



**Baruch S. Blumberg**

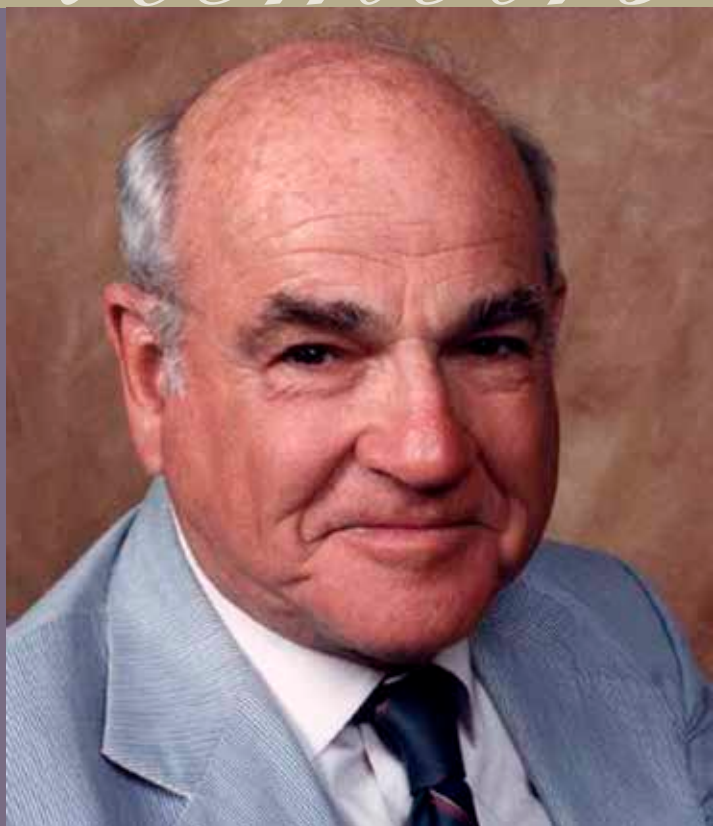
1925–2011

BIOGRAPHICAL

*Memoirs*

*A Biographical Memoir by  
W. Thomas London*

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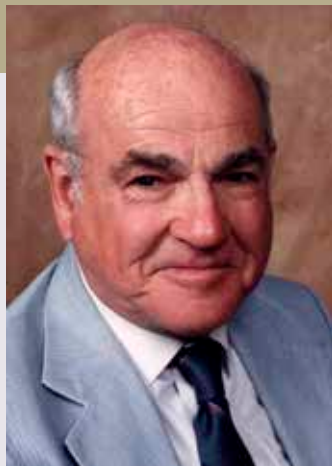
NATIONAL ACADEMY OF SCIENCES

# BARUCH SAMUEL BLUMBERG

July 28, 1925–April 5, 2011

Elected to the NAS, 1975

Baruch S. Blumberg was a research scientist who received the Nobel Prize for Physiology or Medicine for his discovery of the Australia antigen, one of the most important advances in the field of Hepatology. Known to everyone as Barry, he was an unlikely person to have made the discoveries that had such a huge impact on public health, liver disease, infectious disease and virology. Barry was not a virologist, a hepatologist, an infectious disease specialist, or an epidemiologist. He had minimal clinical training in medicine and no formal training in those other disciplines. He was, in fact, more of a 19th century natural scientist than a 20th century laboratory or clinical scientist. Finding the cause of viral hepatitis was not what he had in mind when he began his research career. Yet Barry's discovery, made with teams in Philadelphia and Bethesda, led to the virtual elimination of transfusion-related hepatitis B in most parts of the world, and was essential to the identification of hepatitis A, C, D, and E viruses. When he identified the Australia antigen as the outer coat of the previously unidentified hepatitis B virus, it was the prelude to the invention of the first vaccine to prevent infection with the virus, the demonstration of its association with acute and chronic hepatitis B, cirrhosis, and liver cancer, and ultimately the prevention of liver cancer.



*Baruch S. Blumberg*

By W. Thomas London

## Early life

**B**arry Blumberg was born in New York City on July 28, 1925. His father, Meyer Blumberg, was a lawyer. His mother, Ida, was a vital presence in his life for many years. Barry received his elementary education at a yeshiva, or center for Jewish study, in the Flatbush section of Brooklyn. He always claimed that studying the Torah and Talmud at an early age provided him with the intellectual discipline to learn anything later in life. He attended Far Rockaway High School, a public school in Queens New York that also educated two other Nobel prizewinners, Richard Feynman and Burton Richter.

In 1943 Barry enlisted in the U.S. Navy, which sent him to Union College in upstate New York for both undergraduate education and training as a naval officer. He served as the commanding officer of an LST landing ship at the end of World War II. This experience provided him with a rich supply of aphorisms and anecdotes.

