

50 YEARS

IN HEMATOLOGY

Research That Revolutionized Patient Care



Foreword

The American Society of Hematology (ASH) turns 50 in 2008, and we look back with pride and awe at the momentous changes in our field during the last half century. The explosive progress in the field of molecular biology has yielded fundamental insights into the origin of human diseases and sparked the development of treatments that have transformed medicine. Nowhere are these changes more prominent than in the field of hematology, which serves as a paradigm for the movement of knowledge from the bench to the bedside. The past 50 years have seen major clinical advances that arose from cutting-edge basic research, including, for example, the development of recombinant growth factors that stimulate blood cell production, blood-forming stem cell transplant techniques, safer and more effective products for transfusion, the discovery of water channels that have spread to the fields of nephrology, neurobiology, gastroenterology, and cancer biology, amongst others, and targeted molecular therapies for hematologic malignancies.

On the occasion of our 50th anniversary, ASH celebrates these achievements by documenting some of the profession's compelling successes in treating hematologic disease. We have by necessity been selective, and these snapshots are only a sampling of the array of clinical breakthroughs in our field during the last five decades. Through these vignettes, we hope to convey the excitement of hematology—the thrill of scientific discovery and the triumph of translating that discovery into improvements in human health. We also celebrate the dedication of generations of physicians and physician-scientists who have powered these advances and who continue to strive to take full advantage of the ever-growing armamentarium of scientific tools to better the care of their patients.

We hope this brochure strengthens your understanding of blood diseases and their treatments and enhances your appreciation for the importance of scientific research. We welcome you to share it with anyone who has an interest in learning more about hematology – patients, students, doctors, and others. For additional copies, please contact ash@hematology.org.

Sincerely,

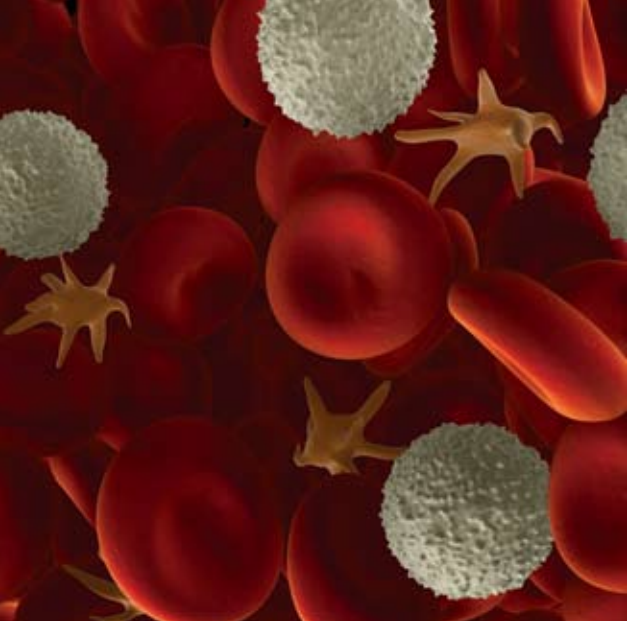


Kenneth Kaushansky, MD
ASH President, 2008



Nancy Berliner, MD
ASH President, 2009





The mission of the ASH is to further the understanding, diagnosis, treatment, and prevention of disorders affecting the blood, bone marrow, and the immunologic, hemostatic and vascular systems, by promoting research, clinical care, education, training, and advocacy in hematology.

Since its founding in 1958, the ASH has grown as a professional association. It now has a membership of nearly 16,000 hematologists, specialists who research the mechanisms of blood and treat patients with blood disorders. Many of the remarkable achievements hematologists have made in the medical field during the last 50 years are highlighted in this brochure in chapters corresponding to the three main components of blood.



Conquering Blood Diseases –
From Research to Patient Care

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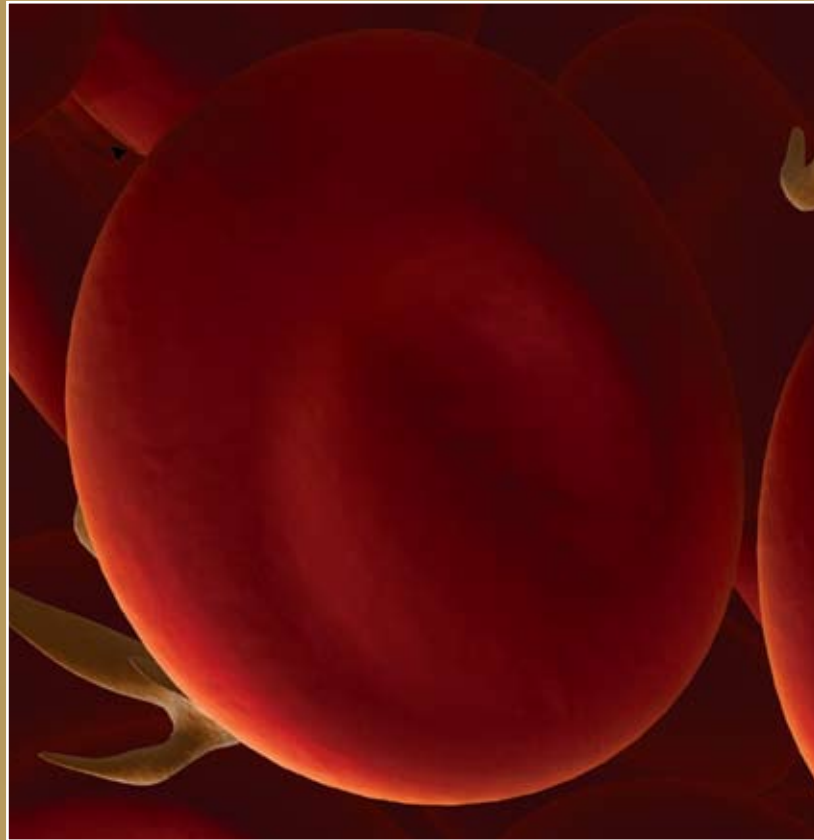
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CHAPTER 1: RED BLOOD CELLS



RED BLOOD CELL, THE DELIVERER:
picks up oxygen in the lungs and delivers it throughout
the body where it is exchanged for carbon dioxide,
which is then returned and expelled through the lungs

Sickle Cell Disease and Thalassemia: Disorders of Globin Production

BY ELLIOTT VICHINSKY, MD, Children's Hospital and Research Center Oakland, Oakland, CA

Sickle cell disease and thalassemia are genetic disorders caused by errors in the genes for hemoglobin, a substance composed of a protein (“globin”) plus an iron molecule (“heme”) that is responsible for carrying oxygen within the red blood cell. These disorders can cause fatigue, jaundice, and episodes of pain ranging from mild to very severe. They are inherited, and usually both parents must pass on an abnormal gene in order for a child to have the disease. When this happens, the resulting diseases are serious and, at times, fatal.

Sickle Cell Disease

Sickle cell disease was first discovered in the early 1900s, described as “peculiar, elongated sickle-shaped erythrocytes [red blood cells].” With further study, a noted pathologist later suggested that the pain experienced by sickle cell patients resulted from the blockage of tiny blood vessels. In a landmark 1949 study, Dr. Linus Pauling

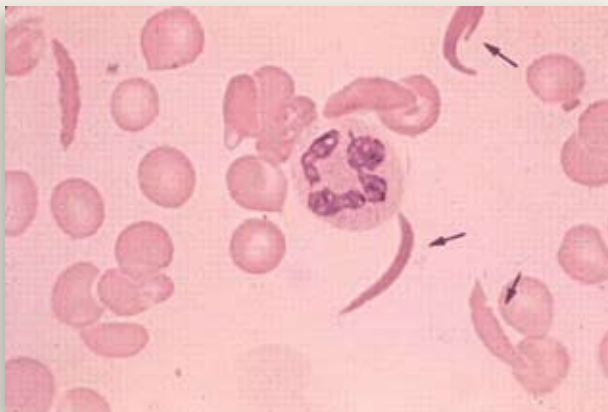
concluded that sickle cell disease is caused by abnormal hemoglobin, referred to as “hemoglobin S.” The disease was among the first to be understood fully at the biochemical level, as researchers learned that the abnormal hemoglobin was actually changing shape (called “sickling”) due to a single amino acid error in hemoglobin S.

Even though the underlying molecular cause of the disease was understood more than half a century ago, progress in translating this knowledge into improved patient care has been slow. This partly reflects the intrinsic difficulty of treating the disease. However, it also results from the fact that, in the United States, sickle cell

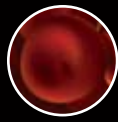
disease occurred in an underserved population for which health research and treatment were neglected. It was not until the civil rights movement of the early 1970s that the poor treatment of these patients was recognized as a prime example of racial inequality in health care. In response, the Sickle Cell Disease Association of America was founded and later helped establish the Sickle Cell Anemia Control Act of 1972, which allotted government health funds for screening, research, and treatment programs.

As scientific progress and technology improved, new treatment regimens evolved for sickle cell disease patients. The Prophylactic Penicillin Study (PROPS) found that giving penicillin, an antibiotic, when patients were not sick could prevent death related to serious infections in sickle cell disease. Later, the Multicenter Bone Marrow Transplant Study demonstrated that 84 percent of children with sickle cell disease who received a bone marrow transplant from a matched relative could be cured. Finally, in the mid-1990s, the U.S. Food and Drug Administration approved a new therapy called hydroxyurea as a treatment to decrease complications of the disease. Hydroxyurea works in part by stimulating the body to resume production of fetal hemoglobin (hemoglobin F), a normal hemoglobin in the fetus that prevents sickling.

In the last decade, further progress has been made in sickle cell research. Researchers have improved outpatient programs for pain control, identified pulmonary hypertension as a common life-threatening



*Blood smear; arrows indicate sickled cells.
Photo by Dr. Stanley Schrier, courtesy of the ASH Image Bank.*



Milestones in Sickle Cell Disease



Linus Pauling. Photo courtesy of The Linus Pauling Papers, Special Collections, Oregon State University.

complication of sickle cell disease, and developed new ways to identify genetic risk factors for other disease complications.

Thalassemia

Thalassemia, or Mediterranean anemia, was first described in 1925 by a Detroit physician who studied Italian children with severe anemia (low levels of red blood cells), poor growth, huge abdominal organs, and early childhood death. In 1946, the cause of thalassemia was found to be an abnormal hemoglobin structure. The body reacts by destroying red blood cells, causing anemia. To compensate for the loss, the body tries to make red blood cells more rapidly, causing other thalassemia complications, such as bone abnormalities and spleen enlargement.

In the 1960s, doctors treating thalassemia patients started to transfuse them with fresh red blood cells every month. This alleviated most of the childhood symptoms and led to a major improvement in survival. It is still used as a treatment today. However, since blood contains large amounts of iron, which the body cannot eliminate naturally, most patients died

1910

James Herrick notes “peculiar, elongated sickle-shaped erythrocytes” in a patient with anemia.

1930s

Lemuel Whitley Diggs suggests that pain in sickle cell patients is due to sickle cells clogging up small blood vessels.

1949

Linus Pauling discovers that sickle cell disease is caused by an abnormal hemoglobin.

1957

Vernon Ingram discovers that a change in one amino acid in hemoglobin S causes sickling.

1970s

Sickle cell anemia becomes the first human disease to be explained at the level of a single nucleotide mutation: Using recombinant DNA technology techniques, scientists find that the nucleotide change in the DNA for sickle hemoglobin results from an A to T substitution.

The civil rights movement calls attention to racial inequality in health care. Charles Whitten establishes the Sickle Cell Disease Association of America to improve research, education, and health care for sickle cell patients.

1972

The Sickle Cell Anemia Control Act allocates government funding for screening, research, and treatment. With these funds, the National Heart, Lung, and Blood Institute establishes the Cooperative Study of Sickle Cell Disease.

1980

Robert P. Hebbel observes that sickle cells stick to the lining of blood vessels and shows that this correlates with severity of illness.

1983

The Prophylactic Penicillin Study (PROPS) finds that treatment of well sickle cell patients with penicillin could prevent death related to serious infections.

1995

The Multicenter Study of Hydroxyurea proves the usefulness of hydroxyurea in preventing complications in patients with sickle cell disease.

1996

The Multicenter Bone Marrow Transplant Study demonstrates a cure for children with sickle cell disease.

1998

The Stroke Prevention in Sickle Cell Disease clinical trials show that transcranial Doppler ultrasonography, a method of analyzing blood flow in the brain, is an effective screening tool.

2000

A published study by Lennette J. Benjamin demonstrates that a day hospital for the treatment of pain improves quality of life and prevents hospitalizations.

Hemolysis (a breakdown of red blood cells) results in free hemoglobin, which decreases the availability of nitric oxide (an important signaling molecule), causing widespread pathologic consequences, including pulmonary hypertension. Further studies determine that pulmonary hypertension is common in sickle cell disease and a strong predictor of death.

2001

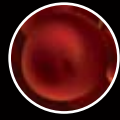
Gene therapy successfully cures a sickle-cell mouse.

2005

Genetic methods are developed to predict complications of sickle cell disease.

