ALBERT AND MARY
LASKER FOUNDATION

2007 LASKER AWARDS
for
MEDICAL RESEARCH

EMBARGOED FOR RELEASE:
For initial publication
on **Sunday, September 16, 2007**

CONTACT: Kendall Christiansen
Geto & de Milly, Inc.
212.686.4551; cell: 917.359.0725
Email: kchristiansen@getodemilly.com

DISCOVERER OF DENDRITIC CELLS AND INVENTORS OF REPLACEMENT HEART VALVES RECEIVE LASKER AWARDS FOR MEDICAL RESEARCH

ARCHITECT OF AIDS AND BIODEFENSE PROGRAMS HONORED WITH PUBLIC SERVICE AWARD

NEW YORK, Sunday, September 16, 2007 – The **2007 Albert Lasker Medical Research Awards** were announced today. Now celebrating their 62nd anniversary, the Lasker Awards are the nation's most distinguished honor for outstanding contributions to basic and clinical medical research, as well as for outstanding public service on behalf of medical research.

The **Lasker Award for Basic Medical Research** honors **Ralph M. Steinman**, 64, of the Rockefeller University, New York City, who **discovered dendritic cells**. These immune cells trigger other components of the immune system to thwart microbial invaders. Steinman's work has opened up novel therapeutic avenues for combating cancer and pathogens.

The **Lasker Award for Clinical Medical Research** honors **Alain Carpentier**, 74, of Hôpital Europeen Georges Pompidou, Paris, and **Albert Starr**, 81, of the Providence Health System, Portland (OR), who **developed prosthetic mitral and aortic valves**. These devices have prolonged and enhanced the lives of millions of people with heart disease, providing treatment where none existed before.

The **Mary Woodard Lasker Award for Public Service**, awarded bi-annually, honors **Anthony S. Fauci**, 66, Director of the National Institute of Allergy and Infectious Diseases, a component of the National Institutes of Health, for **engineering two major U.S. governmental programs, one aimed at AIDS and the other at biodefense**.

Often called "America's Nobels," the Lasker Award has been given to 72 scientists who subsequently went on to receive the **Nobel Prize**, including 20 in the last 17 years.

The Awards will be presented at a luncheon ceremony on **Friday, September 28th** at the Pierre Hotel in New York City. **Jeffrey Sachs, Ph.D.**, noted economist and Director of the Earth Institute at Columbia University, will be the keynote speaker.

Dr. Joseph L. Goldstein, recipient of the 1985 Lasker Award for Basic Medical Research and the Nobel Prize in Medicine in 1985 (both with Dr. Michael Brown) for discoveries regarding cholesterol, is Chair of the international jury of scientists that selects recipients of the Lasker Awards. He explained the significance of this year's Basic Research and Clinical Research Awards with the following comments:

"More often than not, success in science depends on courage, determination, confidence, and the willingness to ignore conventional wisdom—especially when these traits accompany strong logic. This year's Lasker Awards honor investigators whose triumphs relied on these characteristics.

"The discovery of dendritic cells by Ralph Steinman broke open an entire field. While most immunologists were studying events that occur *after* germs trigger an immune response, he focused on the initial steps in that process and came up with an unconventional idea—that the strange, rare dendritic cells he had noticed in spleen preparations stimulated the body's T cells, the key combatants of microbial invaders. Undistracted by popular theories, Steinman doggedly pursued these dendritic cells, establishing that they are our immune system's most potent activators of T cells — something that no one had ever had imagined. Today, many scientists, still led by Steinman, are vigorously exploring an exciting new possibility for dendritic cells — as agents for fighting cancer and AIDS.

"Fifty years ago, heart-valve replacement surgery did not exist. Today, it is the second-most common cardiac surgery in the United States and one of the most successful. The invention of mechanical and tissue-based valves by Albert Starr and Alain Carpentier benefits several hundred thousand people each year, who otherwise would suffer from heart failure or premature death."

