

Explorer, Nobel Laureate, Astrobiologist: Things You Never Knew about Barry Blumberg

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Introduction

BARUCH S. “Barry” Blumberg, winner of the 1976 Nobel Prize in Physiology or Medicine and founding director of the NASA Astrobiology Institute (NAI), passed away suddenly of a heart attack at age 85 on April 5, 2011, during a conference at Ames Research Center. That Barry spent his last day conceptualizing an International Research Park on the Moon befits the unflagging curiosity that characterized his life in general and his scientific career in particular.

In this paper I trace Barry’s scientific career, including his early formative years and the unexpected path that led to the Nobel Prize. I also show that Barry’s perspective and approach to science in general made astrobiology a natural area to attract his attention after he had retired from medical research. Indeed, his priorities as NAI director reflect directly things that were important to him throughout his career.

The Making of a Physician, Scientist, and Adventurer

Barry was born in Brooklyn, New York, in 1925, a grandchild of eastern European immigrants. His father’s career as a lawyer provided for a comfortable middle-class family life, even after the stock market crash of 1929. Nonetheless, Barry grew up a child of the depression and carried with him ever after a need for financial security he could generate by his own labor.

His curiosity was developed and nurtured during primary education at the Yeshiva of Flatbush, a Jewish parochial school in Brooklyn, New York, where in addition to traditional subjects he studied Hebrew as well as the Torah—the first five books of the Old Testament—and the Talmud—extensive commentaries on the Torah written over the last two millennia. The fact-based argumentation of Talmudic study introduced him to an analytical thought process on which he would draw throughout his life (Blumberg, 2002, p 9). He subsequently attended Far Rockaway High School, whose graduates of the period included Richard Feynman, winner of the Nobel Prize in Physics in 1965, and Burton Richter, winner of the Nobel Prize in Physics in 1976, the same year as Barry’s prize. Barry would later reflect that he did not encounter as great an intellectual atmosphere as Far Rockaway High until he reached Oxford over a decade later

following medical school to study for his PhD in biochemistry (Blumberg, 2002, p 9).

After graduating high school, Barry entered the Navy at age 17. The Navy supported his completion of a physics degree at Union College in upstate New York and then commissioned him a line officer serving on small amphibious ships, one of which he eventually captained (Fig. 1). The Navy taught him responsibility, forward planning with contingency options at the ready, and the importance of logistics and infrastructure. These were lessons he would later put to great use, particularly during the extensive fieldwork that formed a central part of his scientific career.

In 1947, after leaving the Navy, Barry followed the advice of his college mentor that he leave physics because he “didn’t have the specific intellectual skill to be successful in that subject” (Blumberg, 2002, p 10). He entered medical school and graduated in 1951 from Columbia University’s College of Physicians and Surgeons. In 1950, as a third-year medical student, he sought an opportunity to work in “the tropics.” Barry found the tropics fascinating, as did many of his generation. He had read extensively on the subject, and while working as a movie usher had seen repeatedly many of the films of the day that depicted the tropics, usually in a way that today we would find inappropriate at best, offensive at worst. He approached a professor of tropical medicine, who offered him the opportunity to work temporarily in Suriname, a country in north central South America then known as Dutch Guiana. Barry accepted the offer and spent 3 months serving in the hospital and public health facilities of Moengo, a town on the Cottica River and site of a bauxite mine that had provided a good part of the aluminum ore needed by the United States in World War II (Fig. 2).

The mine workers were a heterogeneous mix of South American natives, descendants of African slaves (one of the first successful slave rebellions in the New World occurred in Suriname in the mid 18th century), Europeans, Indonesians, and a few Indians, Chinese, and other nationalities. Barry observed a puzzling fact about this diverse population. Although they lived under the same conditions, different ethnic groups had very different susceptibilities to common tropical diseases such as malaria and filariasis, the latter a parasitic infection caused by threadlike roundworms. Field surveys of other areas of Suriname conducted during this period by Barry and a medical student colleague also

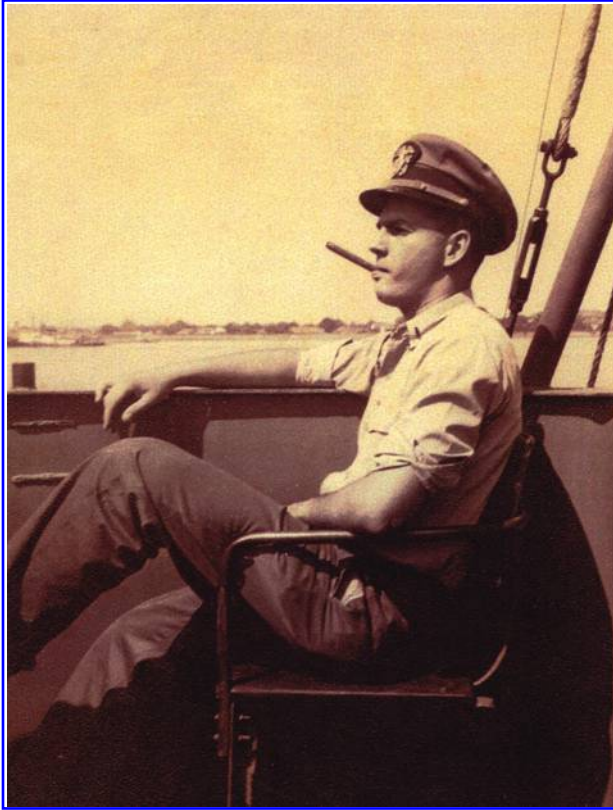


FIG. 1. Ensign Baruch S. Blumberg in 1946 as executive officer on USS LSM-416.

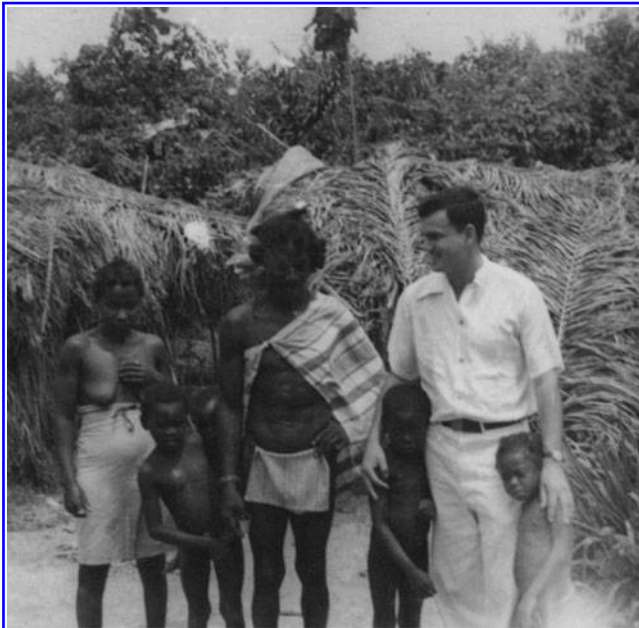


FIG. 2. Barry with a native family in Suriname, 1950. In addition to collecting specimens for the malaria, filariasis, and other surveys, Barry and another medical student conducted daily clinics under the supervision of the physician for the Moengo region.

showed great variation in disease susceptibility. This led Barry to formulate a simple question that would motivate much of his medical career: why do some people get sick while others, exposed to the same environment and infectious agents, remain healthy? Or more precisely, how do inheritance, human behavior, and the environment interrelate in the context of disease (Blumberg, 2002, p 19)?

