in tissue culture, or related viruses that were non-pathogenic but

protective (i.e., smallpox). However, by 1971, we were able to interest Merck, which had considerable experience with vaccines. During the next few years, a series of human and primate observations by scientists including [M.] Hilleman (who was responsible for vaccines at Merck), S. Krugman, R. Purcell, P. Maupas, and others provided additional support for the vaccine. In 1980, the results of the first field trial were published by W. Szmuness and his colleagues in New York City. They showed that the vaccine was highly effective (over 90% were protected) and that no untoward side effects were observed. The FDA approvals were obtained, and by 1982 the vaccine was available for general use." [2] Soon afterwards, recombinant HBsAg vaccine was developed in several laboratories. HBV vaccine was the first vaccine to be produced commercially by recombinant methods. Within a few years of the approval of the vaccine, millions of children and adults were being vaccinated yearly. The vaccine is one of the most commonly used vaccines in the world. It is a compulsory vaccination for a large percentage of the world's population.

In 2002, Blumberg reviewed the grim worldwide statistics of death and liver cancer brought on by HBV infection. At that time, about 1.5 million people were dying each year as a consequence of HBV infection. He wrote: "The presentation of such grim figures as these usually precede a prediction of even more awful events. But that is not the case for HBV. Life – and death – are full of surprises, and while it may be tempting fate to be too optimistic, it appears likely that within the next few decades the virus will be effectively controlled. It is even possible that it will be eradicated." [3]

Israel

Blumberg had an association with Ben-Gurion University of Negev for several years and wrote to the author that he has been gratified to see it grow and continue its valuable research in medicine and the science of arid environments. He recalled that on his first visit to Israel in 1953 he visited Hadassah medical system hospitals in Jerusalem, Safad, Beersheva, and elsewhere. He visited these sites and other sites several times after and commented that he had never been anywhere that has changed as much as Israel.

Blumberg recalled attending meetings with the late Dr. Chaim Sheba and, in March 1973, a memorial symposium in honor of Dr. Sheba on polymorphisms, population biology, and inherited susceptibility to disease. He began his presentation at that meeting with an explanation of the significance of a finding by Dr. Batsheva Bonné (later, Prof. Bonné-Tamir, Human Molecular Genetics & Biochemistry, Tel-Aviv University), who came to his laboratory with a collection of sera from the Samaritan population of Israel. She found the presence of the Australia antigen in the sera of two sibs, products of a consanguineous marriage, of the 125 persons tested. Bonné-Tamir in 1994 established (together with Mia Horwitz) the National Laboratory for the Genetics of Israeli Populations [7–9].

If you save a single life, you save the whole world

Blumberg saw saving lives as the whole point of his career. "It was something that I always wanted to do and is what drew me to medicine. There is, in Jewish thought, this idea that if you save a single life, you save the whole world, and that affected me." [10]

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