BEYOND DISCOVERY

THE PATH FROM RESEARCH TO HUMAN BENEFIT™

CURING CHILDHOOD LEUKEMIA

Cancer is an insidious disease. The culprit is not a foreign invader, but the altered descendants of our own cells, which reproduce uncontrollably. In this civil war, it is hard to distinguish friend from foe, to target the cancer cells without killing the healthy cells. Most of our current cancer therapies, including the cure for childhood leukemia described here, are based on the fact that cancer cells reproduce without some of the safeguards present in normal cells. If we can interfere with cell reproduction, the cancer cells will be hit disproportionately hard and often will not recover.

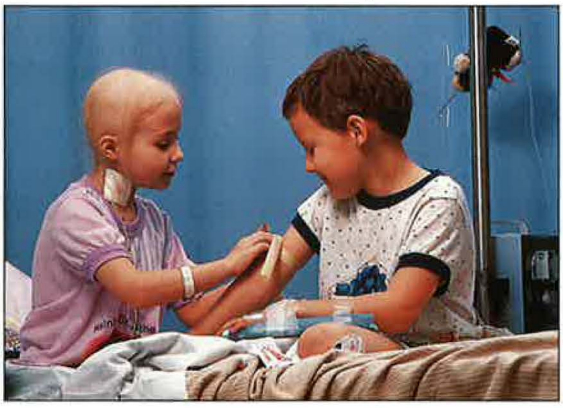
The scientists and physicians who devised the cure for childhood leukemia pioneered a rational approach to destroying cancer cells, using knowledge about the cell built up from a series of basic research discoveries earlier in this century. That research had shown that the machinery of the cell is based on a large set of chemical reactions that follow one after another like the steps in a production line. These reactions, known as the cell's metabolism, convert food to fat, muscle, and energy—with the starting materials for each step supplied by the previous step. Any one of the many production lines will grind to a halt if one of its steps is faulty. The scientists' approach was to take a chemical that they knew was essential for cell reproduction—a building block for making DNA—and modify it so that it jammed the cell's works when the cell mistook it for the usual chemical. Such deliberately defective materials are called antimetabolites. Many of them are now used as drugs to treat not only cancer, but also gout, bacterial infections, viral infections, and many other illnesses.

The fight against cancer has been more of a war of attrition than a series of spectacular, instantaneous victories, and the research into childhood leukemia over the last 40 years is no exception. But most of the children who are victims of this disease can now be cured, and the drugs that made this possible are the antimetabolite drugs that will be described here. The logic behind those drugs came from a wide array of research that defined the chemical workings of the cell—research done by scientists who could not know that their findings would eventually save the lives of up to thirty thousand children in the United States.

A Life Is Saved

Suddenly, it seemed, Debbie Brown became permanently tired. She was so tired that she had to crawl up the stairs, and with any slight contact, she bruised. It was 1954, and Debbie, age 9, had leukemia.

A year earlier, Debbie would have died within months. But it was 1954, and



As many as twelve different drugs, often used in complex combinations and joined with transfusions and radiation therapy, provide doctors with the arsenal needed to combat childhood leukemia, a disease now defeated in nearly 80 percent of cases. (Photo courtesy of the National Cancer Institute)

Debbie's doctor knew about Dr. Joseph Burchenal's work at Memorial Sloan-Kettering Hospital in New York. After a referral, Burchenal's team gave Debbie two experimental drugs, 6-mercaptopurine (6-MP) and methotrexate—and a chance for survival.

The scientists who developed those drugs, which are still used in leukemia chemotherapy, did not stumble upon them in nature or in the laboratory. Instead, they set out to design the drugs, which were among the first ones ever made to order.

Without the drugs, Debbie had a life expectancy of 3 months; with them, she became perhaps the first long-term survivor of childhood leukemia. Although a cure was never mentioned, her visits to Burchenal became less frequent. In 1969, she had her first child, and she now teaches at a school in New Jersey.