Barry's experience in Suriname was seminal in other ways as well. Barry was something of an adventurer. Early in medical school he had crewed on an ill-equipped sailing ship attempting an Atlantic crossing from the Netherlands to the United States. After much difficulty and a harrowing storm at sea, he found himself stranded in Portugal without a visa or seaman's papers. He narrowly avoided arrest before managing to ship out on a US freighter bound back for the United States (Blumberg, 2007, parts 6–8). So Barry was no stranger to challenging and even dangerous situations. In Moengo he found himself surrounded by impenetrable jungle populated, among other things, by huge snakes, with access only possible by means of a river rich in crocodiles. And by all indications he loved it. During his stay, he and a colleague traveled into the interior in a dugout canoe, traversing extensive rapids, to conduct a health survey of remote populations (Fig. 3). This was Barry's introduction to field research, and it would shape his career for decades to come.

Barry wrote in his autobiography about another thing he learned in Suriname that was to shape his approach to science:

It was there that I learned to rely on observations in the field; new observations led to new hypotheses that could not have been induced by laboratory-based experiments. The stark interplay of genetic differences and environmental effects was clear in the harsh tropics. But the field-work was, in turn, very dependent on laboratory techniques, and hypotheses were confirmed or rejected by experimental testing (Blumberg, 2002, p 19).

This interplay between field work, laboratory studies, and theory would form another part of the foundation for Barry's scientific career.

Disease Susceptibility and Genetic Polymorphisms

After medical school, Barry interned for 2 years at Bellevue Hospital in New York City and then spent an additional 2 years as a clinical resident at Columbia Presbyterian Medical Center, a few miles uptown. Barry likened his experience at Bellevue—a city hospital that accepted patients from some of the most dreary and depressed areas of the city—to Dante's descent through the circles of Hell and eventual return to Earth (Blumberg, 2002, pp 21–22). But it was at Bellevue that Barry met and courted his wife Jean, to whom he would be married for 57 years, so all was not Dantesque.

At Bellevue, Barry continued to observe great variation in the susceptibility of various populations to disease, particularly in the tuberculosis wards, which were very busy places at the time. After Barry moved to Oxford in 1955 for his PhD, he continued to be intrigued by

questions of diversity in relation to disease stimulated by my experiences at Bellevue and in the jungle hospital in Suriname...Of particular interest are inherited differences

FIG. 3. Barry in the *corrial*, or log dug-out canoe, that his small group used to travel up the Marowyne River to survey the Paramacanner nation, a remote people living in the interior near the border with French Guiana. Reprinted by permission of Princeton University Press (B.S. Blumberg, 2002, *Hepatitis B: The Hunt for a Killer Virus*).



among individuals and populations that result in differential disease susceptibility because these can often be detected before the person is exposed to the disease hazard. It was this notion that became the driving force in our research. If we could precisely identify the susceptibility factors before a person became sick, then we might be able to intervene to prevent the illness. The idea of a disease-free life—or, to be more realistic, a life with less disease—might be possible (Blumberg, 2002, p 31).

Barry's turn toward research on inherited differences that result in differential disease susceptibility—one dimension of "human genetic polymorphisms"¹—put him firmly in the camp of preventative medicine, a field that did not have high professional status at the time (and, some would argue, even today). Preventative medicine was the province of government-employed public health officers. It was not a focus of either medical training or practice, because "If everything works well, nothing happens. No one gets sick; no blood, no rushes to the emergency room with tubes dangling from arms and legs, masses of equipment covering the patient. It's hard to make a dramatic TV episode out of a no-action scenario" (Blumberg, 2002, p 32). Human genetic polymorphisms weren't so much a part of medicine at the time as they were a part of forensics (think of modern DNA evidence), paternity determinations, and anthropological population studies.

This line of research was countercultural in another way as well. It would require study of diverse populations, an idea that appealed to Barry's sense of adventure.

The research...would require travel, working with populations outside of Western culture, and the prospect of active searching in the fashion of the explorer-scientists of previous centuries. I would dredge up the geographic knowledge I had amassed in my youthful hobby of stamp collecting in the selection of locations for field trips (Blumberg, 2002, p 40).

¹Human genetic polymorphisms are also responsible for non-disease-related differences such as eye color and blood type.

But population studies were considered to be inexact, particularly in comparison to the more conventional reductionist laboratory approach to biological science which sought to explain all in terms of chemistry and physics (Blumberg, 2002, p 57).

So Barry was "swimming against the stream" both by studying human genetic polymorphisms and by using population studies to do so. Nonetheless, he was able to get support for his research, first at Oxford and then at the National Institutes of Health (NIH) in Bethesda, Maryland, where in 1957 he joined the Division of Clinical Research at the National Institute of Arthritis and Metabolic Diseases (NIAMD). Between 1956 and the early 1960s, Barry led field studies in the Basque country of Spain; in Nigeria, Greece, and the Pacific Islands; among Native Americans; in Mexico and South America; and in the American Arctic (Fig. 4). Barry and his team studied blood proteins, since the recombinant DNA techniques to study the genes coding for those proteins would not become available until much later. In many cases their studies piggybacked on other health studies and surveys that involved obtaining blood samples, so that additional invasive sampling was not required. The studies were conducted without a specific hypothesis but within the broad framework that they would find genetic differences between different populations, living in different environments, at risk for different diseases. "Our primary intent was to make observations in the field and in the laboratory in the expectation that we would observe relationships with health and disease that would generate hypotheses that could be tested more directly in subsequent studies" (Blumberg, 2002, p 54).

This was true exploration, both geographic and scientific. Barry and colleagues went out to see what they would find, confident that the data they were acquiring and the questions they were asking would lead to productive outcomes. But what outcomes they couldn't say. Since they were seeking associations between genetic polymorphisms and disease, it is not surprising that they found some, or in some cases were able to formulate testable hypotheses. Their most notable

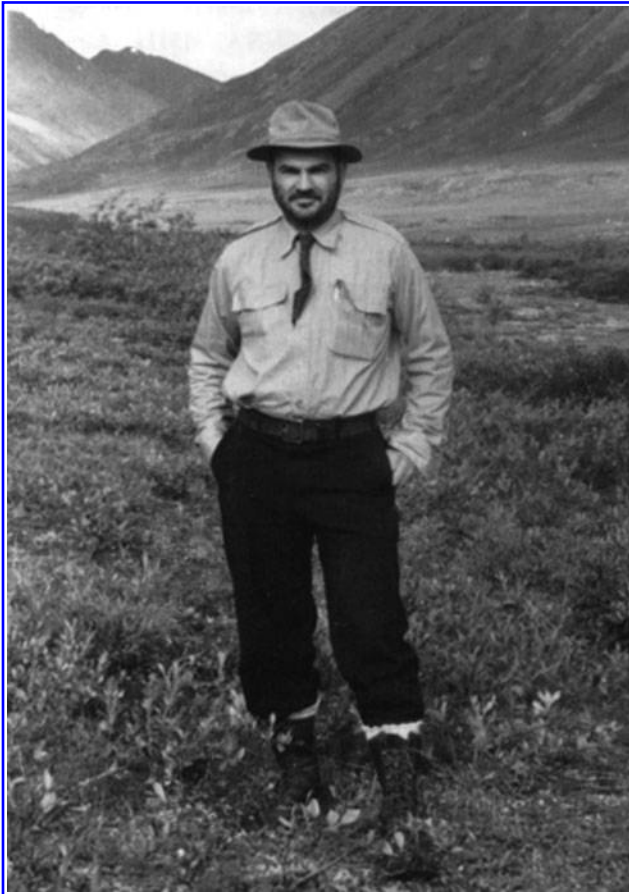


FIG. 4. Barry in August 1958 in Anaktuvuk Pass in the Brooks Range, northern Alaska. He was dressed for a meeting with Inuit village leaders to explain the research program and the purpose of their visit. Reprinted by permission of Princeton University Press.

discovery was probably what they named Ag, a polymorphic system affecting low-density lipoproteins and associated with diseases of the heart, stroke, and diabetes (Blumberg, 2002, pp 65–71, 73–74).