Dr. Alfred Sommer, recipient of the 1997 Lasker Award for Clinical Medical Research and Dean Emeritus and Professor at the Johns Hopkins Bloomberg School of Public Health, is a member of the Selection Committee for the **Mary Woodard Lasker Award for Public Service in Support of Medical Research and the Health Sciences.** He offered this comment on the 2007 Awardee:

"The **Mary Woodard Lasker Public Service Award** honors **Anthony S. Fauci** for the extraordinary way in which he marshaled scientific evidence to construct our nation's response to two global crises: HIV/AIDS and bioterrorism. Fauci's passionate, reasoned persuasion led to the President's Emergency Plan for AIDS Relief, or PEPFAR, the United States' unprecedented commitment of $15 billion over five years to combat AIDS in some of the most heavily affected countries around the world; and to Project Bioshield, our country's principal public health effort to protect the nation from the consequences of bioterrorism. For more than 20 years, U.S. Presidents have sought Fauci's advice in their formulation of national public-health policy and its execution—and he has played a unique role in explaining issues of great concern to our nation's citizens."

The Lasker Awards, first presented in 1946, are administered by the **Albert & Mary Lasker Foundation**. The late **Mary Woodard Lasker** is widely recognized for her singular contribution to the growth of the National Institutes of Health and her unflagging commitment to government funding of medical research in the hope of curing devastating diseases. Her support for medical research spanned five decades, during which she was the nation's foremost citizen-activist on behalf of medical science.

Lasker Award recipients receive an honorarium ($150,000 for each Award), a citation highlighting their achievements, and an inscribed statuette of the Winged Victory of Samothrace, the Lasker Foundation's traditional symbol representing humanity's victory over disability, disease, and death.

The list of the 2007 Lasker Award recipients with their current professional and institutional affiliations follows. Additional materials, available upon request and at www.laskerfoundation.org, include:

- The full citations for each Award category;
- Photos of the Awardees;
- Interviews with the Awardees;
- Information about past Awardees; and,
- Links to Web sites for additional information about the Awardees.

ALBERT LASKER AWARD FOR BASIC MEDICAL RESEARCH

For the discovery of dendritic cells—the preeminent component of the immune system that initiates and regulates the body's response to foreign antigens.

RALPH M. STEINMAN
Professor and Senior Physician
Laboratory of Cellular Physiology and Immunology
The Rockefeller University
New York, NY

ALBERT LASKER AWARD FOR CLINICAL MEDICAL RESEARCH

For the development of prosthetic mitral and aortic valves, which have prolonged and enhanced the lives of millions of people with heart disease.

ALAIN CARPENTIER
Professor of Vascular Surgery
Hôpital Europeen Georges Pompidou
Paris

ALBERT STARR
Director of Academic Affairs
Providence Health System
Portland, OR

MARY WOODARD LASKER AWARD FOR PUBLIC SERVICE IN SUPPORT OF MEDICAL RESEARCH AND THE HEALTH SCIENCES

For his role as the principal architect of two major U.S. governmental programs, one aimed at AIDS and the other at biodefense.

ANTHONY S. FAUCI
Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, MD

The Albert Lasker Award for Basic Medical Research

Presented to Ralph M. Steinman

For the discovery of dendritic cells—the preeminent component of the immune system that initiates and regulates the body's response to foreign antigens.

The **2007 Albert Lasker Award for Basic Medical Research** honors the scientist who discovered dendritic cells, the preeminent component of the immune system that initiates and regulates the body's response to foreign antigens. At a time when conventional wisdom pointed in other directions, **Ralph M. Steinman** proposed that these cells propel other immune cells into action and then pursued that possibility with careful and dedicated experimentation. He revolutionized our understanding of the events that instigate an immune response and unlocked the entire field of T-cell activation.

In the last 34 years, Steinman's work has revealed that dendritic cells scour the environment for microbial invaders and stimulate the T cells of the immune system to respond. These T cells in turn prompt other immune cells to eliminate the threat. Steinman devised techniques that generate large numbers of dendritic cells, which fueled a research boom in this area. His work spawned a major discipline, with hundreds of investigators worldwide studying these cells and their roles in multiple aspects of immune regulation.

Steinman's work touches all major facets of immunology and holds enormous clinical promise. Scores of clinical studies are aiming the immuno-stimulating power of dendritic cells at tumors and HIV, and scientists are developing approaches that could target a broad range of infectious agents. Recent studies have shown that dendritic cells also contribute to tolerance, the process by which the body quiets potential immune reactions to its own cells. This awareness is inspiring researchers to design dendritic-cell-based therapies that treat autoimmune and allergic disorders.