2007

Techniques are developed in sickle-cell mice to convert normal cells into stem cells to be used for gene therapy and transplant.



Milestones in Thalassemia

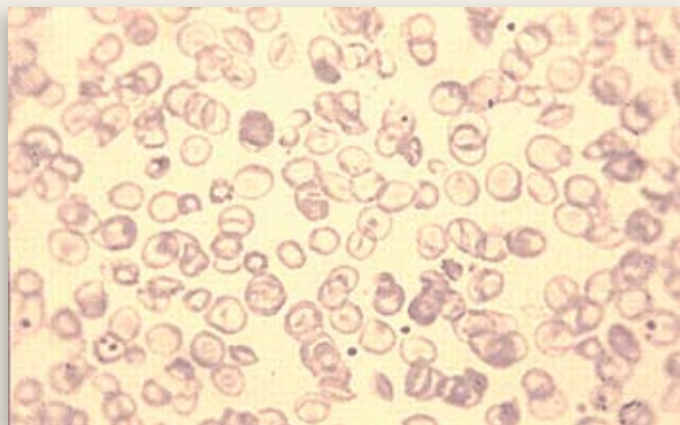
in their teenage years from damage caused by too much iron. Researchers later found that excess iron could be removed from the body by treatment with a drug called desferoxamine. This drug prevented iron-induced heart disease and helped patients live much longer. Recently, two oral drugs have become available to remove iron. They have dramatically improved the quality of life of patients with iron overload from transfusions for thalassemia. Furthermore, specialized imaging tests can now find iron in the heart and allow patients to be treated before they develop iron-related heart failure.

As with sickle cell disease, drugs that increase production of fetal hemoglobin can partially correct the anemia of thalassemia, but efforts to improve the treatment of thalassemia continue.

Future Directions

Medications that increase fetal hemoglobin in both sickle cell disease and thalassemia have greatly improved life for patients suffering from these diseases; however, safer and more effective drugs are still being sought. Stem cell transplantation can be used to treat both illnesses, but it has many limitations. Further research to improve the safety of transplantation, especially when using stem cells from unrelated donors, is necessary before it can be widely accepted as a safe and effective treatment. Finally, the long-term hope for successfully treating both of these diseases is to correct the error in the globin gene itself. While it is possible to do this type of gene therapy in animals, there are several obstacles that must be overcome before human trials will be successful.

- 1925 Thomas Cooley is the first to describe thalassemia.
- 1938 Thalassemia is recognized as a genetic disease.
- 1946 Thalassemia is determined to be caused by an abnormal hemoglobin.
- 1948 The thalassemia mutation is found to protect against malaria.
- 1964 Treatment with regular blood transfusions begins to improve patient survival.
- 1975 Prenatal diagnosis for thalassemia becomes available.
- 1977 Richard Propper discovers that the iron toxicity caused by frequent blood transfusions can be eliminated with desferoxamine.
- 1982 Azacytidine is found to increase fetal hemoglobin in thalassemia patients.
Bone marrow transplantation is first used to cure thalassemia.
- 1998 Oral chelators (such as deferiprone) are shown to be clinically beneficial for the treatment of iron toxicity.
- 2001 Specialized radiology imaging identifies iron toxicity in the heart.
Hepcidin, a hormone that controls iron absorption in the intestines, is first discovered.
- 2003 Deferasirox, a new iron chelator, becomes available.
- 2007 Gene therapy is used for the first time in a patient with beta thalassemia, a more severe form of the disorder.



Blood smear; note the pale color of the red blood cells (hypochromia) and the number of unusually small red blood cells (microcytes), traits that are indicative of thalassemia. Photo by Dr. Stanley Schrier, courtesy of the ASH Image Bank.

The Story of Erythropoietin

BY JOHN W. ADAMSON, MD, University of California and San Diego VA Healthcare System, San Diego, CA

Millions of patients worldwide have benefited from research on erythropoietin spanning many decades. In the last 15 years, epoetin alfa (Epo) has become one of the most widely used drugs created through recombinant DNA technology, in which a nearly identical form of a substance that naturally occurs in the body – in this case, erythropoietin – is created by replicating human DNA in a laboratory. Epo is used to treat anemia, a shortage of red blood cells. Since red blood cells carry oxygen to the tissues and organs, anemia causes symptoms such as weakness, fatigue, and shortness of breath. Epo treats this condition by imitating the action of the hormone erythropoietin, stimulating the body to produce

Erythropoietin: A Patient Perspective

BY NANCY SPAETH

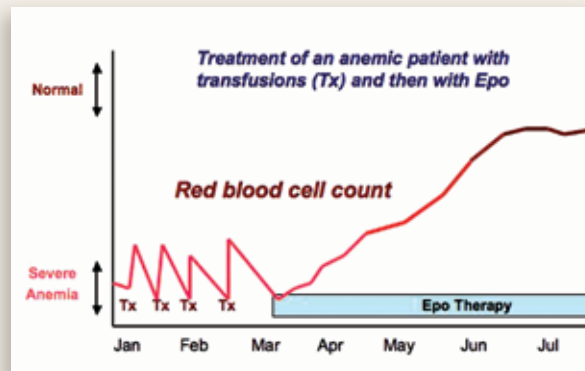
Before dialysis, when I was 15, in 1963, I took first place skiing in a coed slalom race. I beat the boys. Two years later, I couldn't walk from the lodge to the lift.

I started on dialysis in 1966. I don't remember how many transfusions I had. It was many, at least one per month. I had to be desperate before the doctor would order blood.

I was part of the phase III clinical trial in 1987. I was on home dialysis, raising two children, alone. My hematocrit (HCT) was 11-15 percent; I couldn't walk up the stairs. I had to crawl on my hands and knees because I was so out of breath. Once I started on the drug, I could tell there was a change within two weeks. Within 30 days, my HCT was 40! My daughter said, "All of a sudden you were up and going." Eventually, I could run up the stairs.

I used to be asked, "What are you doing?" I answered, "What can I do? My body has me in prison." Epo changed all of that. What a difference it made in my life!

more red blood cells. Patients who may benefit from Epo therapy include those with chronic kidney disease, those who are anemic from AIDS or from a wide variety of hematologic disorders (including multiple myeloma and myelodysplastic syndromes), and some cancer patients who are anemic from receiving chemotherapy. In selected patients, Epo may be used to reduce the need for blood transfusions in surgery.



Adapted from Eschbach et al, *New England Journal of Medicine*. 1987.

A century ago, two French investigators reported that small amounts of plasma from anemic rabbits injected into normal animals caused an increase in red blood cell production (erythropoiesis) within a few hours. They referred to this activity as *hemopoietine*. Over time, as investigators became more convinced that this red-blood-cell-stimulating activity was caused by a

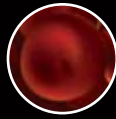
single protein in the blood plasma, they gave it a variety of names – erythropoietic-stimulating activity, erythropoietic-stimulating factor, and, ultimately, “erythropoietin.”

It wasn't until the 1950s and '60s that several American investigators again took up the concept that a hormone regulated red cell production. Refining the work of the French scientists, the American investigators conclusively showed that a hormone stimulated red cell production, that the kidneys were the primary source of erythropoietin, and that low oxygen was the main driver of erythropoietin production. Soon, researchers found that patients with anemia responded by increasing their levels of erythropoietin to stimulate increased red blood cell production. Patients who required an increase in red blood cells in order to make

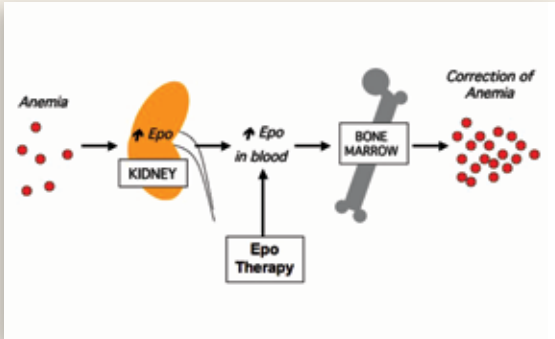
up for low oxygen levels in the blood (such as patients with lung disease or patients living at high altitudes) also had elevated erythropoietin levels.

At the same time, other technologies were being developed that set the stage for a remarkable breakthrough involving a combination of medical

and molecular engineering. In the early 1960s came the development of hemodialysis, a method of removing waste products from the blood when the kidneys are unable to perform this function, to sustain the lives of patients with end-stage kidney disease. As a result of this treatment advance, these patients were able to survive the underlying disease, but their damaged kidneys could no longer make erythropoietin,



Milestones in the Study and Development of Erythropoietin



Recombinant human erythropoietin (rhEpo) is used to treat anemia by stimulating the bone marrow to produce more red blood cells. rhEpo is structurally identical to native Epo, a hormone produced primarily in the kidney. Figure courtesy of Dr. H. Franklin Bunn.

leaving them severely anemic and in desperate need of Epo therapy.

In 1983, scientists discovered a method for mass producing a synthetic version of the hormone. Experiments were conducted to test the safety and effectiveness of the new drug, Epo, for treating anemia in patients with kidney failure. The results of these early clinical trials were dramatic. Patients who had been dependent on frequent blood transfusions were able to increase their red blood cell levels to near-normal within just a few weeks of starting therapy. Patients' appetites returned, and they resumed their active lives. It was the convergence of two technologies – long-term dialysis and molecular biology – that set the stage for anemia management in this group of patients. Since then, millions of patients worldwide have benefited from Epo therapy.

1836

Richard Bright describes anemia as a complication of renal (kidney) failure.

1863

Denis Jourdanet describes an association between an overproduction of red blood cells, called polycythemia, and people living in the low-oxygen environment of high elevations.

1906

Paul Carnot and C. Deflandre describe the existence of a hormone responsible for erythropoiesis: "We have observed, with Mlle. Deflandre, that regeneration of blood after bloodletting is under the influence of a humoral process [a process controlled by a substance in the blood]...we give this substance the generic name Hemopoietine."

1940s

C.L. Krumdieck and other investigators report evidence that a factor in anemic or hypoxic (low oxygen) plasma could increase the release of young red blood cells (reticulocytes).

1950

K.R. Reissman provides evidence of the presence of a humoral mechanism by experiments in surgically-connected rats in which he demonstrates that when one partner is made hypoxic, marrow erythropoiesis is increased in the partner rat with normal oxygenation.

1953

Allan J. Erslev confirms an erythropoietic-stimulating activity in the plasma of anemic rabbits, which he theorizes would be of potential therapeutic value if isolated.

1957

Leon O. Jacobson, Eugene Goldwasser, Walter Fried, and Louis F. Plzak establish that the kidney produces erythropoietin.



Leon O. Jacobson
Photo courtesy of the University of Chicago Medical Center.

1977

Takaji Miyake, Charles Kung, and Eugene Goldwasser purify human erythropoietin from the urine of patients with aplastic anemia.

1983

Two groups of scientists, one under the leadership of Fu-Kuen Lin and the other under Kenneth Jacobs, clone and express the human erythropoietin gene.

1986

Joseph W. Eschbach, John W. Adamson, and colleagues in the U.S., and Christopher G. Winearls and colleagues in England, establish that recombinant human erythropoietin can correct the anemia of chronic renal disease.

1988

Mark J. Koury and colleagues, as well as Catherine LaCombe and colleagues, demonstrate the presence of erythropoietin RNA in kidney and liver cells and large white blood cells called macrophages.

1989

The first recombinant human erythropoietin is approved by the FDA for the treatment of renal anemia.

1990s

Epo is approved for use in treating anemia in some patients with marrow disorders who fail to respond to naturally generated levels of erythropoietin, but who respond to the higher levels achieved with the pharmacologic product.

Advances in Transfusion Medicine

BY NAOMI L.C. LUBAN, MD, Children's National Medical Center, Washington, DC

Blood transfusions are an important part of hematologic care. Transfusion is the transfer of blood, its components, or products from one person (donor) into another person's bloodstream (recipient). Every year in the U.S., more than 20 million units of red blood cells, platelets, and plasma are transfused to treat hematologic conditions such as severe anemia, leukemia, and sickle cell disease.

Transfusions have long been associated with some risk to patients. The HIV epidemic during the 1980s was a major cause of fear; regular transfusions, especially of clotting factor concentrates, spread the virus quickly and nearly undetected. That outbreak prompted the development

of biovigilance or hemovigilance: tracing and tracking transfusion-related adverse events and incidents, both infectious and non-infectious, that affect blood donors and recipients. Another of the most significant issues complicating transfusion safety has been bacterial contamination of blood products, particularly of platelets. However, steps have been taken in the last decade to avoid, detect, and eliminate this complication through improved donor selection, specialized preparation of the arm before needle insertion, and special screening techniques.

Despite ongoing improvements in the collection, processing, testing, delivery, and monitoring of transfusions during the past several decades, concerns over the safety of these therapies and the process in general continue today.