But this work was to take an unexpected turn that would lead to the Nobel Prize. Before describing that turn, an explanation of the technique they were using in the field studies is helpful. The technique of gel electrophoresis, familiar today to any microbiology student, was first introduced in 1955. It replaced paper electrophoresis, which was only capable of distinguishing a few proteins from one another. In gel electrophoresis, a sample, for example of blood serum², is placed in a small well in an agar gel, and an electric field is applied. The blood proteins contained in the serum migrate through the pores of the gel, separating according to their charge, mass, and shape.

In 1960, Barry and the colleague who had introduced him to genetic polymorphisms, Tony Allison, decided to use a variant of this technique called double diffusion. Its use was based on a principle involving patients who had received

multiple blood transfusions. It had become clear by that time that there were genetic variations between individuals and populations and that those variations led to variations among blood proteins. If a patient received several blood transfusions, it was likely that he or she would receive a variant of some protein that was different from the one he or she had inherited. If the protein variant was detected by the patient's body as "foreign," it might induce an immune response, that is, the generation of an *antibody*³. Such a foreign protein is called an *antigen* (from *antibody generator*). The blood serum of a patient having received multiple transfusions was thus likely to contain a large number of antibodies to a range of different antigenic blood proteins.

In the double diffusion technique,

Holes are cut in a thick sheet of agar cast on a glass plate. The serum from the transfused person is placed in a central well, and sera from the [subjects under study] are placed in adjacent wells around the center. Antibodies [from the transfused person's serum] diffuse into the agar. The proteins from the other sera in the peripheral wells also diffuse into the agar, and if the protein specific to the antibody is present, the combined proteins come out of solution and form a line of precipitation in the gel. The precipitation arc can be visualized, or the precipitated proteins can be stained for later study (Blumberg, 2002, p 67).

Use of this technique led to the unexpected turn; it took the form of the "Australia antigen."

The Australia Antigen and Hepatitis B

In 1964, Barry moved from the NIH to the Institute for Cancer Research (ICR—now the Fox Chase Cancer Center). He left the NIH because of a problem.

My main problem at the NIH...was fitting what I wanted to do into the discipline-determined rigidity of the constituent institutes.⁴ My research ranged over several disciplines. In addition to the laboratory work, I had to understand the anthropology of the populations we were studying and do field work and epidemiology. I was interested in how the environment and the host interacted to affect the risk of disease, and I didn't even know what disease I would be dealing with. In addition, there was a strong clinical component to the research. At ICR I would have the freedom and the funds to organize my research group in the way that I preferred. Even though ICR was dedicated to cancer, we were fundamentally a basic science organization, and we were, at least at that time, never asked what relation our research had to immediate cancer applications (Blumberg, 2002, pp 72–73).

Shortly before the move, a researcher in Barry's laboratory ran an experiment that produced a precipitin (the product of a reaction between an antigen and an antibody) different from those observed previously. The antigen was from the blood serum of an Australian aborigine; the antibody with which it reacted was from a New York City hemophilia patient who had received many transfusions. The newly discovered antigen was rare in sera from the

²The liquid portion of blood, with red cells, white cells, and clotting factors removed.

³An antibody is a protein (an immunoglobulin) produced by the immune system to identify and neutralize foreign invaders.

⁴"The several institutes that made up the NIH were mostly named for and dedicated to particular disease categories, e.g., cancer, infectious diseases, arthritis, metabolic diseases, heart, neurological diseases, etc." (Blumberg, 2002, p 72).

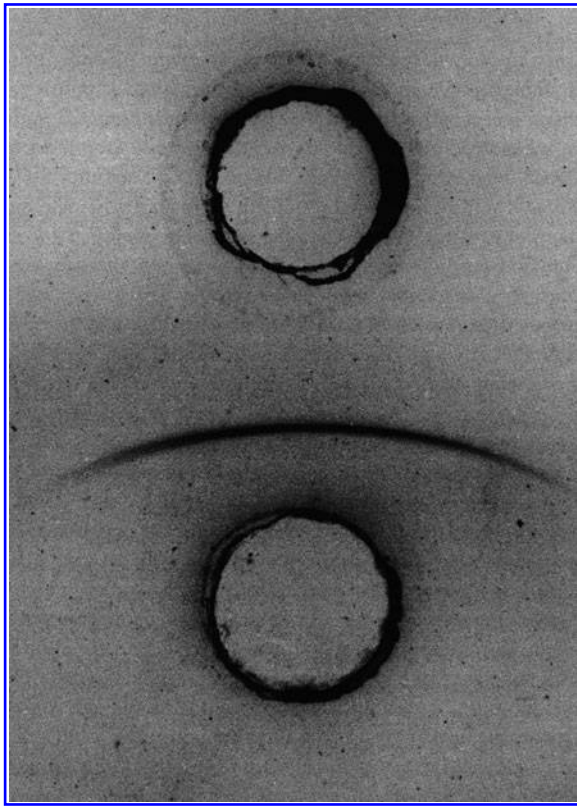


FIG. 5. The first published image of the precipitin reaction in agar gel between Australia antigen and the antibody against it. The two circles are wells in an agar gel. The bottom well contains the serum from a patient with leukemia who was a carrier of the Australia antigen. The top well contains serum from a hemophilia patient who had received many blood transfusions and contains antibody against Australia antigen. The precipitin, *i.e.*, the combination of the antigen and antibody, forms a curved downward-facing arc between the wells. Figure 1 in Blumberg, Alter, and Visnich (1965) “A ‘New’ Antigen in Leukemia Sera,” *JAMA* 191:542. Copyright © (1965) American Medical Association. All rights reserved.

general US population but common in the sera of people from Taiwan, Vietnam, Korea, the central Pacific, and Australian aborigines (Fig. 5; Blumberg, 2002, pp 79–81).

They gave the new antigen the neutral working name of “Australia antigen” (Au). After moving to ICR, Barry built up a team and started a systematic study of the disease and geographic distribution of Au. They found that Au was common in Asia, the Pacific, Africa, and eastern and southern Europe. They naturally sought to interpret their data in terms of an inheritance model, so their initial studies focused on families. They found the expected familial relationships—for example, if both parents had Au, then all their children would as well—but there were some surprising exceptions (Blumberg, 2002, pp 85–88). Perhaps most interesting, they found that most patients in the United States (where Au is rare) who were positive for Au had been transfused! This provided their first inkling that Au might be a blood-transmitted infectious agent. Two subsequent “normal population” studies in the United States showed one instance each of Au-positive individuals, one diagnosed

with hepatitis, the other someone who had just received a transfusion (Blumberg, 2002, pp 91–92).