Branching Out in the Immune System

Since the dawn of immunology, at the end of the 19th century, scientists have grappled with the question of how vertebrates respond to the tremendous array of pathogens that they encounter. In the 1950s, immunologists proposed that immune cells use receptor molecules on their external surfaces to recognize invading germs and other foreign particles, or antigens. Each receptor differs slightly from the next and can "see" a different antigen. Vast numbers of immune cells exist in the body prior to any infection; together, they detect all antigens that an organism meets. Once an antigen contacts its receptor, the associated immune cell multiplies to create an army that rises up to attack that specific antigen.

By 1970, when Steinman began his work, this "clonal selection" theory was well accepted. Scientists had discovered that lymphocytes, a group of cells in the blood and other immune-related tissues, play key roles in fighting microbial trespassers. For example, B cells produce antibodies, which attach to bacteria and mark them for destruction by other components of the

immune system. T cells perform numerous tasks: Some types kill virus- and bacteria-infected cells, whereas others incite B cells to manufacture antibody.

To better understand lymphocytes' functions and interactions, researchers wanted to re-create aspects of the immune response in culture dishes. When they attempted to do so, they encountered a mystery: Adding antigens to lymphocytes in culture dishes did not trigger the cells' duplication. Apparently, something in the body that stimulated lymphocytes to respond to antigen was absent from the culture dish. Steinman set out to find the missing piece.

This issue lay at the center of immunological study at the time. Scientists speculated that lymphocytes could detect foreign agents only if an unidentified "accessory" cell displayed the microbe's antigens on its surface. Macrophages, which engulf and digest cellular debris and pathogens, seemed like strong contenders for this job. B cells and T cells also were candidates. However, convincing evidence remained elusive. For example, if macrophages could activate T cells, the more macrophages a sample contained, the more powerful should be its stimulating power; but the abundance of macrophages did not correlate with T-cell-activating capacity.

Working with the late Zanvil Cohn at the Rockefeller University, Steinman harvested a cellular mixture from mouse spleen that was known to spur T cells to divide in culture dishes. When he peered through the microscope at his spleen-derived substance, he noticed not only macrophages and other established immune cells, but rare, irregularly shaped cells that no one had described before. They moved in a distinctive way: Long projections emerged and floated around before retracting, giving the cells a dynamic star-like appearance. This branching behavior inspired Steinman to dub them dendritic cells, derived from the Greek word for tree. The cells differed from other immune cells in structure and behavior. For example, their surfaces didn't carry molecules that typify macrophages, and they poorly internalized material from their environment. Unlike macrophages, they detached from plastic and glass culture dishes after growing overnight in the lab. Steinman proposed that this newly described cell performs a distinct physiological chore.

A Shot in the Arm for T Cells

By 1978, Steinman had exploited the properties that distinguish T cells, B cells, macrophages, and dendritic cells from one another to separate the spleen mixture into its components. Then he—with his trainees, who included Margaret Witmer, Michel Nussenzweig, Wesley van Voorhis, and Kayo Inaba—added back each cell type individually to lymphocytes in culture dishes.

Tiny quantities of dendritic cells incited T cells to reproduce and kill host cells that bore foreign antigen. Dendritic cells' stimulatory power was more than 100-fold greater than that of B cells, T cells, or macrophages. As few as 0.5 dendritic cells per 100 T cells generate maximum proliferation. No one had anticipated that any cell could so efficiently goad T cells into action.

In 1985, Steinman tested whether this property depended on a long-term association between T cells and dendritic cells. He mixed T cells with antigen and dendritic cells. Then he isolated the T cells and added them to B cells, which multiplied and produced antibody in response. This experiment showed that the dendritic cells stably altered the T cells, triggering them to mature in such a way that they could stimulate B cells, even after the dendritic cells had disappeared.

The work thus far indicated that dendritic cells could activate T cells in culture dishes. But Steinman wanted to make sure that he was studying a phenomenon—priming of the immune system—that occurred in an intact animal's body. He exposed dendritic cells to antigen in culture; then he washed away free antigen and injected the dendritic cells into mice. The animals mounted a strong immune response, converting naïve T cells into ones that reacted strongly to antigen. This observation and others showed that dendritic cells with pre-loaded antigen were sufficient to elicit an immune reaction in animals. Analysis of cell-surface molecules revealed that the T cells produced by the mice were stimulated by the injected cells rather than by dendritic cells that had previously resided in the animals. Thus, researchers could sensitize T cells of an animal to an antigen of choice by inoculating with dendritic cells that had been exposed to that antigen; Steinman pointed out that this prospect holds extraordinary therapeutic implications, an idea that investigators are pursuing today.