After graduating from Union in 1946 with a degree in physics, Barry enrolled in a graduate program in mathematics at Columbia University. A year later he entered The College of Physicians and Surgeons there. Between his third and fourth years of medical school, he took an elective in a mining town in Surinam, South America. While there he studied infections with the parasite *Wuchereria bancrofti*, which causes filariasis (elephantiasis). He noted that the multiple ethnic groups in Surinam displayed wide variations in response to infection with presumably the same parasite.<sup>1</sup> This observation had a profound effect on his views on inherited variation and susceptibility to disease.

More important to Barry's future research than his thesis work was his exposure to the works of the 19th century naturalists Charles Darwin and Alfred Russell Wallace as well as to scientists investigating genetic polymorphisms.

After graduating from medical school, Barry completed an internship in internal medicine at Bellevue Hospital followed by a clinical fellowship in rheumatology at Presbyterian Hospital, both in New York City. After completing his three years of medical training, he went to Oxford University to study biochemistry under the direction of Alexander Ogston. Barry's doctoral thesis was on the physical and biochemical properties of hyaluronic acid.

### Discovering polymorphisms

More important to Barry's future research than his thesis work was his exposure to the works of the 19th century naturalists Charles Darwin and Alfred Russell Wallace as well as to scientists investigating genetic polymorphisms. An important influence was Anthony C. Allison, also working in the biochemistry department at Oxford. Allison had discovered that people with the sickle cell trait were resistant to *Falciparum* malaria, the most lethal form of malaria. This was a polymorphism in action. Homozygotes for sickle hemoglobin (ss) had severe anemia and died. It would be expected that over centuries the harmful gene would have been eliminated from human populations, but the heterozygotes with one sickle gene and one normal gene (sS) had a selective advantage with respect to malaria.

Allison and Blumberg took field trips to Nigeria and Alaska to search for genetic polymorphisms of serum proteins and haptoglobins. Based on their findings, they hypothesized that blood transfusions would expose people to serum protein variants that were different from their own. This would in turn lead to the production of antibodies against such variants. To test this hypothesis they reacted serum samples from multiply transfused individuals against sera from normal individuals in the blood samples they had collected. Using the immuno-diffusion method of Ouchterlony, they detected an immuno-precipitin of a serum lipoprotein.<sup>2</sup>

These observations cemented Barry's view that genetic polymorphisms were likely to be associated with human diseases. As a follower of Darwin and a believer in the central importance of natural selection, he thought all such variants had to be important. Otherwise, they would not have persisted in human populations.

Barry worked at the National Institutes of Health in Bethesda, Maryland from 1957 to 1964 in the Geographic Medicine and Genetics section of the National Institute of Arthritis and Metabolic Diseases. There he continued his research on genetic polymorphisms with colleagues such as Harvey Alter, a clinical fellow in the blood bank at the NIH Clinical Center in 1961.

Independently, Harvey had begun studying serum protein polymorphisms using the same immuno-diffusion method as Barry. In 1962 Barry and Harvey began collaborating on what Harvey later termed "his most important research collaboration." As Harvey described it,

*I went through more Ouchterlony plates than Ouchterlony himself, each day testing multiply transfused patient sera against an array of samples that Blumberg had collected on his many trips around the globe. Characteristic of the lipoprotein reactions was that the precipitin arcs turned blue when Sudan stain was applied. One day, I observed a precipitin line that did not take up the lipid stain, but stained intensely when a protein counter stain was applied...I found that this novel reaction was between the serum of a patient with hemophilia and that of an Australian aborigine....Initially we called this unidentified antigen the "Red Antigen" for its staining properties, but later debated whether to call it the Bethesda antigen for the place where it was discovered or the Australia antigen for the person in whom it was found. Blumberg insisted on the latter in keeping with evolving nomenclature for newly identified hemoglobins.*

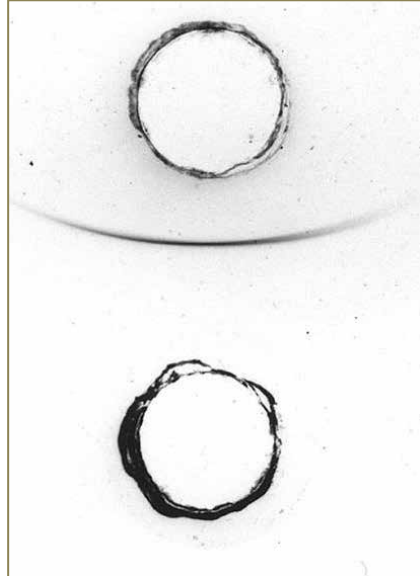
In 1963 and 1964 Harvey and Barry tested many healthy populations and some patient populations. They found that the Australia antigen was present in many supposedly healthy people in foreign populations, but it was detected in only one in a thousand blood donors in the United States. It was, however, detected in 10 percent of patients with leukemia at the NIH Clinical Center. Thus, the first publication about this antigen was *The Australia Antigen: A "New" Antigen in Leukemia Sera*.<sup>3</sup>