Although these results were indicative of an infectious agent rather than an inherited condition, it was a study of Down’s syndrome⁵ patients that led the team to conclude that they had indeed found an antigen associated with the infectious agent of serum hepatitis, or hepatitis B. The focus on Down’s syndrome patients was the result of the observation that Au was common in patients with leukemia. Down’s syndrome patients were at high risk of developing leukemia, so it was natural to ask if they might also have a higher prevalence of Au (Blumberg, 2002, p 94).

Experiments quickly showed that they did. What’s more, studies of institutions of different sizes housing Down’s patients⁶ showed that the prevalence of Au was correlated with institution size; that is, the more patients were in contact with one another, the more likely they were to have Au in their blood. This was clearly consistent with an infectious model. So was the case of one Down’s syndrome patient who had tested negative for Au several times and then suddenly tested positive. It was found that he had a mild case of hepatitis, a strong clue that Au and hepatitis are associated⁷ (Blumberg, 2002, pp 96–99).

This observation led to a focus on testing the sera of hepatitis patients for Au. By mid 1967 the conclusion was clear: Au was significantly elevated in patients with acute hepatitis. At this point Barry and his team did what any good group of scientists would do: they wrote a paper on their results and conclusions and submitted it to a peer-reviewed journal. *The paper was rejected!* The reasons for this rejection, and Barry’s response, are interesting and important to this narrative.

Hepatitis was a well-known and long-studied disease at this time. There are recorded references to hepatitis epidemics as long ago as 2000 B.C. (National Academy of Sciences, 2000). Its most obvious symptom is jaundice, a yellowing of the whites of the eyes and possibly the skin caused by the buildup of bilirubin in the blood. There was a well-established community of hepatitis researchers who had been searching for the cause of this disease, and Barry and his team were not members.

None of us was a virologist, we had not been formally trained as epidemiologists, nor did we have any special expertise as hepatitis clinicians beyond our ordinary experience as physicians (Blumberg, 2002, p 102).

⁵Down’s syndrome is a common form of mental retardation associated with, in most cases, the presence of three copies of chromosome 21...The patients have a low IQ, around 50, but usually a very pleasant and loving personality. There are other physical abnormalities, including a high prevalence of heart disease and susceptibility to acute leukemia (Blumberg, 2002, p 94).

⁶The practice of preceding decades had been to institutionalize Down’s syndrome children. That practice was changing at the time of these studies, but institutions ranging from large, housing thousands of patients, to small group homes were still common.

⁷Others at high risk for leukemia, such as A-bomb survivors from Hiroshima and Nagasaki and Pacific islanders who had been exposed to radioactive fallout from nuclear bomb testing in the 1950s and early 1960s were also studied. The case of a Pacific islander who first tested negative for Au, then positive after a transfusion, and then developed the antibody to Au, also played an important role in the team’s thinking.

The reviewer who actually rejected the paper confessed that he had deemed ours to be just one more in a series of reports claiming that the hepatitis virus had been found. In his experience, previous findings had been subsequently refuted when tested by other investigators. He didn't want to risk another false claim for the identification of the elusive virus; and, erring on the side of caution, he had recommended the rejection of our article (Blumberg, 2002, p 100).

Barry and his team were surprised at the apparent hostility their claims engendered from the hepatitis community (Blumberg, 2002, p 102). It was around this time that Barry read Thomas Kuhn's *The Structure of Scientific Revolutions* (Kuhn, 1962) and realized that his team was on the cutting edge of a grand paradigm shift of the sort described by Kuhn. As Kuhn pointed out, the prevailing paradigm is not easily dislodged. As data accumulate that undermine the prevailing paradigm, its adherents resist. Only when the data become overwhelming, and a new paradigm is available to replace the old, does the scientific community swing quickly to a new way of thinking. This is what Kuhn termed a "scientific revolution." So Barry and his team were not only explorers, they were revolutionaries as well. And although revolutions may erupt quickly, it generally takes a much longer time for the effects of a revolution to become the new normal. And so it would be for the effects of this new understanding of hepatitis.

Saving Lives

Barry was not deterred by the rejection of their paper on the association of Au and hepatitis. "If such rejections are taken too seriously, they can lead to an attitude of martyrdom and of opposition to a recalcitrant establishment... We may have harbored unhappy sentiments for a while, but they didn't last, and the rebuff didn't slow us down" (Blumberg, 2002, p 100).

An earlier paper (Blumberg *et al.*, 1967) with less definitive conclusions about the Au-hepatitis association had been accepted by the same journal that rejected the later paper, so the basic claim was in the literature. But this wasn't enough proof that Au could be equated with the hepatitis virus. At this point, Barry did something that characterized his approach to science and to life in general. Barry cared most that things get accomplished. He didn't much care whether or not he got credit as long as the work got done. So he gave away the results of years of research to anyone who could make good use of them.

In October of 1968 we began to distribute—gratis, to scientists who requested them—reagent kits consisting of a serum containing Australia antigen and a second serum containing the antibody against it. This was one of the best steps we could have taken to move the research forward and speed its application. For years afterward, I met scientists in many parts of the world who recalled how these reagents allowed them to start research immediately without spending a year or more trying to find the reagents by themselves... During the next few months and years a growing understanding of the virus emerged. Some of this work was done at Fox Chase Cancer Center, but most of it was accomplished in laboratories spread throughout the world (Blumberg, 2002, pp 112–113).

One important observation made at the Institute for Cancer Research/Fox Chase Cancer Center was that a highly

purified fraction of Au, isolated from the blood of Au-positive individuals, was not infectious when injected into laboratory animals. But less-purified material did lead to infection. Barry and his team also knew from electron microscope imaging studies that Au particles appeared to be hollow and that the purified fractions did not contain nucleic acids. This indicated that Au was not the virus itself but a part of the virus.

The understanding of the virus that developed from this research around the world is shown in Fig. 6. The Australia antigen turned out to be the protein coating the surface of the virus, designated HBsAg for hepatitis B surface antigen. Beneath this surface coat is the core protein, HBcAg, which forms the viral capsid. The capsid in turn contains the viral DNA (which comprises only four genes), a DNA polymerase, and a reverse transcriptase (a portion of the virus's life cycle involves reverse transcribing an RNA, making the hepatitis B virus a retrovirus, like HIV). This is a very simple virus whose behavior is far from simple (Blumberg, 2002, pp 113–115).

Figure 7 shows an electron micrograph of hepatitis B (HBV) particles, illustrating an important characteristic of these particles in the blood of infected individuals: *the Australia antigen, HBsAg, vastly outnumbers (by roughly 1000:1) active virus particles.* This fact enabled two life-saving applications of the research.