The Two Faces of Dendritic Cells

These observations and others also highlighted a feature of dendritic cells that conflicted with an originally described characteristic—the inability to take up particles from their surroundings. To present antigens to T cells, dendritic cells had to overcome this apparent limitation, a property that initially distinguished them from macrophages. In a separate line of studies, Steinman had begun to solve this conundrum. He discovered that so-called Langerhans cells, which had been identified in 1868, served as dendritic-cell precursors. This and other work led him to propose a scenario for dendritic-cell specialization in the 1990s. After capturing antigen, immature cells from the skin and elsewhere begin to display it on their surfaces. In the presence of stimulatory factors from the environment and other immune cells, they develop into dendritic cells. During this process, dendritic cells lose the capacity to ingest foreign agents. The dendritic cells that sensitize T cells—and the ones Steinman originally characterized—can no longer slurp antigen.

Maturing dendritic cells migrate from tissues such as skin to the lymph nodes, where the body ratchets up immune activities in response to specific invaders. In the mid 1980s, Steinman had noticed dendritic cells at the exact sites in the lymph nodes where T cells percolate through, awaiting instructions about whether their services are needed; dendritic cells thus reside in the ideal location for initiating immunity. A dendritic cell's long extensions constantly probe the parade of T cells until they contact their target: a T cell whose antigen “matches” that on the dendritic cell’s surface.

Tumors, Trespassers, and Tolerance

By the end of the 1980s, dozens of labs were studying dendritic cells—but investigations were hampered by scant supplies. Only about 1% of mouse spleen cells are dendritic cells. In the early 1990s, Steinman's group and several others devised ways to prepare large amounts of dendritic cells. This breakthrough made the cells widely accessible, and the field exploded. Scientists have expanded their studies along multiple avenues and are now delving into potential therapeutic uses of dendritic cells.

The capacity to load antigens onto dendritic cells that then prime T cells in an animal raised the possibility of using dendritic cells to fight cancer. In one version of this scheme, tumor cells are removed from an individual and delivered to dendritic cells from the same person in culture dishes. The dendritic cells are then injected back into the patient's body. This procedure should boost the immune system with cells whose primary mission is to attack that particular person's tumor. Preliminary results are promising: The method shrinks tumors in experimental animals. The approach holds strong appeal because the dendritic cells strike multiple tumor components simultaneously; in contrast, drugs tend to focus on one cancer-related pathway at a time. Dozens of clinical studies are under way and the area is ripe for development, due in large part to Steinman's experimental work and advocacy.

Scientists are exploring similar strategies to create dendritic cell-based vaccines against pathogens. Initial observations suggest that such a tactic might thwart HIV infections. This line of investigation could prove especially fruitful, as HIV is particularly insidious with regard to dendritic cells. Steinman demonstrated that dendritic cells provide a safe haven for replicating HIV-1 and can transmit the virus to T cells. Thus, in the natural setting, dendritic cells help spread HIV-1 rather than quash it.

The importance of dendritic cells extends beyond their capacity to initiate an immune response. They help induce tolerance, the process by which animals learn to ignore their own cells. Scientists might therefore adapt dendritic cells for clinical use in autoimmunity, allergy, and transplantation medicine. These dual roles—of immune stimulation and silencing—bolster dendritic cells' standing as a central modulator of the immune response.

The conceptual framework and practical methodologies that Steinman pioneered not only cracked open the early steps of immune activation, but unveiled mechanisms by which our bodies tune their assaults against particular microbes. Scientists now know that dendritic cells adjust the immune reaction by rousing different classes of T cells, depending on the specific signaling molecules that are carried by other cells and the environment. Steinman's work launched an entire field. He defined the basic biology of dendritic cells and formulated the therapeutic applications of his discoveries.

The Albert Lasker Award for Clinical Medical Research

Presented to Alain Carpentier and Albert Starr

For the development of prosthetic mitral and aortic valves, which have prolonged and enhanced the lives of millions of people with heart disease.

The **2007 Albert Lasker Award for Clinical Medical Research** honors two surgeon-scientists who revolutionized the treatment of heart disease. **Albert Starr** and his engineer partner, the late Lowell Edwards, invented the world's first successful artificial heart valve. This device has transformed life for people with serious valve disease, providing a remedy where none previously existed. **Alain Carpentier** then circumvented the predominant limitation of mechanical valves—a propensity to clot within blood vessels and the associated need to take blood thinners—by adapting animal valves for use in humans. In the embryonic days of open-heart surgery, Starr and Carpentier opened up the entire field of valve replacement. Their work has restored health and longevity to millions of individuals with heart disease.