### The Institute for Cancer Research

In 1964, Timothy Talbot, the director of the Institute for Cancer Research in Philadelphia, recruited Barry to become the head of a new Division of Clinical Research. As a lure Talbot promised Barry he could do whatever he wanted as long as his research ultimately had consequences for disease in humans. Talbot was able to make that offer because he had secured a seven-year grant from the National Cancer Institute to establish cancer clinical research at the Institute, which had none up to that time. The grant contained no money for science, but supported Talbot's wish for a clinical research program.

Barry was intrigued and immediately began assembling a small group of physicians to staff this new enterprise. He asked Harvey Alter to join him in Philadelphia, but Harvey wanted to get more clinical training in hematology. He would likely have shared the Nobel Prize if he had accepted Barry's invitation. Others demurred because the Institute was little known at the time. Barry's job was to convince talented scientists that the Institute for Cancer Research was a scientific gem with brilliant scientists that, although little known at the time, was bound to become an institution of national and international importance. Barry also brought in American graduate students and post-docs, but they were not what the senior scientists expected. He wanted people who, like himself, regarded the world as their laboratory. They included anthropologists, folklorists, sociologists, and botanists, but nary a virologist, oncologist, or liver disease specialist.

Although Barry had limited training or experience in clinical medicine, he had complete faith that his approach—identifying variants in human blood and then finding out what



Original Australia antigen.

they meant—would be much more informative than starting with a disease and trying to identify its cause, as was then and is today the standard method. In 1966, Barry persuaded W. Thomas London, Alton Sutnick, Betty Jane Gerstley and others to focus their efforts on understanding the biological significance of Australia antigen. Initially, Barry and Harvey Alter had only found Australia antigen in foreign populations and if they had repeat samples from the same individuals, persons who were positive remained positive, those who were negative stayed negative.<sup>4</sup>

Based on the finding of the antigen in some patients with leukemia, Barry hypothesized that it might be a marker of susceptibility to leukemia. He went on to test children with Down's syndrome who were known to have an increased risk of leukemia. Amazingly, about 30 percent of boys with Down's from an institution for developmentally disabled children in New Jersey tested positive for the Australia antigen.

When the team was assembled at the Institute for Cancer Research in 1966, they first studied Down's children who did or did not have the Australia antigen, which they abbreviated as Au. One boy who had been negative when first tested was positive on a second test. They assayed his liver functions on the grounds that most serum proteins are made in the liver. Alton wrote in the boy's chart on June 28, 1966. "SGOT slightly elevated! Prothrombin time low! We may have an indication of the reason for his conversion to Au(+)." A liver biopsy showed that he had a mild hepatitis.<sup>5</sup> When the team compared alanyl aminotransferase levels, a measure of liver inflammation, of Down's syndrome patients with and without Au, the levels of inflammation were significantly higher in the positives.<sup>6</sup>

They immediately began testing blood samples from patients with acute hepatitis; many were positive but usually for only short intervals.<sup>7</sup> On the other hand, samples from patients with chronic hepatitis, if they were positive initially, were persistently positive.<sup>8</sup> The nail in the coffin came when Barry's chief technician, who was working on the isolation of the antigen by centrifugation methods, developed fatigue and dark urine. She tested her own blood and found that she had the Australia antigen. That was the first time that the test was used to diagnose hepatitis.

In 1968, in collaboration with John Senior, Miriam Dahlke, and Eugene Goeser from the University of Pennsylvania and the Philadelphia General Hospital (PGH), the team from the Institute began testing blood samples donated to the PGH for the Australia antigen. Blood samples that tested positive were barred from use in transfusions. The teams found that the incidence of post-transfusion hepatitis was reduced from 17.9



percent prior to the testing program to 5.9 percent after transfusions of Au(+) donor bloods were stopped.<sup>9</sup>

### Development of the Hepatitis B vaccine

At the same time that these clinical studies were going on, Barry, in collaboration with Manfred Bayer at the Institute for Cancer Research, found that the Australia antigen was a particle similar in appearance to a virus.<sup>10</sup> That was enough evidence of a virus for Barry to recruit Irving Millman, a microbiologist and vaccinologist from Merck, and begin to develop a unique vaccine, one that was prepared from antigenic particles in human blood. The patent for the vaccine was submitted in 1969 and granted in 1971. Shortly thereafter it was licensed to Merck for development and evaluation. By 1975, before the vaccine had even been tried in humans, Barry predicted, in print, that the vaccine would not only prevent infection with the hepatitis B virus but that it would prevent liver cancer. Therefore, it would be the first cancer vaccine.<sup>11</sup>

In 1976, Barry was awarded the Nobel Prize in Physiology or Medicine (shared with Carleton Gajdusek) for “giving us new views on mechanisms of infectious diseases.”