The first application was eliminating hepatitis B virus from the blood supply. Before the discovery of Au, there was no way to detect the hepatitis virus in the supply of blood used for transfusions. With the explosion of surgery—particularly open-heart surgery, radical cancer surgery, and kidney transplants—that followed post-World War II developments in anesthesia and antibiotics, the need for blood had greatly increased. Hepatitis B infection had become a common and serious problem associated with these surgeries. In the late 1960s, there were more than 150,000 cases per year of post-transfusion hepatitis in the United States alone. But although Barry and his team recognized the potential to reduce and even eliminate post-transfusion hepatitis by eliminating Au-positive blood from the blood-banking system, others had yet to come to the same

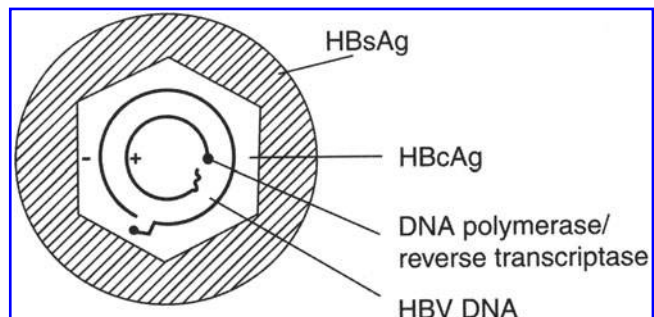


FIG. 6. The structure of the hepatitis B virus, showing the surface antigen (HBsAg) that surrounds the whole virus and the core antigen (HBcAg) that surrounds the circular DNA strands. The strands are double, with a large gap in the inner (positive) strand. The outer (negative) strand is complete. The DNA polymerase acts on the DNA strand. The overall size of the virus is 42 nm. Reprinted by permission of Princeton University Press (Blumberg, 2002, p 114).

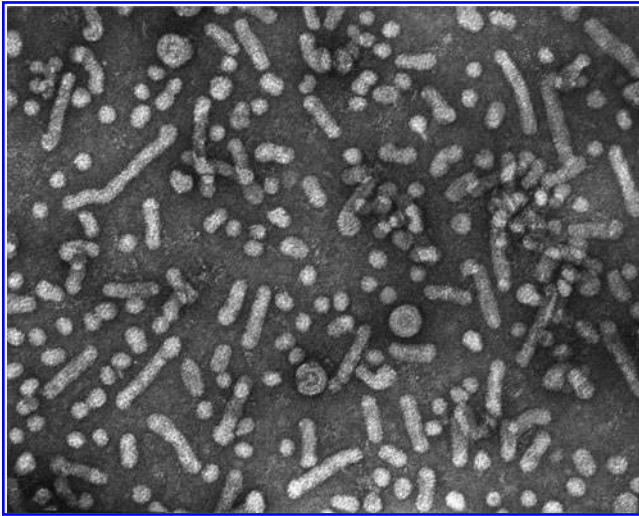


FIG. 7. An electron micrograph of HBV particles. The small circular particles and the elongated particles with the same width are the surface antigen. The small circular particles are about 22 nm in diameter. Three whole virus particles are visible in this image, two near the lower center and one at the top to the left. Reprinted by permission of Princeton University Press.

conclusion. The understanding of the virus described above had not yet been fully developed, and there was resistance to a new idea that upset the established model.

We were told that the medical and blood-banking community would not change their practices based on the available evidence. In addition to the changes required in their day-to-day operations, there would be increased costs that could cut into profits for the entrepreneurial blood bank supplier and impact the economies of the not-for-profit health institutions. We needed to plan a research project that would compel the blood-banking community to take notice (Blumberg, 2002, p 120).

That project began in late 1968 at the Philadelphia General Hospital, with which Barry and some of his colleagues were affiliated. It involved monitoring patients who had been transfused with Au-positive blood in comparison to a control group transfused with blood lacking Au. If the former developed hepatitis at a higher rate than the controls, it would be the evidence needed to move to the next step of screening and eliminating blood containing Au from the blood supply. While this project was underway, but before it had produced significant results, Barry and his team were informed of a similar study in Japan that had demonstrated a statistically significant correlation of Au-positive blood with post-transfusion hepatitis. They decided they could no longer ethically continue the study, that is, allow some patients to be transfused with Au-positive blood, and in July 1969 screening for Au and eliminating Au-positive blood became a routine procedure at the Philadelphia General Hospital.

The results were soon apparent but still not adequately convincing for others. The rate of post-transfusion hepatitis at the Philadelphia hospital dropped by a factor of 3. But it appeared that the test only detected about 25 percent of HBV carriers and hepatitis cases. It wasn't until October 1970 that the National Research Council reversed an earlier

position and recommended that testing begin in all laboratories able to do so. By 1972–1973, testing of all blood used in the United States was required by law (Blumberg, 2002, pp 120–126). From that point on, progress in bringing post-transfusion hepatitis under control proceeded rapidly. The subsequent development of more sensitive HBV tests, and the discovery in the 1980s of HCV and development of a corresponding test, completed the elimination of post-transfusion hepatitis as a major public health threat wherever blood was properly screened.

The second application was the most significant in terms of saving lives. It was the development of a vaccine to prevent HBV infection. HBV is much more infectious than HIV. Transmission requires blood-to-blood or other body fluid contact and occurs mother-to-child at birth, sexually, through contaminated needles, through sharing common personal items such as toothbrushes (via saliva or bleeding gums), and so on. There is even a documented case of transmission through paper cuts from IBM punch cards! About one-quarter of the world's population (~2 billion people) has been infected. Before the introduction of the vaccine, some surveys in China showed infection rates of ~15%. In addition, HBV causes most primary cancers of the liver, killing about 1.5 million people worldwide annually from that disease.

An early observation provided the essential clue leading to the vaccine.

In our early tests on thousands of individual sera, we had rarely seen a person who had HBsAg in the blood—that is, was a carrier of HBV—and, at the same time, had the antibody against the surface antigen (anti-HBs). This is consistent with the hypothesis that anti-HBs is protective against infection (Blumberg, 2002, p 136).

This conclusion was consistent with the observation that “transfused patients who had the antibody [anti-HBs] before transfusion, or developed it after transfusion, were less likely to experience hepatitis events than patients who did not” (Blumberg, 2002, p 136).

In other words, the antibody that protected against HBV infection was the antibody, anti-HBs, produced when an individual was exposed to the surface antigen, HBsAg. In an infected individual, the surface antigen was produced in large quantity by the live virus. But if the surface antigen *alone* were introduced into the blood stream, it should generate the immune reaction producing the antibody that would protect against subsequent infection by the virus itself.

Now the fact that the virus produces very large quantities of the surface antigen in the blood of infected individuals provided a straightforward, if unprecedented, way to make a vaccine.

The purified particles that contained only the surface antigen (HBsAg), which were very common in the blood, could be separated from the infectious particles—which were rare—by centrifugation. The purified particles, without the infectious material, did not transmit HBV...[Our method involved] applying enzymes to remove any serum protein remaining and also to impair or destroy any viable virus that might remain, followed by column separation and treatment...to kill residual virus of any kind. Substances to [boost the immune system's response] and preservatives to increase shelf life...and voila, the vaccine (Blumberg, 2002, p 137).



FIG. 8. Barry receiving the Nobel Prize from Carl XVI Gustaf, King of Sweden.

No vaccine had been made this way before, and there have been none since. But the community was still skeptical. “In 1969, when we first invented the vaccine, there was little faith in the hepatitis community or among the pharmaceutical companies that we had identified the virus—much less produced, by a totally unconventional method, a vaccine that would be practical and economically profitable” (Blumberg, 2002, p 139).

Further, hepatitis was not thought of as a serious disease in the developed world, so to some it was not a matter of great urgency. The association with cancer of the liver was not yet known. In addition there was concern, heightened by the emergence of HIV, that a blood-derived vaccine could in principle contain live virus and hence cause infection.