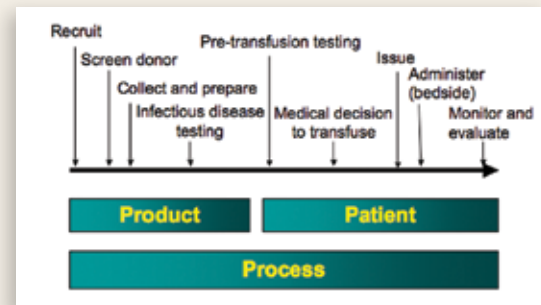
Historically, there was concern about transmitting infectious diseases from a donor to a recipient. Now blood is regularly tested for infectious disease transmission, particularly for viruses such as Hepatitis B and C, HIV, and West Nile Virus. Traditionally, serum has been tested to look for the body's response to past infectious exposure, but many serum tests have been replaced by molecular testing called nucleic acid amplification testing (NAT), which finds active viruses in the donor's blood to determine infection risk. If an active virus is found, the donor unit is

discarded. Experts anticipate that new methods, including new molecular and microarray testing, which can identify many infectious agents rapidly and accurately, will replace or augment serum studies and NAT in the near future. Blood transfusion has never been safer from known infectious risk than it is today.

In addition to infectious disease risks, doctors must also manage other risks, such as post-transfusion reactions. These include transfusion-related lung injury (TRALI), during which the donor's immune antibodies cause breathing problems in the recipient; transfusion-associated cardiac overload (TACO), which is swelling caused by the increased blood volume; and post-transfusion iron overload, which is a buildup of iron in the body, usually caused by multiple or regular transfusions.

Immune reactions, which happen when the body's immune system is affected by the donor blood, also pose several risks to transfused patients. Alloimmunization occurs when the recipient develops an allergic reaction to the donor's red blood cells: transfusion-related immune modulation (TRIM) can lead to increased risk of infections and cancer recurrence, post-transfusion graft-versus-host disease (GVHD, when the donor's immune system attacks the recipient's blood cells), and microchimerism (when a small amount of donor blood persists in the recipient's body, causing ongoing low-grade GVHD).

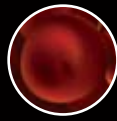
To minimize these risks, researchers studying the body's immune response to transfusions have found that modifying the blood prior to transfusion can reduce reactions. In particular, removing white blood cells or radiating blood to prevent white blood cell growth can reduce the likelihood that the recipient will reject the donor blood. Recently, studies found that using male plasma and platelets may eliminate the transmission of certain antibodies that can cause reactions and are found only in previously



The steps for collecting and preparing blood for transfusion, and administering the transfusion to the patient. Adapted from Dzik S. *Transfusion*. 2003; 43:1190-9.

pregnant women and transfused males. However, using these techniques has reduced the amount of blood available for transfusions, so researchers are working to identify better ways to safely increase available blood sources. For example, new technologies can collect large amounts of red cells and platelets from a single donor, improving collection efficiency and decreasing the number of different donors to which a transfused patient is exposed. Some studies have suggested that blood transfusion may be related to higher death rates in critically ill patients; researchers suggest that aged bank blood may be the reason.

While the hematology community continues to improve current processes, the last decade has also seen dramatic developments in innovative approaches, particularly in high-tech cellular therapies and bio-engineering. New techniques can isolate specialized cell populations from blood – most importantly, hematopoietic progenitor cells (HPCs) that are used for



Milestones in Transfusion Medicine

stem cell transplantation. Because HPCs are easier to extract and the process is safer for donors, HPC transplantation has replaced bone marrow transplantation for many cancers and other diseases.

Researchers are also using umbilical cord stem cells (UCSCs) as a source of HPCs. UCSCs are collected and processed in a method similar to whole blood and are a rich resource for transplantation therapy in pediatric and some adult patients. In the future, these cells may be grown and expanded for clinical use. Furthermore, researchers have isolated specialized cell types other than HPCs that play an important role in cellular therapy because they can modify proliferation and immune responses during the engraftment of transplanted cells.

Today, the hematology community continues to advance its transfusion systems, guided by the AABB, American Red Cross, American Society of Hematology, U.S. Food and Drug Administration, and other federal and professional organizations. Researchers are also establishing new surveillance systems that record data and transfusion outcomes to better understand and manage the risks associated with transfusion. They are offering more personalized treatment, limiting transfusions based on careful assessment of need, and ultimately improving patient care.

Transfusion medicine today is using lessons learned from the past to dramatically improve outcomes in the future. Areas of study include technologies that will more precisely identify blood components to increase patient safety and simplify blood inventory; improved automation to increase efficiency and decrease error; and screening methods that will help reduce the risk of infection. In addition, novel cellular therapies continue to be developed and tested to offer more effective treatment options. These innovations will help hematologists not only to reduce the risks associated with blood transfusions, but also to provide new therapies for a wide range of diseases.

1818

The first successful human-to-human blood transfusion is performed by James Blundell.

1900

Karl Landsteiner develops the classification of blood into A, B, and C (later changed to O) groups.

1902

Alfred Decastello and Adriano Sturli add AB to the blood classification system.

1907

Ludvig Hektoen is the first to suggest that donors and patients should be screened for compatibility (now known as cross-matching).

1912

Roger Lee shows that O blood can be given to a person with any blood type (universal donor) and that a person with AB blood can receive blood from any blood group (universal recipient).

1939

Karl Landsteiner, Alex Wiener, Philip Levine, and R.E. Stetson develop the Rhesus (Rh) blood classification system.

1943

J.F. Loutit and Patrick L. Mollison develop a solution of acid citrate dextrose, which allows greater volumes of blood to be transfused and makes longer-term storage possible.

1950

Audrey Smith successfully freezes red blood cells using glycerol cryoprotectant.

1950

Carl Walter and W.P. Murphy Jr. develop the plastic bag for blood collection.

1958

Jean Dausset discovers the first human leukocyte antigen (HLA) on the surface of blood cells, which determines whether blood from one person might be successfully transfused into another individual. Rose Payne and others identify other HLAs, key discoveries for understanding tissue compatibility.

1960

Alan Solomon and John L. Fahey develop plasmapheresis, a procedure for separating whole blood into plasma and red blood cells.

1964

A method of concentrating clotting factors from fresh frozen plasma is discovered by Judith Pool, allowing patients with hemophilia to receive transfusions outside of the hospital.

1968

Rh Immune Globulin, the first treatment that addresses the differences between negative and positive blood types, proves effective in preventing hemolytic disease of the newborn. This condition, once a major cause of fetal death, occurs when an incompatibility between the mother's and the baby's blood causes her antibodies to destroy the baby's red blood cells.

1969

Scott Murphy and Frank Gardner develop a method for storing platelets at room temperature.

1971

The practice of testing donated blood for hepatitis B begins.

1972

The use of apheresis, the process of separating out only plasma or one specific type of blood cell from donated blood, and then returning the remaining blood cells back to the donor, begins.



A young man undergoing apheresis.
Photo courtesy of the Children's National Medical Center.

Mid-1980s

The practice of testing donated blood for HIV begins.

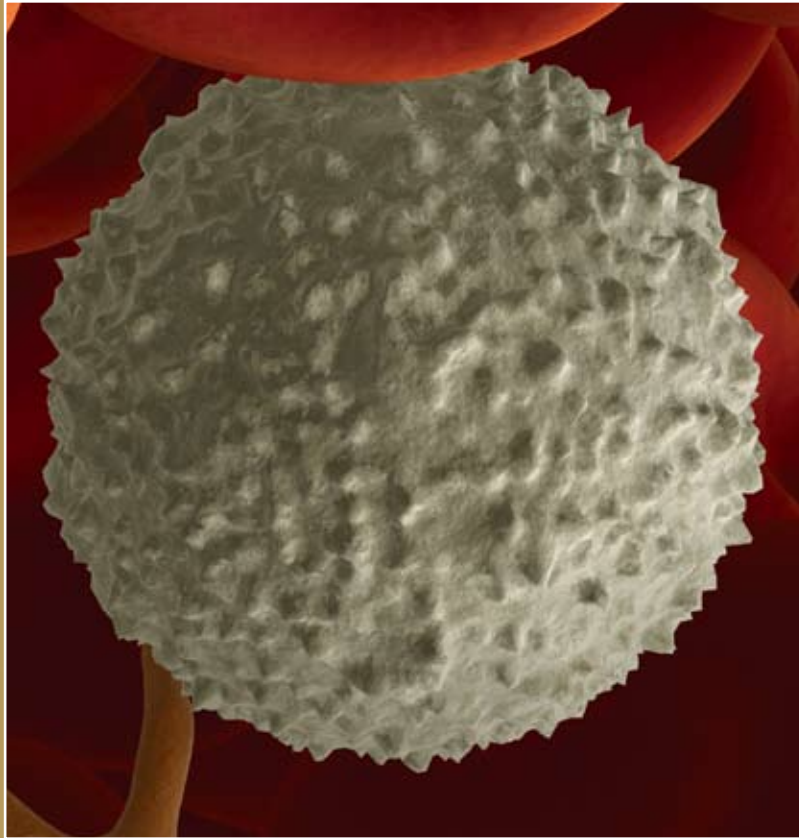
1999

The use of nucleic acid amplification testing for active viruses in donated blood begins.

2005

The FDA approves the first West Nile virus blood test to screen blood donors.

CHAPTER 2: WHITE BLOOD CELLS



WHITE BLOOD CELL, THE PROTECTOR:
helps the body fight off diseases and infections

Curing Pediatric Acute Lymphoblastic Leukemia

BY JOSEPH V. SIMONE, MD, University of Florida Shads Cancer Center, Gainesville, FL

The road to curing most children with acute lymphoblastic leukemia (ALL), the most common childhood cancer, may be the greatest success story in the history of cancer.

The modern therapy for childhood ALL began in Boston when Dr. Sidney Farber, a pathologist at the Children's Hospital, developed an interest in childhood leukemia. The years before World War II had seen the cure of pernicious anemia, a disorder caused by vitamin B-12 deficiency characterized by the overwhelming presence of immature red blood cells in the bone marrow, a feature that resembled leukemia. At the time, an essential food chemical, folic acid, was found to cure similar anemias seen in infancy and pregnancy.



Sidney Farber. Photo courtesy of the Dana-Farber Cancer Institute.

Farber wondered whether folic acid would also cure ALL because it too featured immature blood cells and anemia. He tried it in some children, and it failed and seemingly made them worse. He then reasoned that folic acid may have stimulated the growth of leukemia cells as well as normal cells and instead tried to block that stimulation with an antagonist of folic acid, aminopterin. Remarkably, this drug produced temporary remission with the return of normal blood cells and health. A new era was born. Farber reported his findings in the June 3, 1948, issue of the *New England Journal of Medicine*. This laid the groundwork for important advances in the 1950s and beyond.

In 1950, Gertrude Elion and George Hitchings, who subsequently received the Nobel Prize, developed 6-mercaptopurine (6-MP), which was designed to interfere with DNA synthesis and kill rapidly growing cells like leukemia. At about the same time, cortisone-based drugs (corticosteroids) were new and were tried for virtually every disease, including cancer. Both 6-MP and corticosteroids, like methotrexate (another anti-folic-acid drug), resulted

in a transient improvement in the duration and quality of survival for children with ALL.

Still, all of the children treated at this time eventually died because resistance to these drugs invariably developed. Nevertheless, these earlier successes generated a great deal of interest and, more importantly, organized action. Because of the relative rarity of childhood leukemia, investigators from several institutions began to work together. Two multi-institution "Leukemia Groups" were developed to speed up the study of new therapies.

Between 1949 and 1954, the first clinical trials that tested combinations of chemotherapy drugs methotrexate, corticosteroids, and 6-MP for childhood ALL were carried out. The latter studies were the first controlled clinical trials in leukemia, perhaps in cancer history, that simultaneously compared two drugs – in this case methotrexate vs. 6-MP. The results were very informative and were accompanied by wide-ranging laboratory research, particularly in animals. Patients lived longer with these new combinations of chemotherapy drugs, but all still died, usually within a year.

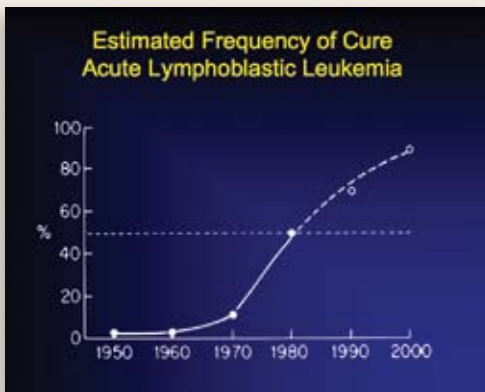
A series of trials was performed at St. Jude Children's Research Hospital that used new combinations of drugs to improve response. Because ALL tended to come back in the central nervous system, a major advance was made by aggressively treating the brain and spinal fluid with radiation and



Milestones in Pediatric Acute Lymphoblastic Leukemia

drugs that markedly decreased this form of relapse.

These studies proved to be a breakthrough, and, ultimately, one-half of the patients were cured of leukemia. The idea that the cure of ALL was now possible was published in 1971 and again in 1972. Many colleagues thought this was irresponsible and gave false hope; thankfully, they were wrong.