Starr's and Carpentier's contributions extend beyond these landmark innovations. In an era before the Food and Drug Administration (FDA) regulated medical devices, Starr set up the infrastructure for conducting clinical trials on his valves, including an informed-consent procedure and long-term patient tracking. This practice allowed him to evaluate valve-replacement outcomes and seek solutions to clinical problems. Furthermore, his surgical patients required a new type of postoperative care. To deliver it, he assembled a multidisciplinary healthcare team, creating what corresponds to today's cardiac intensive care unit. Carpentier, in turn, augmented his own initial discovery by formulating techniques to repair rather than replace valves—a venture that was aided by the availability of prosthetic valves as a backup. He continues to probe the suboptimal areas of heart-valve surgery, relentlessly pursuing superior strategies.

Prior to the introduction of the Starr-Edwards valve, no human with a valve replacement had survived longer than three months. As of 2004, four live patients had replacement valves that had been implanted at least 40 years earlier. Currently, more than 90,000 people in the United States and approximately 300,000 people worldwide receive new valves annually; the procedure is the second most common heart surgery in the United States, exceeded only by coronary bypass operations. A combination of valve manufacturers' 1998 estimates and approximate usage since then indicates that more than four million valves total have been replaced. Today, slightly more than half of all valves implanted are mechanical, but the proportion of tissue valves is growing rapidly. Initially, animal-tissue valves were used only in elderly patients. Now, with increased durability, young people receive them as well. Individuals under 60 years old undergo valve-replacement surgery primarily for congenital, rheumatic, and degenerative heart disease. Those over 60 years old take advantage of the procedure primarily to correct valve degeneration.

Heart of Darkness

In the 1950s, when Starr trained as a surgical resident and intern, complications from rheumatic fever loomed large. Inflammation from this disease can thicken and narrow the heart valves—tissue flaps that open and allow blood to flow through the organ and then close to prevent leakage back. Other conditions too—for example, congenital problems and degenerative processes—constricted valves or made them leak. Surgeons sometimes could blindly use a finger through an incision in the chest to widen the valve opening, but if that procedure didn't work, no alternative existed. Many patients remained incapacitated or died. The world desperately needed a way to replace flawed valves.

Charles Hufnagel, of the Georgetown Medical Center in Washington, DC, took a step toward addressing this challenge in 1952 by implanting an artificial valve in a patient's aorta, a site that normally does not contain a valve. The surgeon was trying to alleviate problems associated with the patient's aortic valve, which was allowing blood to trickle backward into the heart. The procedure helped this individual and others, but the operation did not constitute a true valve replacement because Hufnagel was adding rather than replacing a valve. Hufnagel's achievement, however, demonstrated that a device in the circulation can force blood to flow in one direction only and the feat unlocked the possibility of placing mechanical valves in humans.

Heart-to-Heart Conversation

In 1958, recently retired engineer Lowell Edwards visited Starr at his office of what is now called the Oregon Health and Science University in Portland. Edwards was a prolific innovator. He had filed 63 patents, mostly in the aviation and paper industries, and he had a strong background in hydraulics. The idea of mechanizing blood flow through the heart—a biological pump—captivated him. He proposed to Starr that they collaborate to build an artificial heart. Starr persuaded him that the project was too ambitious; the first order of business, Starr argued, was to develop a valve.

Edwards agreed and within a few weeks, he came back with a prototype. It consisted of two silicone-rubber flaps, or leaflets, that hung on a central solid Teflon crossbar. The leaflets functioned like saloon doors that snap shut after allowing fluid to pass. A "sewing ring" that encircled the contraption allowed it to be stitched into the heart and held it in place.

Tell-Tale Hearts

Starr used this apparatus to replace the mitral valve—a valve that separates two chambers of the heart—in dogs. These and subsequent experiments established that the devices could function briefly in animals, but they promoted lethal clot formation and tore tissue at the implantation site. Starr and Edwards disposed of the latter issue by cushioning the sewing ring. The first item posed more of a problem. Clots began at the spot where Starr had attached the device and crept inward until they obstructed the central orifice. The team decided to explore other designs.