It was not until 1975, 6 years after the vaccine’s initial development, that the Merck Corporation was licensed to develop the vaccine commercially. And it was another several years of testing and review before the vaccine received approval from the Food and Drug Administration in the early 1980s. At about the same time, the use of recombinant DNA techniques allowed the vaccine to be manufactured without the use of human blood products. Within a few years, millions of children and adults were being vaccinated yearly. Estimates are that the total number of doses administered to date number in the low billions. As of 2009, 177 countries had national vaccination programs. It is now one of the most commonly used vaccines in the world and the first to protect against a major human cancer. It is second only to smoking prevention as a cancer-prevention program.

The Nobel Prize and Its Impact

In 1976, Barry and Carlton Gajdusek were awarded the Nobel Prize in Physiology or Medicine “for their discoveries concerning new mechanisms for the origin and dissemination of infectious diseases” (Figs. 8–10). Gajdusek studied Kuru, a disease of the brain that particularly afflicted

a neolithic people living in the highlands of New Guinea. He showed that the transmission mechanism was a form of ritual cannibalism of a deceased relative that particularly exposed women and children to infection as they prepared the funeral meal.⁸

Barry was cited for his work elucidating the mechanisms of hepatitis B infection and developing both the blood test to detect carriers and infected individuals as well as the vaccine to prevent infection. But the Nobel committee made another important observation about Barry in announcing the prize: “Since his original discovery Blumberg has continued to be the leading figure within the field of hepatitis research” (Karolinska Institutet, 1976, para 3). Indeed, what the prize meant for Barry more than anything was the opening of doors that enabled him to promote the adoption of blood testing and vaccination that would save hundreds of millions of lives and continues saving lives today.

Nowhere was Barry’s influence more important than in China (as I will refer to the People’s Republic of China throughout). In the mid 1970s, Chinese scientists submitted a paper to an international cancer congress showing that primary cancer of the liver was one of the most common cancers in China, with a higher incidence rate than found anywhere else in the world at that time. It was clear to Barry that transferring knowledge about his team’s research and the vaccine was imperative for saving countless lives in the most populous country on Earth. But this was a time when the United States and China did not have diplomatic relations, and Western ideas and technologies were viewed with some suspicion. President Nixon’s unexpected visit to China occurred in 1972, but normal diplomatic relations would not be established until 1979.

Upon learning of the public health problem presented by liver cancer in China, Barry contacted Chinese medical

⁸Nobel Prize Web site http://www.nobelprize.org/nobel_prizes/medicine/laureates/1976/press.html.



FIG. 9. Barry and his fellow Nobel Laureates of 1976. From left to right, Burton Richter (co-recipient in physics); Carleton Gajdusek, who shared the prize with Barry; William Lipscomb (chemistry); Saul Bellow (literature); Samuel Ting (co-recipient in physics and currently Principle Investigator for the Alpha Magnetic Spectrometer experiment on the International Space Station); Milton Friedman (economics); and Barry.

authorities and offered to travel to China. But an invitation was not extended until just after the Nobel Prize was awarded. Providentially, the Gang of Four was arrested and deposed just a week before the prize was announced. It was most likely the confluence of these two events that made it possible for Barry to travel to China in 1977.

The trip to the People’s Republic of China was one of the most important, if not the most important foreign excursion I have ever undertaken in respect to the impact that it had on

the public health. I reported on the latest research on hepatitis and its application to audiences who knew little of it, and even carried information from one laboratory in China to another. I told them about our HBV vaccine, provided a copy of the patent (which had already been published), and set up for contacts with Merck, with whom we had signed our patent licensing agreement. Arrangements were made later by Merck and the Chinese authorities for technology transfer that allowed the construction of facilities for the manufacture of the vaccine [in China]. In later years, visiting Chinese scientists would often tell me that they had heard me speak, and of the effect my visit had on accelerating research and initiating the huge vaccination program that is now in place (Blumberg, 2002, pp 172–173).

A subsequent trip to Taiwan in 1978 also had great impact. The Taiwanese had already adopted blood testing for HBV, but blood that tested positive was discarded. Barry recommended that they freeze the separated blood serum and use it as a source of surface antigen for vaccine manufacture. When he returned to Taiwan in 1986, he found that they had followed his suggestion and commemorated his visit by hanging his picture on the wall of the Taipei Blood Donor center. It was not the last time Barry was to be honored for his contributions to public health in that part of the world.

In 2002, Barry and his wife Jean toured China at the invitation of the Cancer Center at Sun Yat-Sen University of Medical Sciences, a World Health Organization Collaborative Center in Cancer Research. Barry was lavished with praise and recognition during the trip. It was for him, as he wrote in his diary, “completing a cycle, a story with a beginning, a middle, [but] not [yet] an end, for the effects of [our] research will continue for many years.”

In 2009, Barry was honored by the Chinese Hospital of San Francisco and the San Francisco Hepatitis B Free Campaign. He was presented with the 3rd Annual Hep B Free Super Hero Award which included a blue cape with the “B Superhero” emblem emblazoned on the back. His



FIG. 10. The celebration at Fox Chase Cancer Center after the Nobel Prize was announced. Barry is in the center. His wife Jean is applauding behind his right shoulder.

birthday, July 28, has been celebrated as World Hepatitis Day since 2010.

Master of Balliol College

Before discussing how Barry's scientific career shaped his perspectives on astrobiology, it's worth pausing at another point in Barry's story. In 1989, Barry was elected Master of Balliol College, the Oxford college with which he had been associated as a graduate student in the 1950s and at which he had served as the Eastman Professor in 1983. The college, one of the oldest at Oxford, was best known for educating future politicians, philosophers, and economists—not particularly scientists. Barry was the first American to serve as master, and the first scientist if we don't count a 14th-century alchemist. He served for 5 years until 1994.

Barry observed that as master he

had no power, but a great deal of influence...So, I had to learn to govern without power, to enlist the voluntary interest of Fellows when there was a specific task to do, guide the College meetings to decrease friction and unneeded controversy, and spend much time doing it. Learning to lead without actual power came in good use in later years when, at the NASA Astrobiology Institute, I had considerable administrative power, but only rarely had need to use it (Blumberg, 2006, Addendum para 33).

Barry and Astrobiology

Barry's introduction to NASA and astrobiology came by way of Stanford University in Palo Alto, California. In 1997, he was invited to teach in Stanford's Human Biology Program. NASA's Ames Research Center lies just a few miles to the south. Ames had a long tradition of space and life science research, so when NASA Administrator Dan Goldin proposed a new NASA Astrobiology Program that same year, he naturally turned to Ames for leadership. In 1998, Ames scientists organized the Astrobiology Roadmap Workshop to develop a working definition of the new program's scope. A colleague of Barry's at Stanford who worked with some of the Ames scientists invited Barry to attend.

Barry was totally fascinated. And it's easy to see why. First, astrobiology poses big, fundamental questions. Barry had spent much of his career studying a tiny virus, but he was asking questions about the grand design of nature—about how pathogens, inheritance, behavior, environment, and many other factors interact to influence the acquisition and progress of disease. And even how these factors operate and affect society in broader ways as well.⁹ Barry was attracted to big, fundamental questions. So when he learned

⁹Barry frequently noted that viruses must confer advantages as well as disadvantages, because otherwise they, or susceptibility to them, would have been weeded out by evolution. This is particularly true of hepatitis B, which affects around one-third of Earth's population. One possible advantage is that anti-HBs appear to protect against other diseases in addition to hepatitis B. Another effect of the virus unrelated to disease is that *parents who are chronic carriers of the hepatitis B virus are more likely to produce male children than females*. This is a somewhat startling finding, since gender ratio is one of the most stable human biological features, probably playing an important role in evolutionary history (Blumberg, 2002, pp 182–186; Blumberg, 2007, parts 43–44).

that NASA was studying “the origins, evolution, distribution, and future of life on Earth and in the universe,” he was more than intrigued. “How does life begin?” “Are we alone?” “What is the future of life on Earth and beyond?” Barry recognized that implicit in these questions is the even more profound question “What is life?” And how would we recognize alien life? Applying scientific methods to these questions—centuries-old subjects of inquiry by philosophers, theologians, and ethicists—was enormously appealing to Barry.