This graph illustrates the estimated frequency of cure for acute lymphoblastic leukemia patients since 1950. With the advent of new therapies, survival rates continue to climb.

The 1970s were a fertile time for leukemia investigators throughout the U.S. and Europe. Better control of infection and bleeding, better nursing, increasing resources from the National Institutes of Health and the public, and especially the courage and faith of the children and families who participated in studies, made steady progress possible. Work from then to the present has led to a cure rate now approximating 80 percent.

It may be a cliché, but it is nonetheless true: if we all have achieved more, it is because we stand on the shoulders of those early giants. Because of them, the cure of childhood ALL may be the greatest cancer story ever told.

1948

Sidney Farber treats leukemia with aminopterin, which blocks folic acid and becomes the first agent to cause remission in children with ALL.

1950

George Hitchings and Gertrude Elion develop 6-mercaptopurine to block DNA metabolism and kill rapidly growing leukemic cells.

1950s

The first combination chemotherapy regimens are designed by Emil Frei, Emil Freireich, and James Holland.



*Gertrude Elion and George Hitchings
Copyright GlaxoSmithKline. Used with permission.*

1960s

Criteria are established for the diagnosis of ALL.

The phases of therapy become recognized as important: remission induction, intensification, central nervous system therapy, and continuation (maintenance) therapy.

New treatment drugs are introduced: vincristine, asparaginase, cytoxan, daunomycin, and cytosar.

1970s

Donald Pinkel develops a "total therapy" approach to prevent a relapse of the cancer in patients' central nervous systems (leukemic meningitis).



A team of leukemia researchers at St. Jude Children's Research Hospital in the early 1970s (left to right): Joseph Simone, Luis Borella, Omar Hustu, Donald Pinkel, and John Aur.

Supportive care, such as platelet transfusions and antibiotics, improve patient outcomes.

1975

For the first time, ALL is classified into subtypes for better treatment strategies.

1980s

About 50 percent of ALL patients become long-term survivors in much of the U.S. and Western Europe.

Cytogenetics (the study of chromosomes and cell division) emerges as a key tool in predicting outcome in ALL.

1998

Researchers begin individualizing the dosage of chemotherapy to increase survival rates in children with ALL.

Targeted Therapy for Chronic Myeloid Leukemia

BY BRIAN DRUKER, MD, Oregon Health and Science University Cancer Institute, Portland, OR

Many advances in the treatment of cancer can be traced to the therapy of leukemia. The development of a specific therapy for chronic myeloid leukemia (CML) is a remarkable story of scientific discovery that proved that a precise understanding of the molecular cause of a cancer can lead to an effective and non-toxic “targeted” treatment.

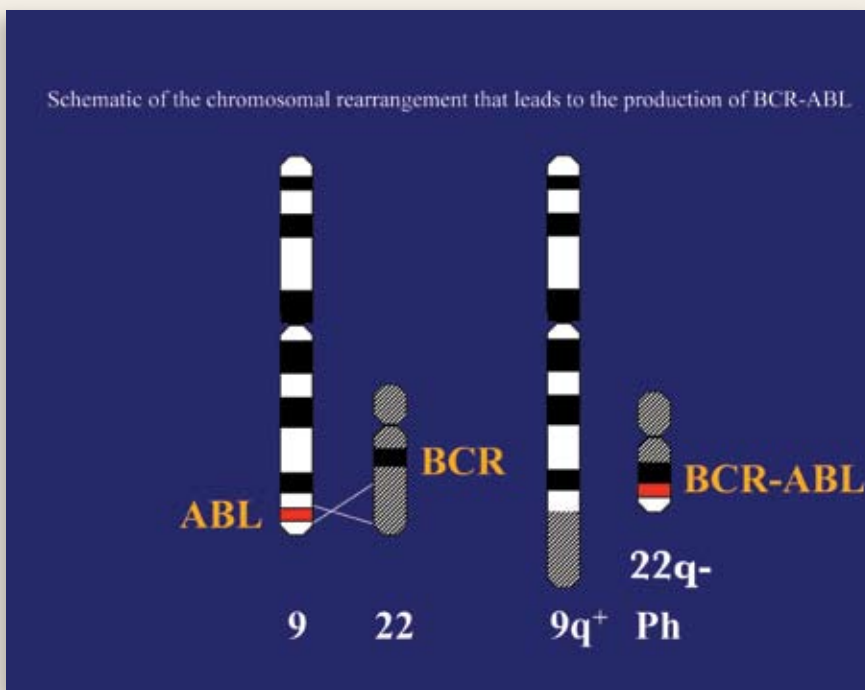
CML is one of the four main types of leukemia, affecting approximately 5,000 people per year in the United States. The disease can occur at any age but is primarily a disease of adults. CML is characterized by a massive over-production of white blood cells. A normal white blood cell count ranges between 4,000 and 10,000; in contrast, patients with CML typically

have white blood cell counts ranging from 100,000 to as high as 500,000. Because the white blood cells mature and function normally, infections are not a common feature of CML. Rather, symptoms include fatigue due to anemia or abdominal discomfort due to an enlarged spleen. Historically,

patients with CML lived no more than three to five years, during which time the disease would quickly transform from a chronic leukemia to an aggressive and fatal acute leukemia.

CML has become the “poster child” for targeted cancer therapy, demonstrating that a precise understanding of the cause of a disease allows an effective therapy to be developed. To achieve this, however, required decades of scientific discovery to unravel the cause and develop a targeted therapy. In 1960, Peter Nowell and David Hungerford, working in Philadelphia, described a shortened chromosome in the blood and bone marrow of patients with CML. This was the first consistent chromosomal abnormality associated with a human cancer. Then, in 1973, Janet Rowley showed that this abnormal chromosome, now called the Philadelphia chromosome, came about because of an exchange of genetic material between two chromosomes. In the 1980s, it was demonstrated that the consequence of this chromosome exchange was the production of an abnormal gene called *BCR-ABL*. This gene acted like the gas pedal in a car stuck in the “on” position, fueling the excess growth of white blood cells in CML.

With the target identified, a drug discovery program was started, aimed at developing a drug to shut down the activity of *BCR-ABL*. The compound that became known as imatinib (Gleevec) was developed in 1992, and studies showed that this compound killed CML cells without harming normal cells. In 1998, the



An abnormal exchange of genetic material between two chromosomes produces a gene called BCR-ABL, which fuels an excess growth of white blood cells in CML patients.

Imatinib: A Patient Perspective

BY DOUG JENSON

I had been a high-energy guy all my life, always able to keep going as long as necessary, whether for work or for fun. I did several of the Cascade Runoffs, Cycle Oregons, and Hood to Coast Relays. Then in September 1997, things changed. My wife joked that maybe “Mr. Indestructable” was just getting older, but then I started coughing, sometimes so hard and so long that I’d choke and nearly pass out.

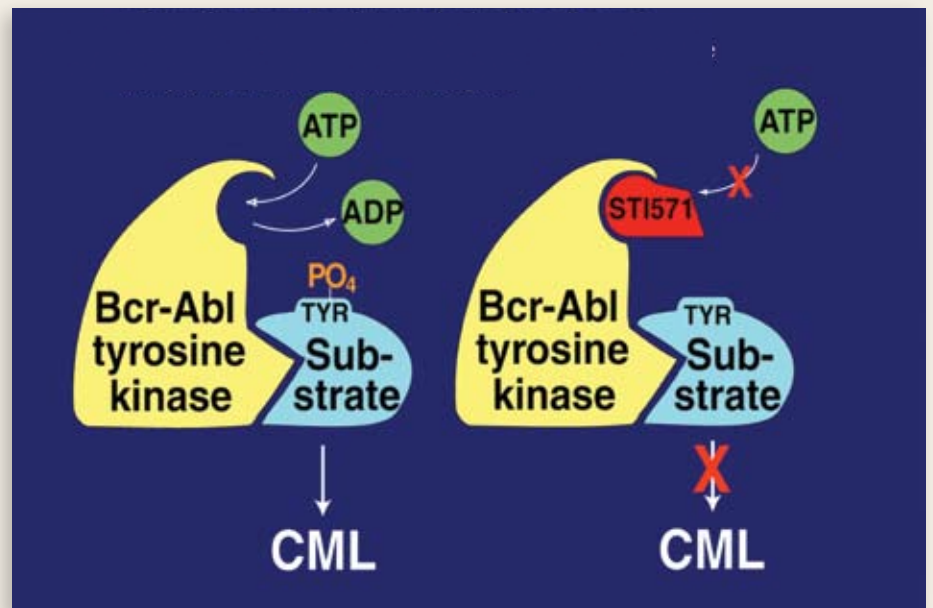
After several months of prescribing antibiotics, my physician decided it was time to do a CBC blood test. Well, maybe I have to admit to getting older, but it turned out that chronic myelogenous leukemia was the culprit.

I was referred to Dr. Jeffrey Menache who gave us the sobering news of a three- to five-year life expectancy under current treatments. He also gave us the hopeful news that OHSU was doing some really interesting things with CML; however, they were not yet conducting human trials. About the time that we found that my body wouldn’t tolerate interferon, I got the call from OHSU that Dr. Druker was ready to evaluate my suitability for their human study, which would start in the spring.

Long story short, I have been taking the drug Gleevec for nine-and-a-half years. I am healthy, happy, and active. There are few side effects and those few are minor. For six years, bone marrow and nested blood tests have shown no detectable Philadelphia chromosomes. Needless to say, my family and I are profoundly grateful to Dr. Druker and his team, including Carolyn Blasdel, my nurse.

drug was tested in patients with CML who had exhausted standard treatment options and whose life expectancy was limited. Within six months of starting the clinical

trials of imatinib, all of the patients had their blood counts return to normal. Remarkably, this once-a-day pill had minimal side effects. These unprecedented results were



Mechanism of action of STI571 (imatinib). BCR-ABL binds ATP and transfers energy to substrates that lead to cell growth. Imatinib blocks the binding of ATP to BCR-ABL and inhibits the ability of BCR-ABL to cause cells to grow.

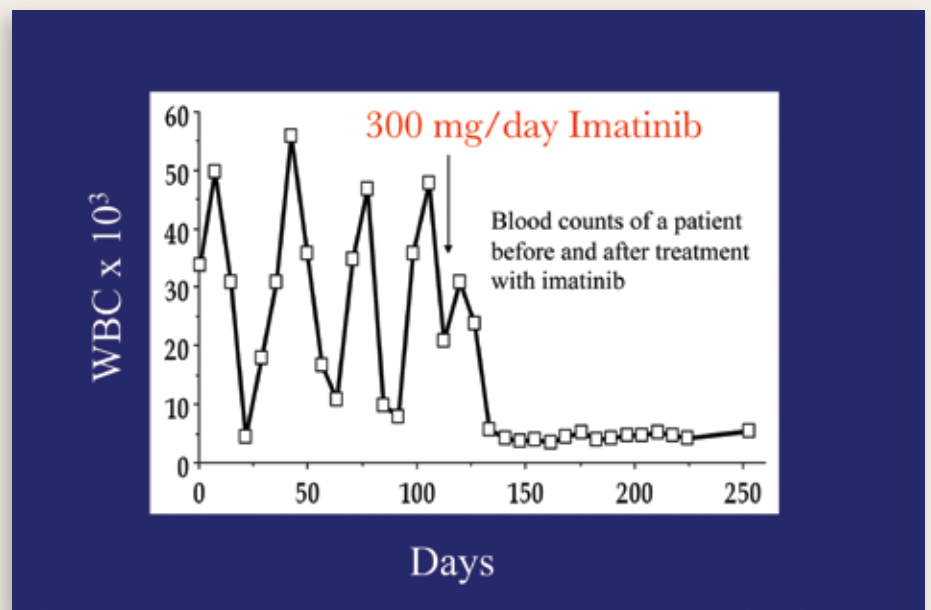


Figure courtesy of Druker et al. New England Journal of Medicine. 2001; 344:1031-7.



Milestones in Targeted Therapies for Chronic Myeloid Leukemia

confirmed in much larger clinical trials, and imatinib was approved by the U.S. Food and Drug Administration (FDA) in 2001, less than three years from the start of the clinical trials. With longer follow-up, this once routinely fatal leukemia now has a five-year survival rate of 95 percent.

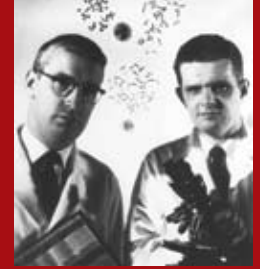
But imatinib is not perfect, and some patients have had their leukemia return. Once again, scientific discoveries into the cause of resistance have allowed new therapies to be developed. It has been determined that the major cause of resistance to imatinib is changes (or mutations) that occur in *BCR-ABL*, which is imatinib's target. These changes prevent imatinib from binding to the target to shut it down. If *BCR-ABL* was a lock and imatinib was the key, in the case of resistance, the lock has been changed, so the key no longer fits. These changes allow *BCR-ABL* to regain its foothold and once again drive the growth of white blood cells. Newer drugs (dasatinib and nilotinib) have been developed that can shut down most of the mutated forms of *BCR-ABL*, and have significant activity in patients with resistance to imatinib; these drugs are also FDA-approved. Thanks to these remarkable scientific advances, patients with CML now have numerous treatment options available and the prospect of a normal life expectancy.