The hepatitis B vaccine was approved by the Food and Drug Administration in 1981. Five years later the plasma-based vaccine was replaced by a recombinant vaccine. In 1982 Barry visited Taiwan, where the director of the blood bank at a major hospital in Taipei showed him large refrigerators full of blood from people infected with hepatitis B. What should they do with all these contaminated bottles of blood, the director asked? Barry’s answer: they should make hepatitis



Blumberg celebrates receiving the Nobel Prize in 1976.

B vaccine. The Taiwanese hospital adopted his recommendation, which led by 1984 to Taiwan establishing the world's first program of universal hepatitis B vaccination.

In 2013, investigators in Taiwan published a 30-year follow-up on the results of their vaccination program. Not only did the vaccine reduce the percent of people infected with the hepatitis B virus in the vaccinated population from 20 percent before the program to less than 2 percent, but the vaccine had reduced expected deaths from chronic liver disease and liver cancer by more than 90 percent. Barry's prediction from 1975 was fulfilled. The hepatitis B vaccine was the world's first proven cancer vaccine.

Following his early successes and Nobel Prize, Barry continued to pursue aspects of hepatitis B infection on populations, particularly its effect on mortality.<sup>12</sup> He collaborated with physicians on population studies in Senegal, West Africa. These studies demonstrated a lack of perinatal transmission of hepatitis B infection, in contrast to Asia, where such transmission was the norm.<sup>13,14</sup> He also promoted his conviction that hepatitis B was an eradicable disease with the combination of universal vaccination of newborn babies and effective treatment of those individuals who were already chronically infected.<sup>15</sup>

### **Balliol College, Oxford**

Gradually, however, Barry turned his attention to other academic and administrative pursuits. He had returned to Oxford for one year in 1972 as a visiting fellow at Trinity College, and subsequently served, from 1983-84 as George Eastman Professor at Balliol College. In a break with tradition, Balliol College, founded in 1263, elected Blumberg its Master in 1989. He was the first United States citizen and the first scientist elected to head the college, which traditionally chose scholars from the humanities. He served as Master of Balliol College until 1995. While there, Barry took full advantage of all the scholarly and social activities Oxford had to offer.

After returning to the Institute, now called Fox Chase Cancer Center, in 1996 Barry began collaborating with investigators at the National Aeronautics and Space Administration (NASA). In 1999 he was named the first director of NASA's Astrobiology Institute in Ames, CA. Astrobiology addresses three fundamental questions: "How did life begin and evolve?" "Is there life beyond Earth?" and "What is the future of life on Earth and beyond?" These questions intrigued Barry as did the opportunities to go to space launches and to visit sites of extremophile collecting, like active volcanoes, and the deepest parts of the ocean. Barry served as director of the Astrobiology Institute until 2002, and he continued to be involved with NASA for the rest of his life.



After his stint at NASA Barry returned once more to Philadelphia, where he was elected President of the American Philosophical Society (APS) in 2005. The APS, the oldest learned society in the United States, had been founded in 1743 by Benjamin Franklin for the purpose of “promoting useful knowledge.” Once more Barry found a home that appealed to all of his wide-ranging interests. He was particularly interested in having the APS fund field investigations of biological problems.

Barry passed away on April 5, 2011, while still serving as President of the APS, and shortly after speaking at a conference on lunar exploration at NASA’s Ames Research Center.

### **Personal life and honors**

Barry had a rich and rewarding life after his great early successes. He was a happy person who had a warm close relationship with his wife, four children and, nine grandchildren. He celebrated his own life by living it to the fullest. Barry was always a participator, never a spectator. He ran, hiked, climbed mountains, kayaked, canoed, and traveled to the four corners of the earth. He left a legacy of accomplishments that saved an enormous number of lives and prevented hundreds of millions of people from becoming ill with the hepatitis B virus. For Barry, the world was his laboratory and playground.

Barry was a founding member of the Library of Congress’s Scholars Council. His work with NASA and the Library of Congress led to the establishment, after his death, of the Baruch S. Blumberg NASA/Library of Congress Chair in Astrobiology.

In 2010 the World Health Organization recognized Baruch Blumberg’s contributions by designating July 28th, his birthday, World Hepatitis Day.

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