Second, astrobiology is highly interdisciplinary. Barry had built his career on research that transcended disciplinary boundaries. His medical research spanned genetics, virology, epidemiology, population anthropology, environment-host interactions, clinical medicine, and so on. He left the NIH because of how difficult it was to pursue such interdisciplinary research within the confines of its disease-oriented structure. Astrobiology requires the coming together of scientists from the astronomical, biological, and geological sciences, as well as chemists, physicists, engineers of several sorts, and a sprinkling of philosophers, theologians, and other humanists for good measure. Barry appreciated the significance of NASA's astrobiology program, not only for the grand questions it asked but also for the structures that were being created to break down barriers between disciplines. And the structure that addressed the need for interdisciplinarity most directly was the NASA Astrobiology Institute.

Third, astrobiology requires extensive fieldwork. Astrobiologists study life in the most extreme environments on Earth, from hot springs of boiling sulfuric acid, to ice and permafrost in polar regions and at high altitudes, to underground caverns, to Earth's driest and hottest deserts. What could appeal more to a man who had reveled in travel to some of Earth's most remote populations?

In 1999, Dan Goldin asked Barry to become the founding director of the nascent NASA Astrobiology Institute. Barry initially suggested that perhaps Dan would prefer someone younger. After all, Barry was then 74, an age at which many who haven't yet retired are winding down their professional activities. But Dan was clear: he wanted “an 800-pound biologist”¹⁰ to lead the NAI and establish astrobiology's place on the scientific map. And he was confident that Barry was just the man for the job.

The basic structure of the NAI had been established before Barry became involved, and the first cohort of teams had been selected in 1998. Barry's role as founding director was to establish the NAI's scientific direction and principles and to work out what a virtual institute actually was and how it would function.

I understood that my mandate was to establish a basic science organization that could discover and understand natural phenomena that related to early life and to life elsewhere. At an introductory address to the members of the Institute [Executive Council], I told them that I did not expect them to do exactly what they said they would do in the [grant] applications since, in a fast moving field, observations made

¹⁰In later years, when as NAI director I had the opportunity to introduce Barry to various audiences, I liked to mention Dan's “800-pound biologist” metaphor, noting that Barry was actually a pretty slim and trim guy.



FIG. 11. Barry with members (back row) of the Minority Institution Astrobiology Collaborative at the 2006 Astrobiology Science Conference in Washington, DC. Seated next to Barry, from right to left, are Todd Gary of Tennessee State University, the administrator at the time of the NAI Minority Institution Research Support (MIRS) program; Melissa Kirven-Brooks of NAI Central (NASA Ames Research Center); and the author.

after the application had been written could greatly change the path of research. This was greeted with cheers (Blumberg, 2006, Addendum para 39).

One could hardly have expected a different approach from a man who began studying genetic polymorphisms and found himself shaking hands with the King of Sweden (Fig. 8) for solving the mystery of one of humanity’s most serious diseases.

One of the first puzzles Barry had to work out was how to create a “culture of collaboration.” Most scientific research is of course done collaboratively, but the collaboration is frequently among small groups of researchers in the same or similar disciplines. The NAI posed a particular challenge. Larger collaborative teams would form to write interdisciplinary proposals that were then subjected to an intensely competitive evaluation process. The selected teams were then expected to collaborate for 5 years, following which they would potentially become competitors again. Further, the collaboration while a part of the NAI had to take place not only across disciplines but also across distance, institutions, national borders, and even generations.

This was fundamentally a challenge of nurturing particular human behaviors. But of course Barry was a student of human behavior. He had taught medical anthropology, and so much of his research had involved understanding how human behavior interacts with other factors to affect disease susceptibility. So Barry’s response to the challenge presented by the NAI should not have been surprising. *He hired an anthropologist!* Probably not what most directors of an organization studying life in the universe would do, but entirely in character for Barry.

The anthropologist, Lisa Faithorn, had been a graduate student in the University of Pennsylvania’s Anthropology

Department while Barry was affiliated with the department, but they didn’t meet until Barry interviewed her in 2000 for the NAI job. Lisa worked with Barry, other NAI managers¹¹, and scientists across the institute to understand the impediments to collaboration and how to link diverse and widely dispersed individuals and groups to form a cohesive “virtual” organization. Characteristically, Barry was concerned not only with the technologies needed for a virtual institute but with “the sociology and even psychology of scientists and the way in which they interact” (Blumberg, 2003). The “lessons learned” that emerged focused on the interrelationships between the many different aspects of collaboration (Faithorn and Blumberg, 2009).

Barry recognized as well that it would be important for scientists on NAI teams to come together with scientists not affiliated with the NAI. Collaboration and interaction could not be an insular affair. Focus Groups, open to all who were interested, were formed to promote this broad interaction. The nature of Focus Groups was deliberately not defined, with the expectation that each group would determine its own character (Stedman and Blumberg, 2005). This also provided Barry an opportunity to contribute his personal expertise through co-leadership of the Virus Focus Group, formed to promote the study of viruses in extreme environments and their implications for extraterrestrial biospheres.

Another aspect of astrobiology, common to many sciences, is the distribution of interest and expertise around the

¹¹The NAI was, and is, managed by a small group (currently about a dozen) at the NASA Ames Research Center. The group is called NAI Central.



FIG. 12. Barry at Houghton Crater, Devon Island, Nunavut, Canada, with members of the Houghton Mars Project Team in the summer of 2000.

globe. Barry was a strong supporter of international collaboration, reflecting his experience of working with partners all around the world in striving to understand the nature of disease. Shortly after the NAI was formed, a new astrobiology group in Spain proposed a formal partnership. This was established at the government-to-government level, and the Spanish government soon provided funding for a major dedicated research facility near Madrid known as Centro de Astrobiología. This was the first, and most impressive, demonstration of one aspect of the NAI's international partnerships: affiliation with the NAI helps its international partners acquire resources in their own countries. Thus the international relationships begun and fostered under Barry's leadership have not only contributed to progress in astrobiology, they have increased the resources worldwide being dedicated to the field.

Barry empowered his Associate Director, Rose Grymes, to make the international partnership program one of her major foci. In the next few years, five additional international partners were added to the institute, one at the government-to-government level (Australia) and four at the institute-to-institute level. Today the NAI has 13 international partners, and the number continues to grow. Astrobiology is truly a global endeavor, and Barry played a key role in setting it on that path.

Another thing Barry appreciated was the role that underserved communities had to play. Part of the NAI's charter is to "train the next generation of astrobiologists." Barry knew that this could not be done properly without reaching out to underserved communities. He charged one of the NAI Central staff, Karen Bradford, with determining what it would take to engage the minority institution community with the NAI Executive Council and NASA Headquarters in a partnership that would be meaningful for all involved. When Karen reported back on her research, he asked her to lead the formation of the partnership. The result is known today as the Minority Institution Research Support (MIRS) program. It provides summer sabbatical support to faculty from minority-

serving institutions and academic year support to the sabbatical recipients and their students to become more deeply engaged in astrobiology research (Fig. 11).