1845

John Hughes Bennett and Rudolph Virchow describe the first cases of CML.

1960

Peter Nowell and David Hungerford identify an abnormal chromosome in the blood cells and bone marrow of patients with CML.



Peter Nowell and David Hungerford. Reprinted, with permission, from the *Annual Review of Medicine, Volume 53, copyright 2002 by Annual Reviews, www.annualreviews.org.*

1973

Janet Rowley determines that the abnormal chromosome identified by Nowell and Hungerford results from the exchange of genetic material between two chromosomes.



Janet Rowley. Photo courtesy of the University of Chicago.

1982-1985

John Groffen, Nora Heisterkamp, Gerard Grosveld, E. Cannani, David Baltimore, and Owen Witte show that an abnormal gene and protein called *BCR-ABL* is produced as a consequence of the chromosome rearrangement that characterizes CML.

1987

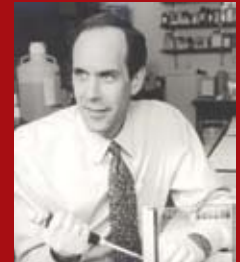
Nicholas Lydon and Alex Matter begin a drug discovery program to target proteins such as *BCR-ABL* in collaboration with Brian Druker, Thomas Roberts, and Charles Stiles.

1993

Brian Druker's laboratory shows that STI571 (imatinib) is the best of the compounds developed by Nicholas Lydon's group at specifically targeting and killing CML cells.

1998

Brian Druker, Charles Sawyers, and Moshe Talpaz begin clinical trials of imatinib.



Brian Druker
Photo by Laura Sikes.

2001

Imatinib is FDA-approved for patients with CML.

2001

Charles Sawyers, Brian Druker, Andreas Hochhaus, and François-Xavier Mahon report that mutations of *BCR-ABL* are the major mechanism of resistance to imatinib.

2006

Follow-up data show a 95 percent five-year survival for patients with CML treated with imatinib.

2006, 2007

Dasatinib and nilotinib are FDA-approved for patients with imatinib resistance.

The Cure of Hodgkin Lymphoma

BY SANDRA J. HORNING, MD, Stanford Cancer Center, Stanford, CA

The cure of Hodgkin lymphoma in the 20th century is another one of cancer's biggest success stories. Breakthroughs in radiation therapy and chemotherapy paired with careful clinical research transformed an invariably fatal disorder into one that is routinely cured. The impact of this success story was, however, much greater because it created optimism for the treatment of cancer in general, and demonstrated the potential for a multidisciplinary approach to diagnosis and management. In the vanguard, Hodgkin lymphoma investigators conducted rigorous, randomized controlled clinical trials as a means to advance therapy. Another important lesson from the Hodgkin's experience was the price of cure. The recognition of late adverse effects from radiation therapy and chemotherapy in the form of second cancers, heart and blood vessel disease, and sterility shaped subsequent research efforts to maintain or improve cure rates with fewer complications, an important goal in a disease that primarily affects individuals in their 20s and 30s. Today, as more than 80 percent of patients are cured after primary treatment, a major emphasis is now placed on survivorship.



In the 1960s, Vincent DeVita Jr. (pictured) and colleagues studied the MOPP combination chemotherapy regimen for advanced-stage Hodgkin lymphoma.

Sir Thomas Hodgkin is credited with the initial description of the clinical disorder that bears his name. In 1832, he reported on a group of patients with enlargement of lymph nodes and spleen that differed from the major known maladies of the day. Some 60 years later, pathologists in Germany and the U.S. independently described the diagnostic microscopic characteristics of Hodgkin lymphoma. At about the same time, two physicians applied X-rays, then newly discovered by William Roentgen, to enlarged lymph nodes in Hodgkin patients, reporting remarkable tumor reductions. These observations, together with increased understanding of the patterns of spread, led to advancements in the application of radiation therapy to larger fields in the 1930s through the 1950s. The introduction of the linear accelerator (a radiation machine used to treat cancer) in the treatment of Hodgkin lymphoma at Stanford University resulted in cures of early-

stage lymphoma. Meanwhile, a team at the National Cancer Institute safely combined four chemotherapy drugs (mustard, vincristine, procarbazine, and prednisone) known as the "MOPP" regimen and reported the first cures of advanced Hodgkin lymphoma in 1964. Steadily improving techniques for defining the extent and location of disease (staging) has allowed appropriate modalities of treatment to be selected for individual patients.

The late 1970s and 80s presented new challenges in the recognition of adverse effects associated with MOPP and radiation therapy, some of which were not apparent for decades after treatment. This time period also featured another major advance in an alternative four-drug chemotherapy regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine), known as "ABVD," that proved to be more effective than MOPP in treating advanced disease and had fewer side effects. In the 1990s, even more effective and less toxic treatments for early-stage lymphoma were devised by reducing the dose and area of the body treated with radiation therapy in combination with brief chemotherapy such as ABVD. The German Hodgkin Study Group introduced an intensive seven-drug chemotherapy program, "BEACOPP," to address the fact that approximately 30 percent of advanced Hodgkin lymphoma was not cured with ABVD. Although associated with more severe early toxicity and sterility, a higher cure rate and improved survival were achieved with BEACOPP in a randomized clinical trial. Other advances in the 90s included the routine application of immunologic markers (specific proteins on the cell surface that define subsets of lymphocytes) that improved the



Milestones in the Study and the Cure of Hodgkin Lymphoma

precision of pathologic diagnosis and single-cell analyses revealing that the cell of origin of Hodgkin lymphoma, a mystery for more than 100 years, was a B cell akin to the cell that causes the majority of non-Hodgkin lymphomas.

The most recent advance in Hodgkin lymphoma management has come in the form of diagnostic imaging. FDG-PET scans are more specific for tumor identification than CT scans and can be used to assess the success of treatment at an early time point. Application of FDG-PET in clinical studies allows physicians to limit more toxic treatments to the subset of patients who are likely to benefit while sparing the majority from adverse effects. Due to the success of conventional treatments, newer biologic agents must be cautiously introduced in Hodgkin lymphoma therapy. However, high response rates have been reported with the anti-B-cell antibody rituximab in a subtype of Hodgkin lymphoma with B-cell characteristics, and there is active research with new agents that target the microenvironment (non-malignant cells and tissues surrounding sites of lymphoma that modify the activity of the tumor cells) as well as Hodgkin cells.



Gianni Bonadonna

Today, children, adolescents, and young and older adults worldwide routinely survive Hodgkin lymphoma with modern treatment. Current efforts seek to maintain optimal health for these survivors, to define the least complicated cures for newly diagnosed patients, and, ultimately, to better understand risks for and prevention of this disease.

- 1832 Sir Thomas Hodgkin publishes "On Some Morbid Appearances of the Absorbent Glands and Spleen," about a series of six patients with clinical findings that were different from tuberculosis, syphilis, and inflammation.
- 1865 Samuel Wilks reports on similar cases with lymph node and splenic enlargement and names the disorder "Hodgkin's disease." This invariably fatal illness is treated with herbs, surgery, and arsenic.
- 1900s German pathologist Carl Sternberg (1898) and American pathologist Dorothy Reed (1902) independently provide detailed accounts of the giant "Reed-Sternberg" cells, which are the microscopic hallmarks of Hodgkin lymphoma.
- 1902-03 W. Pusey and N. Senn note remarkable regressions of Hodgkin lymphoma upon exposure to X-rays.
- 1931 Rene Gilbert administers large fields of radiation therapy to patients with Hodgkin lymphoma.
- 1943 Temporary reduction in the size of lymph nodes is reported in six Hodgkin patients treated with nitrogen mustard by Rene Gilbert and colleagues.
- 1950 Vera Peters reports excellent survival rates in Hodgkin patients treated with radiotherapy to adjacent lymph nodes not known to contain disease.
- 1962 Henry Kaplan introduces the linear accelerator in the treatment of Hodgkin lymphoma at Stanford University. Cures are reported after wide-field radiotherapy treatment of localized Hodgkin lymphoma.
- 1964 Vincent DeVita Jr. and colleagues are the first to demonstrate the cure of advanced-stage Hodgkin lymphoma in approximately 50 percent of patients with combination chemotherapy using the MOPP (mustard, vincristine, procarbazine, prednisone) regimen.
- 1966 Robert J. Lukes and James J. Butler describe the natural history of Hodgkin lymphoma related to histopathologic classification. Saul Rosenberg and Henry Kaplan describe the orderly progression of Hodgkin lymphoma and Rosenberg reports on the staging of this disease.
- 1975 Gianni Bonadonna reports on a chemotherapy combination, ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), which is effective after failure of MOPP. ABVD later becomes the standard chemotherapy regimen for Hodgkin lymphoma, curing more than two-thirds of patients with advanced or bulky disease.
- 1980s Adverse effects of MOPP, including secondary leukemia and sterility, are reported. Late effects of radiotherapy are observed in the form of secondary cancers (particularly lung and breast) and cardiovascular disease. Remissions are achieved with high-dose chemotherapy and autologous transplantation in Hodgkin lymphoma recurrent after chemotherapy and radiation therapy. This approach becomes the standard second-line therapy for advanced disease.
- 1994 Ralf Küppers plucks individual Reed-Sternberg cells from Hodgkin tissues and establishes that they represent malignant B cells by gene rearrangement analyses.
- 1990s Randomized trials in North America and Europe combine limited field, lower-dose radiotherapy with a brief course of less toxic chemotherapy (e.g. ABVD), resulting in cure rates of 90 percent or greater in limited-stage disease. Brief chemotherapy (Stanford V) and radiotherapy are introduced for advanced disease. The German Hodgkin Study Group reports superior survival with an intensive chemotherapy regimen, escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone), in advanced Hodgkin lymphoma.
- 2000s Positron-emission-tomography scans early in the treatment course predict the outcome of treatment with ABVD, suggesting that therapy could be more personalized, reserving radiotherapy and prolonged or more intensive treatments for a subset of patients. First successful treatments of lymphocyte-predominant Hodgkin lymphoma with a monoclonal antibody, rituximab, are reported by investigators in Germany and at Stanford University.



Henry Kaplan and Saul Rosenberg

Targeted Therapy for B-Cell Lymphoma: The Story of Rituximab

BY RONALD LEVY, MD, Stanford University School of Medicine, Stanford, CA

DAVID G. MALONEY, MD, PHD, Fred Hutchinson Cancer Research Center, Seattle, WA

RICHARD MILLER, MD, Principia Biopharma, Inc., Portola Valley, CA

The development of the drug rituximab as a therapy for B-cell lymphoma (a type of cancer affecting cells of the immune system) provides an excellent illustration of how great improvements in patient care were made through the discovery of a therapy that destroys cancer cells without harming other cells in the body.

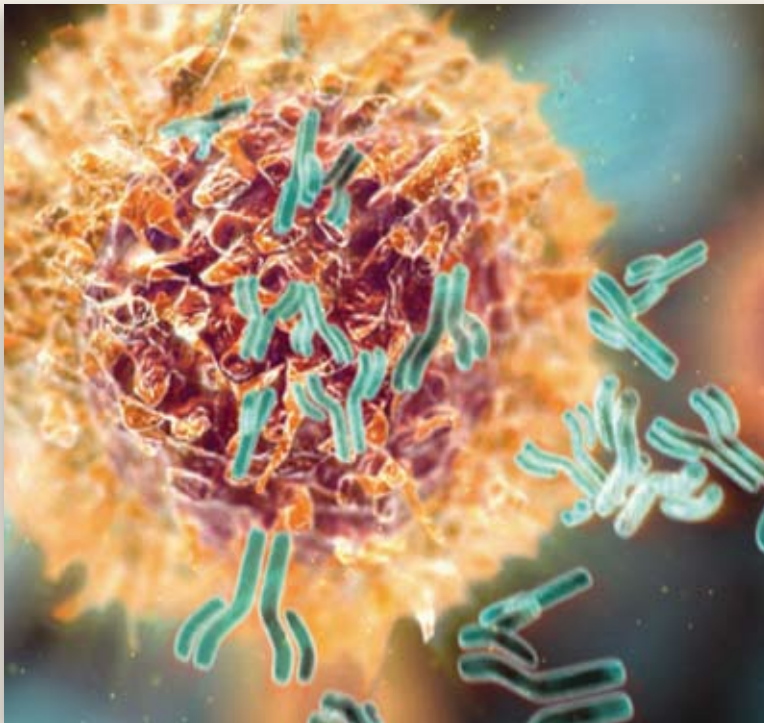
Prior to 1975, rapid progress had been made in the use of chemotherapy for the treatment of lymphoma. Increasingly intense regimens, however, increased toxicity while making only incremental improvements in patient survival. Consequently, investigators were looking for a new approach, and it was clear that antibodies (proteins made by the immune system) might provide the clues needed to diagnose and treat cancer. Antibodies

are one way the immune system recognizes and destroys foreign invaders. Cancer cells are not foreign, since they are part of our own body,

but they often exhibit alien features that could make them appear foreign. The main hurdles for making antibodies in a lab to fight cancer were figuring out how to find the right antibodies and how to make them in sufficient quantities with adequate purity. The first problem was solved by cloning the cells of the immune system responsible for making antibodies. The second problem was solved by making those cells “immortal” – in other words, most cells die in culture after several months, but these immortal cells continue to grow and divide indefinitely.