They settled upon a valve composed of a free-floating ball inside a cage, which had been used since it was patented as a bottle stopper in 1858. The ball sits snugly in the sewing ring at the back of the cage. As pressure builds outside the device, it pushes the ball away from the opening and fluid flows. After the pressure drops, the ball moves back and re-forms a seal.

Several groups had attempted to place mechanical valves in humans before Starr and Edwards did, and some utilized this general valve-ball scheme. All of the gadgets failed, in large part because they induced clot formation. Most members of the field were reaching consensus that the mitral valve required a mechanical substitute that copied nature—a leaflet design. Resisting this conventional wisdom, Starr and Edwards decided to choose function over form. They adopted the caged ball even though it looked nothing like a real heart valve. The almost constant motion of the ball would remove clots as they formed, the investigators reasoned, and Edwards' concentrated engineering efforts could eventually surmount the challenges that the enterprise presented.

After several more rounds of experiments and design modifications, Starr had a kennel full of dogs that carried artificial mitral valves. The animals licked, barked, played, and generally behaved like healthy beasts. The incidence of clot-related complications plummeted and survival times lengthened.

Starr wanted to track the dogs and learn about long-term complications before implanting the device in humans. However, the Chief of Cardiology and the Chairman of the Department of Surgery at Portland pressured him to begin operating on people. Patients were dying and Starr had his hands on a potential therapy.

He decided to proceed, but numerous items that we take for granted today had to be put in place. No precedent existed for addressing liability issues, so Starr and Edwards developed the first informed consent procedure. Starr also had to build the equivalent of a cardiac intensive care unit to attend to the very sick patients who would emerge from the surgery.

A Song in the Heart

In September 1960, Starr performed the first successful valve-replacement operation on a person. This individual was the first human to live more than 3 months with a mitral valve replacement. He survived for 10 years after the implantation and died after falling from a ladder. By the end of February 1961, Starr had implanted six more valves. Patients' cardiac functions improved dramatically and most of them survived for unprecedented amounts of time.

The FDA did not yet regulate devices, so its clinical trial system had not been applied to prostheses. By this time, Edwards had founded Edwards Laboratories, Inc. (now Edwards Lifesciences) to manufacture the valves and Starr became a consultant. Starr and Edwards decided to restrict sale of the valve to medical centers with extensive experience in open-heart surgery to guarantee quality control on the procedure. These institutions agreed to report back any adverse reactions they observed. Thus, Starr established the first clinical-research tracking system for long-term follow-up in patients carrying implanted medical gear.

Starr invited surgeons from all over the world to visit so he could teach them the procedure. The advance rippled through the United States, Europe, Japan, and then into South America, India, Thailand, and beyond. Less than a year after introducing the world's first commercially available replacement mitral valve, Edwards and Starr unveiled its counterpart for the aortic valve; a tricuspid valve followed. Starr performed the first triple valve replacement surgery in 1963. Over the years, Starr and Edwards tuned the design to improve function and durability; the lack of FDA oversight allowed them to move much more quickly than they could have today. The Starr-Edwards 1965 version is still in use; it operates as well as today's most widely used artificial valve, the St. Jude Medical® mechanical heart valve.

Heart's Desire

Starr and Edward's triumph was stupendous, but the approach held a significant drawback. Patients with synthetic valves must take blood thinners for the rest of their lives. These medications increase the risk of serious bleeding and they are particularly onerous for some groups of people, such as women of childbearing age. Furthermore, the blood thinners diminish, but don't obliterate, the risk of clot formation.

In 1964, Alain Carpentier, who was doing his surgical residency at Hôpital Broussais in Paris, treated an artist whose fate influenced that of cardiac surgery. Carpentier and his colleagues had used a Starr-Edwards valve to save this patient's life, but a few weeks after the operation, a clot formed on the device, broke off, and lodged in his brain. Paralyzed, this man could no longer paint. Carpentier realized that the surgical team had saved the artist's life, but profoundly compromised it. He pledged to devote himself to solving the problem of clotting that results from valve surgery.

In contrast to synthetic substances such as metal and silicone rubber, tissue does not trigger clot formation. Carpentier began working with valves from cadavers, an endeavor that others had begun to explore. However, French law forbade doctors from harvesting organs until 48 hours after death. As a result, bacteria contaminated many valves by the time surgeons could use them. Moreover, limited availability of valves from cadavers restricted their potential utility.