Of course Barry's passion for being in the field carried through to the NAI portion of his career. He personally participated in numerous field trips as director and later as Distinguished Visiting Scientist at both the NAI and its sister organization, the NASA Lunar Science Institute (NLSI). Two trips that he often spoke about were to Devon Island in the Canadian high Arctic, where NASA and other groups are studying life in a large ~40 million-year-old impact crater, and to the Iron Mountain Mine near Redding, California, where he had to overcome claustrophobia to see firsthand the underground biofilms growing under highly acidic conditions that were of interest to astrobiologists (Blumberg 2007, parts 54–55; Figs. 12 and 13). Barry particularly liked astrobiology field trips because he loved the outdoors. Mines aside, astrobiology field sites are generally outdoors, whereas his medical fieldwork was typically performed in a clinic or other building.

Barry also saw the connection between fieldwork and training the next generation of astrobiologists. When he became President of the American Philosophical Society¹² (APS) in 2005, he established the Lewis and Clark Fund for Exploration and Field Research to provide small grants supporting fieldwork by doctoral candidates in diverse subject areas. In 2006, the NAI and the APS in partnership established the Lewis and Clark Fund for Exploration and Field Research in Astrobiology, administered by the APS. In the years since, many young investigators who received

¹²The American Philosophical Society, the oldest learned society in the United States, was founded in 1743 by Benjamin Franklin in Philadelphia for the purpose of "promoting useful knowledge." Today the APS promotes useful knowledge in the sciences and humanities through excellence in scholarly research, professional meetings, publications, library resources, and community outreach: <http://www.amphilsoc.org/about>.



FIG. 13. Barry at the Iron Mountain Mine near Redding, California, September 2002.

these awards have reported how dramatically the experience influenced their work and career path.

Another initiative of Barry’s as NAI director, and one that showed he was again ahead of his time, was the establishment of an institute “photo directory” that we might recognize today as a precursor of Facebook. Barry insisted that having a resource that enabled one to put a face with a name and other information about the individual was an essential

element of building a cohesive virtual organization. In the earliest days of digital cameras, he had a digital photo booth set up at the April 2001 General Meeting of the NAI in Washington, DC, to ensure that there were pictures of as many people as possible in the directory.

One of Barry’s final initiatives in astrobiology came to fruition only posthumously. Barry was a founding member of the Scholars Council of the Library of Congress, which

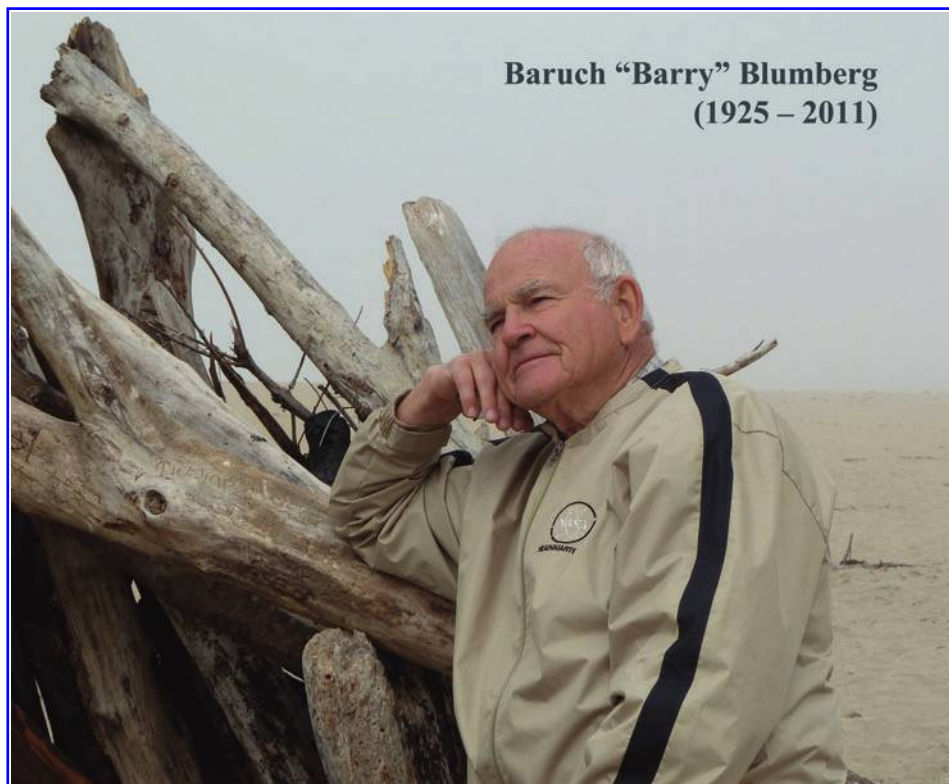


FIG. 14. Barry at Half Moon Bay in November 2010 (photo courtesy of Estelle Dodson).

advises the Librarian on scholarly matters. Although scholarship at the Library focuses on the humanities, Barry's presence on the Council reflected the Librarian's desire to expand Library activities into the sciences. Barry felt that astrobiology was a perfect candidate for this expansion, given astrobiology's implications for philosophy, theology, and other humanistic areas. Barry introduced the author to Carolyn Brown, Director of the Library's John W. Kluge Center, and together the three of us began developing the concept of a scholarly chair in astrobiology. The chair would be selected competitively to spend up to a year in residence at the Kluge Center, conducting research at the intersection of the science of astrobiology and its humanistic aspects, particularly its societal implications. On December 1, 2011, NASA and the Library of Congress announced the establishment of the Baruch S. Blumberg NASA–Library of Congress Chair in Astrobiology. It seems a particularly fitting tribute to a man whose vision embraced not just science but the positive impact science can have on humanity.

Concluding Observations

In many ways, Barry's career was exemplary of how science *should* be conducted and increasingly how it *will have to be* conducted in the future. Barry always worked across the traditional academic disciplines. He recognized that these disciplines were not inherent to nature but were created by academics to help organize knowledge and educate future scientists. While disciplinary education and thinking still has a role to play, it has become common for disciplinary distinctions to be a barrier to advancing knowledge rather than a conduit. The development of Earth system science in the 1980s and 1990s is one example of integration across disciplines that was necessary to enable advancement in a field of overriding importance to society.

Barry was exemplary in his generosity and selflessness as well. He shared the products of his work freely, asking not for credit but only that the work be advanced and applied as quickly and effectively as possible. This was particularly important for a medical researcher, since the outcome was more lives saved and disease prevented. But it goes against many of the pressures of a modern career in which credit and priority typically play a major role in determining stature, employment, and remuneration.

Barry was also remarkably successful in attracting first-rate researchers to join him. That was surely in part because he had good ideas, but I think it was also—perhaps even most importantly—because he was a genuine, warm, thoughtful, kind human being. People were attracted to Barry because of all his personal qualities. Could an unpleasant and unkind person have accomplished all that Barry did? Perhaps, but I doubt it. Good people attract other good

people. In Barry's case, I believe that his innate goodness contributed as much to his ultimate accomplishments as did any of his specific professional skills.

Abbreviations

APS, American Philosophical Society; Au, Australia antigen; ICR, Institute for Cancer Research; NAI, NASA Astrobiology Institute; NIH, National Institutes of Health.

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