With these obstacles overcome, scientists set out to find targets against which to direct the antibodies. In order to make this approach clinically useful, a key objective was to destroy cancer cells without damaging normal cells. The first target that was chosen was a specific protein present on lymphoma tumor cells, but not on normal cells, termed an “idiotype.” Each lymphoma tumor has its own unique idiotype; therefore, it was necessary to make a different antibody for each patient. In 1981, the first patient was treated with one of these “anti-idiotypic antibodies,” and, amazingly, the tumor melted away without significant side effects. Motivated by this dramatic result, researchers treated 50 more patients with custom-made antibodies, and many of them are alive and well more than 20 years later.

However, this customized approach was circumvented by the discovery of rituximab, an antibody that recognizes CD20, a target shared by malignant lymphoma cells from almost all



Rituximab binds specifically to a cell-surface marker known as CD20, found on developing B cells and mature B cells, but not on stem cells or plasma cells. When rituximab binds to CD20, it triggers mechanisms that result in targeting this select B-cell population. Copyright © F. Hoffman-La Roche Ltd., Basel, Switzerland.



Milestones in the Development of Rituximab

Mid-1970s

Monoclonal antibodies are developed by Georges J.F. Köhler and César Milstein to fight cancer. Their technique allows a specific antibody molecule to be produced in unlimited quantities.

patients, but also found on normal, immune B cells. Rituximab proved to be effective in treating B-cell lymphoma, and the elimination of normal B cells was surprisingly not harmful. Because rituximab does not affect other normal cells in the body, it can be combined with other therapies. Today, rituximab is part of the regular treatment for almost all patients with B-cell lymphoma, and it has prolonged the lives of many of them.

The next surprising discovery was that rituximab could treat non-cancerous diseases caused by overactive B cells of the immune system. Rituximab has been used to treat rheumatoid arthritis, multiple sclerosis, and a growing list of non-cancerous conditions.

This is a success story that shows that new discoveries in the laboratory can lead to new treatments in the clinic. It represents a combination of scientific intuition, luck, and hard work by many individuals and organizations. From the scientists who made the original discoveries to the clinical investigators, investors, and patients who were willing to take the risk of trying something new, to the regulatory agencies that recognized that novel approaches to treatment deserved flexibility in evaluation, many possible roadblocks that could have prevented this successful therapy were overcome. Today, we must ask how many other potential new therapies are out there and how we can be creative enough to bring them forward.



César Milstein (left) and Georges J.F. Köhler (right) were the first to develop monoclonal antibodies. Photo courtesy of the Celia Milstein/MRC Laboratory of Molecular Biology.

1982

The first successful treatment of a cancer patient with a monoclonal antibody takes place.

1993

For the first time, rituximab is used to treat lymphoma.

1997

The U.S. Food and Drug Administration (FDA) approves rituximab for the treatment of lymphoma.

2008

Nine monoclonal antibodies are approved by the FDA for the treatment of various cancers.

Hematopoietic Cell Transplantation: From a Curative Concept to Cure

BY KARL G. BLUME, MD, Stanford University Medical Center, Stanford, CA

In 1868, two investigators from Prussia and Italy were the first to report that bone marrow generates blood cells in mammals. This observation was the starting point of intense efforts to replace malfunctioning marrow through the transplantation of blood-forming (hematopoietic) cells in humans. However, it took an entire century to develop reliable techniques to identify suitable donors, design potent antibiotics, and establish essential supportive care methods to successfully perform clinical hematopoietic cell transplantation (HCT) procedures. This important accomplishment would not have been possible without decades of intense pre-clinical research in animals, especially to understand issues related to graft rejection and the prevention of graft-versus-host disease (GVHD), a serious reaction caused by the donor's immune cells attacking the recipient's vital organs. The research team at the Fred Hutchinson Cancer Research Center in Seattle, under the leadership of Dr. E. Donnall Thomas (Nobel Laureate in Medicine and Physiology, 1990), deserves the credit for the major contributions to our knowledge in the field of HCT – although countless investigators around the globe have also made many essential research observations.

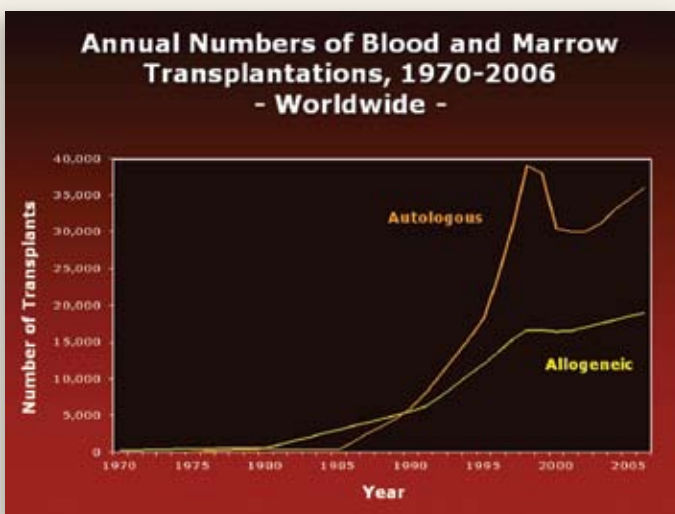
Hematopoietic cells can be obtained from suitably matched related or unrelated volunteer donors (allogeneic HCT) or from the patient's own tissues (autologous HCT). Sources of hematopoietic cells include the bone marrow, blood, or umbilical cord blood. International unrelated volunteer donor banks containing information on approximately 12 million volunteers are interconnected by worldwide computer systems. Approximately 3,500 HCT procedures from unrelated donors are now performed annually, and almost 40 percent of such transplants involve a donor who is from a different country from the recipient. In parallel, umbilical cord blood banks are rapidly growing in size and usage. To date, some 10,000 HCT procedures with umbilical cord blood grafts have been performed.

In 1968, three patients in the United States and the Netherlands suffering

from severe combined immunodeficiency syndromes, in which the ability of the body's immune system to fight infections is compromised, were successfully transplanted and cured by HCT. Since then, the number of HCT procedures has risen to 50,000-60,000 per year, and the cumulative number of patients treated worldwide has now reached

800,000. The majority of HCT recipients are patients with leukemia, lymphoma, myeloma, myelodysplasia, bone marrow failure conditions, severe red blood cell disorders such as sickle cell disease or thalassemia, and certain solid tumors.

The choices of which type of HCT (allogeneic or autologous) and the source of the graft (bone marrow, blood, or cord blood) depend mainly on the patient's underlying disease and whether it is in remission. Before transplant, the patient is treated with high-dose chemotherapy, with or without radiation therapy, to eradicate the cancerous cells (prior to both autologous and allogeneic HCT), and to suppress the patient's immune system to prevent it from attacking the donor hematopoietic cells (prior to allogeneic HCT). More recently, it has been established that less intensive pre-transplant treatment also allows successful transplantation, but with less severe side effects. Such "reduced intensity" transplants prevent later relapses by maintaining the body's ability to launch an immune attack by the new marrow against the cancer.



Number of autologous (self graft) and allogeneic (donor graft) HCT procedures performed yearly since 1970. Graph courtesy of Dr. Mary M. Horowitz and the Statistical Program of the Center for International Blood and Marrow Transplantation Research.



Milestones in Hematopoietic Cell Transplantation (HCT)

1868

The bone marrow is first described as blood-forming tissue.

1939

The first clinical marrow transplant is attempted, but unsuccessful.

1949-56

The humoral and cellular hypotheses of marrow reconstitution are debated.

1956-59

Efforts are renewed in marrow grafting in human diseases.

1956-present

Advances in marrow grafting through animal studies in murine and canine models.

1968-69

The first successful allogeneic HCT procedures are performed in patients with severe combined immunodeficiency diseases.

1975

The first large series of allogeneic HCT for leukemia is performed.

1977, 1980

Successful HCT procedures from unrelated marrow donors.

1978

The first series of successful autologous HCT for lymphoma is performed.

1987, 1989

Isolation of the murine and human hematopoietic stem cells is achieved.

1990

The Nobel Prize in Medicine/Physiology is awarded to E. Donnall Thomas for the development of HCT as a curative therapy for life-threatening hematologic disorders.

2008

More than 800,000 patients have been transplanted worldwide during the past four decades.



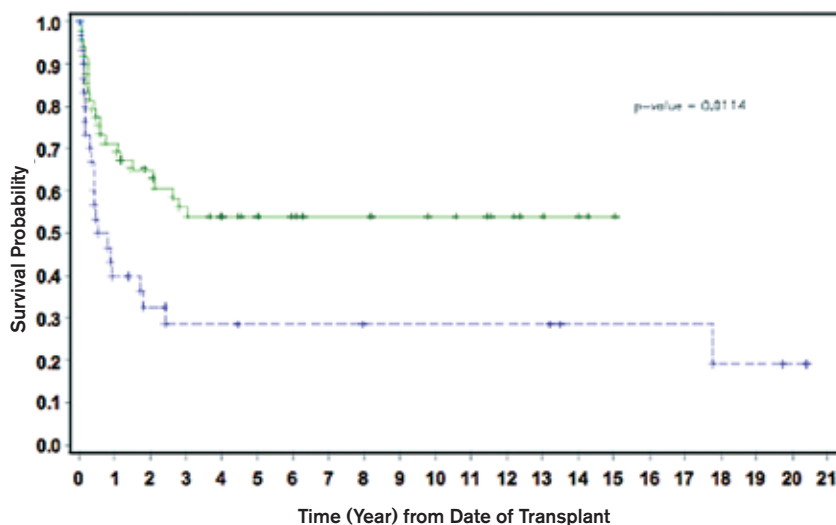
E. Donnall Thomas
Photo by R. J. McDougall.

This “graft-versus-malignancy effect” is a critical element for cure through allogeneic HCT. Reduced-intensity regimens have also made it possible to extend HCT to older patients (up to 75 years) and younger patients with health problems that make them ineligible for high-intensity regimens.

Significant post-transplant problems can result from toxic effects related to the preparatory treatments, GVHD, infections, and relapse of the underlying disease. Continued research is leading to further improvements and better survival results. The long-term outcome of HCT procedures depends on whether or not the patient is in remission. While 50-80 percent of leukemia patients can be cured by allogeneic HCT if performed during first remission, the expectation for success is markedly reduced for those whose HCT is carried out in more advanced stages of their disease. Likewise, the long-term results of autologous HCT are strongly influenced by the amount of cancer in the patient’s body at the time of transplantation, with relapse being the leading cause for treatment failure.

Social studies conducted over an extended period of time indicate that the quality of life in the years after a patient receives HCT usually ranges from good to excellent, and, ultimately, the majority of patients are successfully reintegrated into their personal and professional lives.

HCT for Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia



Long-term survival after HCT of 79 patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. The outcome of 49 patients transplanted while in their first complete remission (1CR, solid line) is compared to that of 30 patients who underwent HCT post-first-complete-remission, after relapse of their leukemia (>1CR, dashed line). The graph illustrates that remission status at the time of HCT is an important prognostic factor for outcome, with approximately half of patients cured if they undergo transplantation while in 1CR. Graph courtesy of Dr. Ginna G. Laport. Blood. 2008; 112: 903-9.

CHAPTER 3: PLATELETS AND BLOOD CLOTTING



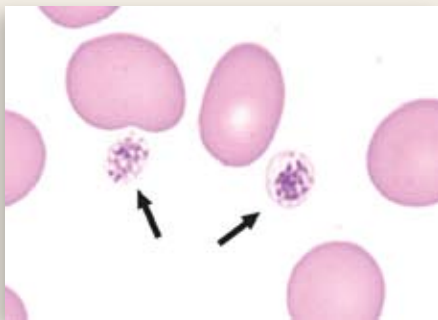
PLATELET, THE CONTROLLER:
clots blood and controls bleeding

Antiplatelet Therapy

BY ANDREW I. SCHAFER, MD, Weill Cornell Medical College, New York, NY

Once thought to be just “dust” particles in blood, platelets were first recognized as a special class of blood cells (actually cell fragments) by an Italian researcher in 1882. Hematology research over the past century has subsequently unraveled what platelets normally do, why they can cause cardiovascular disease under certain conditions, and how they can be effectively targeted with antiplatelet therapy to prevent and treat heart attacks and stroke.