So Carpentier decided to adapt animal valves for use in people. He began exploring tactics to sterilize and preserve pig valves. Having trained earlier with Robert Judet, inventor of the artificial hip, Carpentier knew that a mercurial solution served those purposes for human skin employed in joint-reconstruction operations. He decided to try that approach.

In September 1965, Carpentier and Jean-Paul Binet performed the first successful replacement of a human valve with an animal valve at Hôpital Broussais. Results from this patient and others in the first several groups initially appeared promising. However, the mercury-treated valves began deteriorating within two years of implantation, in part because harmful inflammatory cells infiltrated the replacement tissue and compromised its integrity. Carpentier minimized this problem by inserting a physical barrier—Teflon cloth—at the graft-host interface. However, major hurdles remained. He wanted to devise a method that would strengthen the tissue as well as render it immunologically inert. Aspiring to bolster his fundamental knowledge of biochemistry, he enrolled in a Ph.D. program at the University of Paris.

Heartening Results

Eventually Carpentier found that a compound called glutaraldehyde sterilizes tissue, reduces its immunogenicity, and links collagen molecules with one another, thus increasing durability. Glutaraldehyde outperformed all other substances tested in decreasing immunoreactivity and increasing tissue stability.

In the meantime, Carpentier had begun to mount his tissue valves in Teflon-coated metallic frames with the hope that this practice would make the device as simple to insert as mechanical valves. The development minimized the complexity and time required for suturing, and it laid the groundwork for large-scale production. The synthetic material did not spur clot formation because it composed a non-moving portion of the apparatus: Cells grow over the valve housing, which slashes the risk of clot formation.

Carpentier coined the term bioprosthesis to describe this gadget, indicating its origin as well as its purpose. In March 1968, Carpentier and Charles Dubost implanted the first bioprosthesis. The patient survived for 18 years with that device.

Carpentier's achievement impressed Starr, who introduced Carpentier to Edwards. This act was particularly remarkable, given that Carpentier's valve might compromise the success of Starr's. Carpentier worked with Edwards' laboratory to develop a commercial product composed of glutaraldehyde-treated pig valves, held in a frame for easy insertion. This collaboration produced standardized bioprosthetic valves of variable sizes that could be kept on the shelf. Other companies, too, began to manufacture this type of valve using Carpentier's glutaraldehyde-based process, a technique that is still in use today.

Tissue valves boast important advantages over mechanical valves. The risk of clotting is lower; as a result, patients can avoid long-term treatment with blood thinners. Furthermore, the nature of the occasional valve failure is progressive and thus allows time for re-operation. In addition to these benefits, the bioprosthesis incorporates the power of prosthetic valves: availability, standardization, and ease of implantation.

Carpentier's achievements did not stop with the tissue valve. He developed a surgical treatment, sometimes called the "French correction," intended to avoid a prosthesis altogether. With this improvement, he repaired rather than replaced valves. His key innovation was the Carpentier-Edwards ring. This apparatus stabilizes and reshapes the structure that holds the valve, thus improving its function; thus, many patients can keep their own valves. After a short period, tissue grows over the ring, incorporating it into the body. Similar to Carpentier's bioprosthesis, the ring does not require use of blood thinners. This advance sparked the development of many valve-repair strategies and ushered in the modern era of valve reconstruction.

The tale of heart-valve surgery is still unfolding and significant challenges remain. In particular, the durability of bioprostheses correlates roughly with the age of the person carrying them. The devices tend to calcify and eventually break down, especially in young people. Clinician-scientists, including Carpentier, are tackling these problems. Future chapters will likely echo the themes of success so clearly articulated by Starr and Carpentier in the early chapters of this story.

The Mary Woodard Lasker Award for Public Service in Support of Medical Research and the Health Sciences

Presented to Anthony S. Fauci

For his role as the principal architect of two major U.S. governmental programs, one aimed at AIDS and the other at biodefense.

The **2007 Mary Woodard Lasker Award for Public Service** honors a scientist and public servant who engineered two major US governmental programs – the President's Emergency Plan for AIDS Relief (PEPFAR) and the strategy for defending the nation against dangerous biological agents – and who has spoken eloquently on behalf of medical science to the public, Congress, and successive Administrations. **Anthony S. Fauci** established himself as a world-class investigator before accepting the directorship of the National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health. In addition to that role, in which he oversees an extensive research program aimed at preventing, diagnosing, and treating immune-mediated and infectious diseases, Fauci serves as a key adviser to the White House and Department of Health and Human Services on global AIDS/HIV issues and public health preparedness against natural and man-made biological threats. Fauci rose to prominence in the biomedical community and to AIDS patients through his HIV research in the early 1980s, but today, millions across the United States know him as the man who explains the science behind emerging biological hazards.