The story of childhood leukemia did not end in 1954. In that year, Debbie was a lucky exception. To reach the nearly 80% cure rate of childhood leukemia seen today, doctors have had to marshal up to 12 drugs, used in complex combinations, and add transfusions and radiation therapy. But the drugs that gave doctors hope that this fast-moving disease was even worth tackling were the ones that cured Debbie Brown—the "antimetabolites."

Defining the Target

The cell is the fundamental unit of life. A human being starts as a single cell—a tiny fertilized egg—which grows and divides to produce the more than 10 million million (10,000,000,000,000) cells of an adult. The drugs directed at Debbie's cancer cells were aimed at specific protein molecules in these abnormal cells. A prerequisite for designing the drugs was a detailed understanding of the contents and workings of cells. Scientists had been looking at cells since 1655, the year in which Robert Hooke described the characteristic box-like shapes that he saw in cork. But for a long time they were hard put to understand them. What were the cells doing, and how were they able to grow and divide?

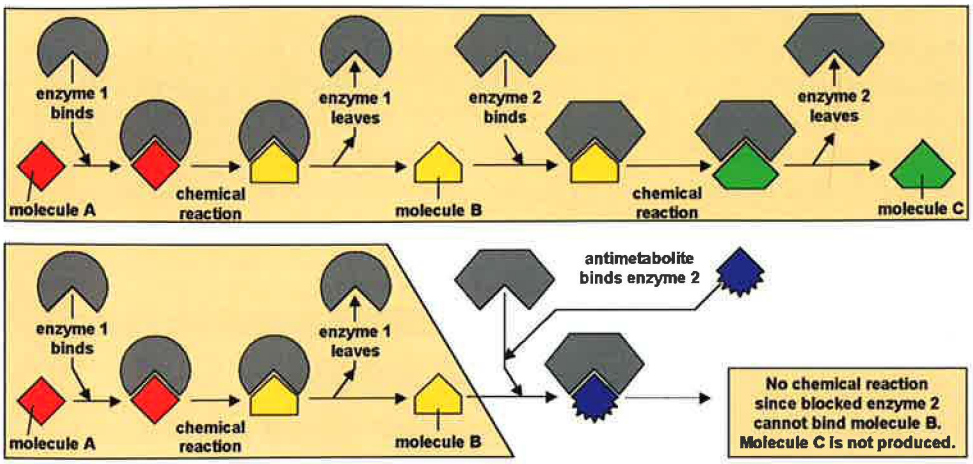
The age-old process of fermentation gave scientists a clue to one cellular activity: yeast cells could make alcohol. As the understanding of chemistry developed, it became clear that fermentation was a chemical reaction. Something was driving the chemical reaction, and the first step was to describe that entity. In 1878, W. Kühne defined an "enzyme" as something that directed chemical reactions—something that was inside, but separable from, the cell. Kühne's idea was rejected by Louis Pasteur, the originator of the germ theory of infectious disease. Pasteur maintained that fermentation was inseparable from living cells—that it was a special property of the organism as a whole and not of one of its parts. Pasteur's theory died in 1897, when E. Buchner ground up yeast cells so that they all burst. Buchner showed that fermentation still took place in the remaining extract of destroyed cells, just as Kühne would have predicted.

As scientists analyzed more and more reactions in cell extracts, it became clear that enzymes are the workhorses that drive all of the chemical reactions in the cell. But to see exactly what an enzyme was, scientists had to separate enzymes from the other components of the cell. In 1926, James Sumner of Cornell University successfully purified an enzyme called urease. He could finally prove that urease, the agent responsible for driving an important chemical reaction in cells, was a large protein molecule.

Locks and Keys

Once pure enzymes were in hand, the activities of these crucial proteins could be studied and manipulated in a predictable, controlled environment. Those studies helped to establish that enzymes are finicky. Like an assembly-line robot, a given enzyme can only pick up a particular part, and it always makes the same product. This idea had been proposed by Emil Fischer in 1894, before pure enzymes were available. Fischer assembled a set of chemicals that were similar to each other, but not identical. Enzymes in the cell were able to differentiate between these chemicals, and Fischer suggested that the starting chemical was like a key that fits perfectly into its lock (the enzyme)—an analogy that is still used today.