We now know that platelets are born in the bone marrow, from which they are released into circulating blood. At any given time, the blood of an average adult carries over a trillion platelets throughout his or her body, each one surviving for about a week before being replenished



Though the shape of a platelet may vary, its distinct granular appearance makes it easily recognizable in blood smears. Photo by Dr. Peter Maslak, courtesy of the ASH Image Bank.

by new platelets arising in the marrow. Platelets are like microscopic circulating band-aids, constantly looking for leaks in the vascular system and then instantaneously plugging these bleeding sites by sticking to the wound (a process called adhesion), becoming activated locally, and then attracting other circulating platelets to build an impermeable clump (a process called aggregation) at the exact point of damage. This protective mechanism, which is a desirable function of platelets, is called hemostasis. But under some conditions platelets can become harmful, causing plugs to form where there is no bleeding and they are not needed. This typically happens in arteries that have become diseased with atherosclerosis, a condition in which deposits of fat or plaque collect and harden in the arteries, blocking the normal flow of blood. Platelets can stick to atherosclerotic plaques in the coronary and brain arteries and obstruct, or occlude, these vessels causing heart attacks and strokes. This undesirable, pathological process is called thrombosis.

It was first noted more than 50 years ago by a private practitioner that aspirin, which had been used in its native form since antiquity to treat fever and pain, was remarkably able to protect individuals from heart

attacks. The ability of aspirin to prevent cardiovascular disease was subsequently found by hematologists to be due to its effects on platelets. Beginning in the mid-1960s, several investigators conducted basic hematology research to clearly identify the precise mechanism by which aspirin inhibits platelet activation and aggregation. Aspirin thus became the first effective antiplatelet drug. It is still in wide use today to prevent cardiovascular complications that are caused by pathological platelet occlusion of atherosclerotic arteries.



Aspirin, originally derived from the bark of the willow tree, has been used since antiquity to treat fever and pain.

Understanding exactly how aspirin blocks platelets demonstrated the power of hematology research in translating observations made by physicians in their practice to basic science mechanisms (“bedside to bench” research). In subsequent years, hematologists discovered the precise sequence of molecular events that normally occur to instantaneously transform an inactive, circulating platelet to one that sticks to and aggregates with other platelets on the inside surface of a diseased vessel wall. This basic knowledge, in turn, has permitted the development of new antiplatelet drugs to target one or more of these molecular events.



Milestones in Antiplatelet Therapy

Based on fundamental hematology research that defined the mechanisms of platelet aggregation, an American hematologist developed the next clinically effective antiplatelet agent, a monoclonal antibody against the platelet membrane protein that initiates aggregation (the glycoprotein (GP) IIb/IIIa complex). This drug (abciximab) was approved by the FDA in 1994 to reduce the thrombotic complications of coronary angioplasty. Other GP IIb/IIIa receptor antagonists soon followed, and this class of drugs is now in wide use to also treat acute coronary syndromes.

Yet another class of antiplatelet drugs called ADP receptor antagonists (ticlopidine, clopidogrel) were first found in 1998 to greatly reduce the occlusion of coronary stents (devices placed inside an atherosclerotic artery to hold it open and prevent further narrowing), a particularly thrombosis-provoking intervention. These new antiplatelet drugs may have wider application in the prevention of vascular disease by improving on or adding to the beneficial actions of aspirin.

Thus, basic hematology research to understand how platelets work and how their function can be blocked has transformed our modern approach to the prevention and treatment of cardiovascular disease. Excessive interference with platelet function with any of these antiplatelet agents carries with it the risk of causing the opposite of thrombosis, namely bleeding complications. To provide optimal protection from thrombosis with no risk of bleeding will be the next frontier of hematology research in antiplatelet therapy. It will require the identification of agents that can selectively block undesired, pathological thrombosis without interfering with physiologically protective hemostasis.

1882

Giulio Bizzozero describes blood platelets.

1953

Lawrence Craven reports that aspirin prevents heart attacks.

1960s

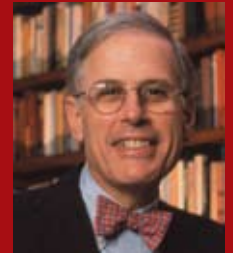
Harvey Weiss, Sir John Vane, Philip Majerus, Gerald Roth, and others elucidate the antiplatelet actions of aspirin.

1970s

Alan T. Nurden, Jacques P. Caen, David R. Phillips, and others describe the molecular basis of platelet aggregation.

1994

Barry Collier's monoclonal antibody to platelet GP IIb/IIIa is approved for use in coronary angioplasty.



Barry Collier

1998

ADP receptor antagonists are shown to be effective antiplatelet agents in preventing coronary stent thrombosis.

Hemophilia: From Plasma to Recombinant Factors

BY JEANNE M. LUSHER, MD, Children's Hospital of Michigan, Detroit, MI

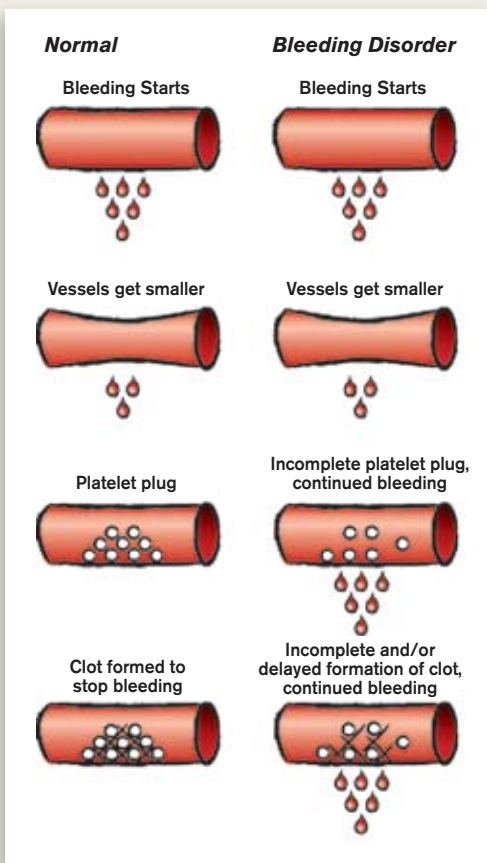
Hemophilia is caused by the failure to produce certain proteins required for blood clotting: factor VIII (hemophilia A) or factor IX (hemophilia B). Because the genes encoding these factors are on the X chromosome, these diseases (termed “X-linked”) usually affect only men, who carry only one X chromosome. Women carrying the disease gene are “carriers” and can transmit the disease to their sons, but women are rarely affected because they also carry a normal X chromosome. Patients with severe hemophilia produce less than 1 percent of the normal amount of the affected clotting factor and are dependent on factor from intravenous infusions to treat or prevent bleeding episodes.

By the late 1960s, scientists and manufacturers developed methods for separating factor VIII and factor IX from pooled plasma, resulting in neatly packaged bottles of freeze-dried (lyophilized) factor VIII or factor IX concentrates. Each bottle had a label indicating the amount of factor VIII or factor IX it contained, allowing more accurate dosing. By the early 1970s, the availability of these concentrates led to home treatment, greatly changing the lives of people with hemophilia.

However, there was a price to be paid for this newfound independence. Thousands of plasma donations were combined as starting material for one batch of plasma-derived factor VIII or factor IX concentrate, and by the early 1980s, human blood, plasma, and plasma-derived products were discovered to be transmitting potentially deadly blood-borne viruses, including hepatitis viruses and HIV. Manufacturers of plasma-derived clotting factor concentrates attempted to kill these viruses with dry heat, solvent-detergent treatment, and pasteurization, with varying degrees of success. By 1985, most patients with hemophilia in the U.S. had been switched to heat-treated concentrates, but many had already been infected with HIV and a large percentage of them succumbed to it. Great concern about the safety of plasma-derived products continued in the hemophilia community.

In the late 1950s and much of the 1960s, fresh frozen plasma (FFP) was the mainstay of treatment for hemophilia A and hemophilia B. Each bag of FFP contained only minuscule amounts of factor VIII and factor IX, thus large volumes of intravenously administered FFP were needed to stop bleeding episodes. Children were usually hospitalized for treatment of bleeding into a knee, an elbow, or other joint. Many adolescents were reluctant to tell their parents that they were bleeding, delaying treatment and gradually leading to chronic joint disease with crippling deformities.

A great advancement came in the mid-1960s with the discovery of a method for preparing factor VIII from FFP by allowing it to thaw in the cold (cryoprecipitated plasma). This preparation could be stored in frozen form as “cryoprecipitate.” This allowed intravenous administration of more factor VIII in a smaller volume, allowing outpatient treatment for bleeds and even elective surgery in persons with hemophilia A. This more concentrated form of clotting factor VIII rapidly became the preferred treatment for acute bleeding episodes in patients with hemophilia A.



Hemophilia is caused by the failure to produce certain proteins required for clotting, which results in continued bleeding. Figure courtesy of the National Hemophilia Foundation.

Eventually better screening methods for blood donors were developed, improving the safety of donated plasma. Screening of donors for the hepatitis B virus was already in place, and in 1989 the hepatitis C virus (HCV) was isolated, allowing HCV antibody testing of donors to begin in 1990. HIV was identified in 1984, and by 1985 a blood test for HIV antibodies was instituted in blood and plasma collection facilities.

The successful cloning of the factor VIII gene in 1984 was a major breakthrough, allowing production of recombinant human factor VIII (r factor VIII). Clinical trials in humans began three years later, and this was truly an exciting time, especially for families who had



Judith Pool, who discovered a simple way to make cryoprecipitates (blood particles that contain clotting factors) for the treatment of hemophilia. Photo courtesy of the National Hemophilia Foundation.

lost loved ones to AIDS. The boys and young men participating in the studies of r factor VIII were overheard saying, “This is so exciting, being

on the cutting edge of science!” By 1992, two pharmaceutical companies had licensed r factor VIII products for use in hemophilia A. Cloning of factor IX was first reported in 1982, and a licensed r factor IX product (BeneFIX) became available for people with hemophilia B in 1997.

Hemophilia: A Patient Perspective

Excerpt from *The Gift of Experience*, a collection of oral histories.

BY ROBERT MASSIE

When I was twelve, two things happened that had an extraordinary impact. One was that, in 1968, I was taught to self-infuse. I still remember the nurse who taught me... she also taught my father how to infuse, so sometimes my father would do it; sometimes I would do it under his supervision. Gradually, I gained the ability.

Secondly, the factor VIII concentrates began to appear. These made an enormous difference because not only were they much more powerful, but the key piece there for me was that the concentrates could be kept cool rather than frozen. That opened up an absolutely enormous vista for me to do things on my own, because I could take my bottles of factor with me.

Eventually they learned that factor could be kept at room temperature...I could quite literally pack a backpack and go. I was able to give myself shots on camping trips or in the bathroom of an airborne 747.

Just at the moment of adolescence, when your life is expanding anyway, my ability to manage hemophilia improved in a way that allowed me this freedom.

Other significant advances that have been made in recent years include treatment for patients with inhibitors (antibodies that inhibit or interfere with the function of factor VIII or factor IX) and prophylaxis (treatment to prevent disease). Inhibitor antibodies develop in approximately 30-35 percent of people with hemophilia A and 1-3 percent with hemophilia B. We now have a much better understanding of the causes (genetic, racial/ethnic, etc.) and natural history of these inhibitors, how to detect and measure them with greater certainty, and how best to eliminate them by manipulating the immune system. Scientists have also developed



Milestones in Hemophilia

innovative treatment products for “bypassing” the inhibitor, such as recombinant activated factor VII (r factor VIIa), which was first licensed for use in hemophilia in 1997. Newer second-generation products to treat inhibitors are actively being developed, and while much progress has been made in treating inhibitors, this complication remains the greatest problem in the management of hemophilia today.

Now that we have safer clotting factor replacement products, preventive (prophylactic) treatment has gained acceptance as a means to preserve normal joint and musculoskeletal function in boys and young men with hemophilia. First described by Swedish physicians 40 years ago, then recommended by the (U.S.) National Hemophilia Foundation’s Medical and Scientific Advisory Council in 1994, and recently documented as effective in a multicenter controlled trial, increasing numbers of young boys with severe hemophilia A or B are being started on prophylaxis with r factor VIII or r factor IX. Because of these developments, the future for those with hemophilia looks much brighter than it was only a few decades ago.

1950s

The use of fresh frozen plasma, which often required hospitalization, is the mainstay of treatment for hemophilia.

1964

Judith Pool discovers a simple way to make cryoprecipitates (cold insoluble precipitates that contain factor VIII) for the treatment of hemophilia.

1970s

The availability of lyophilized (dried) factor VIII or factor IX concentrates allows home infusion therapy to become a common treatment practice.

1973

The Hemophilia Act of 1973 allows federally funded comprehensive hemophilia treatment centers to be established.

1982

Using gene sequencing techniques, researchers clone factor IX.

1984

Using gene sequencing techniques, researchers clone factor VIII.

Luc Montagnier and Robert Gallo discover the virus that causes AIDS.

1980s

The hepatitis viruses and HIV threaten the worldwide blood supply. To combat this, manufacturers of plasma-derived clotting factor concentrates attempt to kill the viruses with dry heat, solvent-detergent treatment, and pasteurization. Screening methods for these viruses, such as the ELISA test, are also developed.

1990s

After only a few years of successful clinical trials, recombinant human factor products become licensed and are available to hemophilia patients.

2000s

Recent advances include a better understanding of the cause, detection, and elimination of inhibitor antibodies found in many hemophilia patients.