Fauci has made noteworthy contributions to basic and clinical research on infectious and immunologically based diseases. During the early 1980s, he recognized – before most investigators – that AIDS posed a major public health problem. He refocused his laboratory's efforts toward studying this illness before anyone had even identified the microbe that causes it. Twenty-five years later, Fauci is still probing the pathogenesis of HIV/AIDS and discerning how to harness the resulting knowledge to design prevention and therapeutic strategies. He has earned a place in the highest tier of the research establishment, and in 1992, he was elected to the U.S. National Academy of Sciences.

Aid for AIDS

As director of the NIAID, a position he has held since 1984, Fauci has gone well beyond his basic duties. He has articulated problems of enormous public-health significance to the federal government and guided the design and implementation of effective policies. Foremost among these efforts has been the formulation and development – at the request of the President – of what is now known as PEPFAR, a program with the potential to save millions of lives in more than 120 countries, with a special emphasis on 15 nations in Africa, the Caribbean, and Asia that represent approximately half of the world’s infections. PEPFAR aims to prevent 7 million new HIV infections, treat 2 million HIV-infected individuals with antiretroviral therapy, and care for 10 million HIV-infected individuals and AIDS orphans over a 5- to 7-year period. This $15 billion, multifaceted approach to combating the disease around the world is the largest commitment ever by any nation for an international health initiative dedicated to a single disease. In May, President Bush announced that he will reauthorize the program for another 5 years and has proposed to double the initial U.S. pledge. The United States now leads the world in its level of support for the fight against HIV/AIDS, due in large part to Fauci's efforts.

Disarming Biological Threats

After the 9/11 attacks on the World Trade Center and the Pentagon, Fauci conceived a research and public-health program designed to rapidly improve countermeasures against potential bioterror agents. This plan intends to spur basic biomedical discoveries and quickly translate them into diagnostics, therapeutics, and vaccines. In addition, Fauci has played a major role in the development and implementation of Project Bioshield, whose purpose is to protect Americans against a chemical, biological, radiological, or nuclear attack. Its main goal is to provide a secure source of funds with which to guarantee purchase of effective vaccines or medications. In addition, it endeavors to accelerate the pace of relevant research and give the Food and Drug Administration powers to swiftly distribute countermeasures in an emergency.

Following the anthrax scare of 2001, Fauci became one of the most visible faces of the federal administration on bioterrorism-related issues. He calmly and logically laid out what was known about various threats and described the scientific and policy questions that remained to be answered. For example, he explained that anthrax is not spread from person to person. Without creating unnecessary panic, he told the public that an attack using biological agents was possible—and that the United States needed to prepare itself. His honest yet non-hysterical manner rallied support for national expenditures on public-health infrastructure, including vaccines.

Simultaneously, Fauci pointed out weaknesses in this nation's arsenal against potentially devastating scourges such as smallpox; in 2001, the United States had only 18 million doses of the smallpox vaccine. He implemented a plan that now has produced 400 million doses. He was also influential in convincing President Bush to bolster the United States' preparedness against natural dangers such as seasonal and avian flu.

Compelling Diplomacy

Fauci has dealt successfully with many U.S. Presidents and their Administrations, as well as Congress: He began directing the NIAID at the end of the Reagan era, and then advised George H.W. Bush, Bill Clinton, and, most recently, George W. Bush. He has also worked with various heads of the Department of Health and Human Services and testified before Congress many times. He is widely respected by politicians and political appointees of different ideologies for concerning himself with public health rather than politics and for speaking the scientific truth. Throughout his tenure as a national adviser, he has stressed the importance of paying attention to emerging and reemerging biological menaces, whether they arise naturally or get "help" from nefarious humans.

Fauci activated the HIV program that became U.S. and then international policy. He engineered the United States' strategies to biological warfare, promoting a reasoned and scientific approach to a variety of domestic and international threats. This tactic has earned him first-class marks and tremendous powers of persuasion among federal administrations, scientists, and the general public. From HIV/AIDS to biodefense, he has engaged the public and propelled significant global health issues to the top of research and policy agendas in the United States and abroad.