Antithrombotic Therapy

BY JACK HIRSH, MD, McMaster University, Hamilton, Ontario, Canada

Normally, blood flows through our arteries and veins smoothly and efficiently, but if a clot, or thrombus, blocks the smooth flow of blood, the result – called thrombosis – can be serious and even cause death. Diseases arising from clots in blood vessels include heart attack and stroke, among others. These disorders collectively are the most common cause of death and disability in the developed world. We now have an array of drugs that can be used to prevent and treat thrombosis – and there are more on the way – but this was not always the case.



Aggregated Platelets and Fibrin: Arterial thrombi are composed of aggregated (clumped) platelets supported by fibrin strands (black).

Classes of Antithrombotic Drugs

The most important components of a thrombus are fibrin and platelets. Fibrin is a protein that forms a mesh that traps red blood cells, while platelets, a type of blood cell, form clumps that add to the mass of the thrombus. Both fibrin and platelets stabilize the thrombus and prevent it from falling apart. Fibrin is the more important component of clots that form in veins, and platelets are the more important component of clots that form in arteries where they can cause heart attacks and strokes by blocking the flow of blood in the heart and brain, respectively, although fibrin plays an important role in arterial thrombosis as well.

There are two classes of antithrombotic drugs: anticoagulants and antiplatelet drugs. Anticoagulants slow down clotting, thereby reducing fibrin formation and preventing clots from forming and growing. Antiplatelet agents prevent platelets from clumping and also prevent clots from forming and growing.

Anticoagulant Drugs

The anticoagulants heparin and dicumarol were discovered by chance, long before we understood how they worked. Heparin was first discovered in 1916 by a medical student at The Johns Hopkins University who was investigating a clotting product from extracts of dog liver and heart. In 1939, dicumarol (the precursor to warfarin) was extracted by a biochemist at the University of Wisconsin from moldy clover brought to him by a farmer whose prize bull had bled to death after eating the clover.

Both of these anticoagulants have been used effectively to prevent clots since 1940. These drugs produce a highly variable anticoagulant effect in patients, requiring their effect to be measured by special blood tests and their dose adjusted according to the results. Heparin acts immediately and is given intravenously (through the veins). Warfarin is swallowed in tablet form, but its anticoagulant effect is delayed for days. Therefore, until recently, patients requiring anticoagulants who were admitted to a hospital were started on a heparin infusion and were then discharged from the hospital after five to seven days on warfarin.

In the 1970s, three different groups of researchers in Stockholm, London, and Hamilton, Ontario, began work on low-molecular-weight heparin (LMWH). LMWH is produced by chemically splitting heparin into one-third of its original size. It has fewer side effects than heparin and produces a more predictable



Milestones in the Development of Anticoagulant Drugs

Heparin

1916

Heparin is discovered in dog liver by a team from The Johns Hopkins University in Baltimore, MD.

1930s

Scientists purify heparin and produce enough pure material for clinical use.

1932

A U.S. clinical scientist shows that heparin requires a plasma factor (now known as antithrombin or AT) for its anticoagulant action.

1970s

The mechanism of the interaction between heparin and AT is explained by scientists from Harvard University and from the University of Uppsala.

Warfarin

1920s

Cattle in the northern U.S. and Canada are dying from a bleeding disease caused by a substance in moldy sweet clover.



Sweet clover

1930s

A Danish scientist discovers that dietary vitamin K is necessary to prevent bleeding.

1939

Researchers at the University of Wisconsin identify the substance in moldy clover as dicumarol. Over the next several years, warfarin, a related compound, is made in this laboratory.

1941

Dicumarol is first given to patients at the Mayo Clinic.

1950s

Clinical studies with warfarin begin in the U.S., and the drug is approved for clinical use in 1954.

1970s

The mechanism of action of vitamin K is explained by scientists who discover that warfarin's anticoagulant effect is caused by interference with the action of vitamin K.

Low-Molecular-Weight Heparin (LMWH)

1970s

Researchers begin work on LMWH.

1980s

The first clinical studies of LMWH are performed in the mid-1980s and show that LMWH is effective for preventing venous thrombosis in high-risk patients.

1990s

LMWH can now be administered safely in an out-of-hospital setting.

Fondaparinux

1979

Scientists determine the structure of the high-affinity binding site on heparin and soon after demonstrate that this high-affinity site is a pentasaccharide (five-sugar unit) with a unique structure.

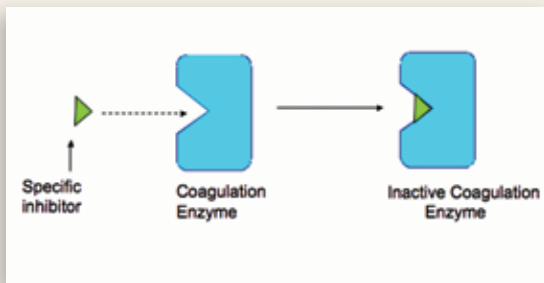
1980s

The pentasaccharide is synthesized, and, over the ensuing two decades, the synthetic compound is developed into a drug for clinical use.

2000s

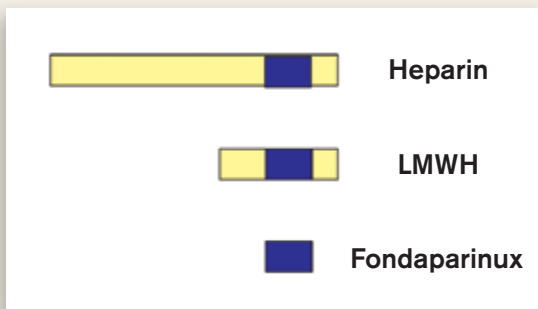
Multicenter clinical trials show that fondaparinux is an effective antithrombotic drug.

anticoagulant response. By the mid 1980s, LMWH preparations were being tested in clinical trials, and they have now replaced heparin for most indications. Because LMWH is injected subcutaneously (under the skin) in a fixed dose without the need for anticoagulant monitoring, patients can now be treated at home instead of at the hospital.



Designer Drugs: Drugs are designed to fit into the active center of clotting enzymes, thereby blocking their function.

With the biotechnology revolution has come genetically engineered “designer” anticoagulant molecules that target specific clotting enzymes. Anti-clotting substances and their DNA were also extracted from an



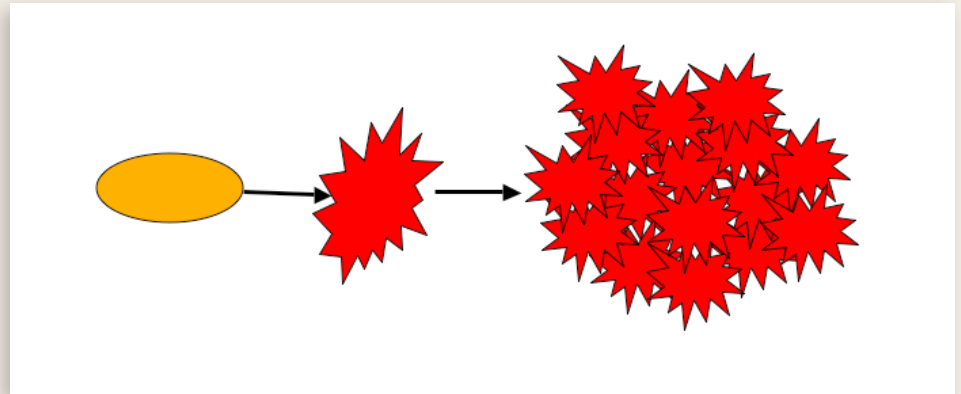
Heparin Derivatives: The three heparin-like molecules are heparin (the largest), low-molecular-weight heparin, and the synthetic compound fondaparinux. Fondaparinux is a modified form of the active pentasaccharide. The activity of all three species is derived from the pentasaccharide (blue) component.

array of exotic creatures (ticks, leeches, snakes, and vampire bats) and converted into drugs by chemical synthesis or genetic engineering. Structural chemists next began to fabricate small molecules designed to fit into the active component of clotting enzymes, like a key into a lock.

The first successful synthetic anticoagulants were fondaparinux and bivalirudin. Bivalirudin, a synthetic molecule based on the structure of hirudin (the anti-clotting substance found in leeches), is an effective treatment for patients with heart attacks. Fondaparinux is a small molecule whose structure is based on the active component of the much larger LMWH and heparin molecules. It has advantages over LMWH and heparin and has recently been approved by the FDA. Newer designer drugs that target single clotting factors and that can be taken by mouth are undergoing clinical testing. If successful, we will have safer and more convenient replacements for warfarin, the only oral anticoagulant available for more than 60 years.

Antiplatelet Drugs

Blood platelets are inactive until damage to blood vessels or blood coagulation causes them to explode into sticky irregular cells that clump together and form a thrombus. The first antiplatelet drug was aspirin, which has been used to relieve pain for more than 100 years. In the mid-1960s, scientists showed



Steps in Platelet Activation and Clumping: Platelets circulate as inert cells (orange oval). When activated, they change shape, become “sticky,” and clump.

that aspirin prevented platelets from clumping, and subsequent clinical trials showed that it reduces the risk of stroke and heart attack. In 1980, researchers showed that aspirin in very low doses (much lower than that required to relieve a headache) blocked the production of a chemical in platelets that is required for platelet clumping. During that time, better understanding of the process of platelet clumping allowed the development of designer antiplatelet drugs directed at specific targets. We now have more potent drugs, such as clopidogrel, dipyridamole, and abciximab. These drugs are used with aspirin and effectively prevent heart attack and stroke; they also prolong the lives of patients who have already had a heart attack.

Impact of These Developments on Health

Antithrombotic therapy has had an enormous impact in several significant ways. Heparin has made bypass surgery and dialysis possible by blocking clotting in external tubing. Antithrombotic therapy has

reduced the risk of blood clots in leg veins (also known as deep-vein thrombosis or DVT), a condition that can lead to death from pulmonary embolism (a clot that blocks an artery to the lungs) by more than 70 percent. And most importantly, it has markedly reduced death from heart attacks, the risk of stroke in people with heart irregularities (atrial fibrillation), and the risk of major stroke in patients with mini-strokes.



Milestones in the Development of Antiplatelet Drugs

Aspirin

- 1899 Aspirin is introduced for pain and fever control by a German scientist and is patented in 1900.
- 1960s Scientists demonstrate that aspirin impairs platelet aggregation and prevents arterial thrombosis in experimental animals.
- 1975 Aspirin's mechanism of action is determined by scientists from Washington University in St. Louis.
- 1978 The first randomized trial showing the beneficial effects of aspirin is reported by a Canadian group who show that aspirin reduces the risk of stroke in patients with minor strokes. Soon after, several clinical trials demonstrate that aspirin is effective in treating heart attacks and stroke.

ADP-Receptor Antagonists

- 1980s The irreversible platelet ADP antagonist ticlopidine is developed and later shown to be effective in stroke patients in 1989.
- 1990s Clopidogrel, an analogue of ticlopidine, is developed and shown to be effective clinically.
- 2001 The combination of clopidogrel and aspirin proves to be effective in patients with acute coronary syndrome.

GPIIb/IIIa-Receptor Antagonists

- 1970s/1980s The glycoprotein IIb/IIIa (GPIIb/IIIa) receptor is found to mediate platelet aggregation by binding to soluble adhesive proteins.
- 1990s Monoclonal antibodies to block the GPIIb/IIIa receptor are developed and show promise as an antithrombotic treatment.
- Soon after, a region of the monoclonal antibody c7E3 Fab (abciximab, ReoPro™) is found to be effective in patients with coronary stents; several studies then identify a pivotal role that the blockage of GPIIb/IIIa has in the management of acute coronary syndromes. Small intravenous GPIIb/IIIa antagonists are then developed and shown to be effective.

Disclosures

ASH is dedicated to advancing the specialty of hematology through a variety of activities in the areas of research, education, training, and advocacy. The integrity of ASH and the activities it undertakes depends on the avoidance of conflicts of interest, or even the appearance of conflicts, by the individuals involved with those activities. In the interest of full disclosure, ASH has asked each of the authors of this brochure to identify any relationships that could influence – or could be perceived as influencing – the content of his or her article. These disclosures are listed below.

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Antithrombotic Therapy

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The American Society of Hematology recently launched *Blood: The Vital Connection*, a public awareness campaign to educate the public about blood diseases and related disorders. We invite you to visit the campaign Web site at www.bloodthevitalconnection.org to find information and resources for patients, doctors, students, and others, such as:

- Detailed descriptions of blood disorders
- A “Find a Hematologist” service to help match patients with blood specialists in their area
- Tips for how to communicate with your doctor
- A guide to clinical trials
- Career resources for medical students
- Medical advances in the history of hematology

blood
the vital connection

Linking Blood Research to Care

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Find a Hematologist

▶ Blood Basics ▶ For Patients ▶ For Providers ▶ For Students

Do you know blood's vital connections?

Hematologists study, diagnose, and treat blood diseases. Some of the most common include blood clots, anemia, and leukemia. Think you know a lot about blood disorders? Take this quiz and see if you can make the right connections.

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