From this point to the anti-leukemia drugs, the remaining intellectual leap was the recognition that a defective key could jam the lock. The first defective key that was useful in medicine was a dye called Prontosil. The German fabric industry had long been using similar dyes, all containing a chemical group called the sulfonamide group, because these dyes did not bleed when applied to silk or wool. Prontosil's debut in biological research came in 1935, when Gerhard Domagk casually included it in a group of chemicals that he was testing for their ability to stop mouse cells from engulfing bacteria. Prontosil had no effect on this process, but he observed that it kept the



Schematic representation of a metabolic production line: To start this chain of chemical reactions, enzyme 1 binds molecule A and converts it to molecule B. Molecule B then binds to a different enzyme, enzyme 2, and is changed to molecule C. Molecule C will then bind to a third enzyme to continue the process of converting molecule A into a substance needed by the cell. If an antimetabolite binds tightly to enzyme 2, it will prevent the conversion of molecule B to molecule C and could thereby block cell growth.

mouse that had been inoculated with bacteria alive. Prontosil and similar sulfonamides soon became the first effective antibacterial agents, and this landmark in medicine resulted in the awarding of a Nobel Prize to Domagk in 1939. By 1943, nearly 10 million pounds of sulfonamides were being produced each year. They played a critical role in fighting infections during World War II, although other antibiotics, such as penicillin, were soon to overshadow them.

Blocking the Production Line

Sulfonamides worked, but no one knew how. D. D. Woods and Paul Fildes, of the Bland Sutton Institute of Pathology in London, suggested in 1940 that sulfonamides starved the cells by interfering with chemicals, termed essential metabolites, that were needed for cell growth. They defined essential metabolites as any of the chemical intermediates in the assembly lines for making complex biomolecules (such as proteins or DNA) from simple organic chemicals.

The idea that cells require specific chemicals was consistent with nutritional studies. For example, vitamins are chemicals that animals need (if only in tiny amounts) for survival. Vitamin research began with trial-and-error dietary cures for several medical disorders: limes for scurvy, cod liver oil for rickets, rice husks for beriberi, and liver for pernicious anemia. During the 1930s and 1940s, various workers isolated vitamins, the active components of such remedies.

Meanwhile, others worked on defining what the tiny single-cell organisms known as bacteria need to live and grow. This was no simple matter: most bacteria need a complex mixture of chemicals. But those who persisted found out that there is a hierarchy of bacterial needs and abilities. Some bacterial assembly lines can be thought of as starting by putting together a tire and a hubcap, and others as needing to be supplied with preformed wheels. Earlier results had been varied and confusing precisely because different bacteria pick up the construction process at different points in each multistep reaction pathway. Once the concept of these pathways was in place, it was clear that blocking one of them should stop the cell in its tracks, but that supplying a chemical beyond the blocked point would circumvent this block.

Woods guessed that sulfonamides were blocking a pathway by mimicking an essential metabolite. He tested a number of chemicals that looked like the sulfonamides and found that large amounts of one of them, *p*-aminobenzoic acid (PABA), could be used to bypass the sulfonamide block. We now know that the sulfonamides do, indeed, beat out PABA for access to a particular enzyme, thus preventing that enzyme from converting PABA to the next chemical in the pathway.

Early Chemotherapy

Before the 20th century, treatments for diseases had arisen somewhat haphazardly. Early doctors touted salves and balms of varied usefulness, but the active components were rarely known, and how they worked remained mysterious.

The originator of the modern culture of drug treatment was Paul Ehrlich, who, in the late 19th century, began the search for specific chemicals that could be used to target specific diseases. Ehrlich's drug treatment, or chemotherapy, was too toxic for humans, but the sulfonamides were far more successful, and the other antibiotics that followed and cured previously

fatal diseases cemented the idea of chemotherapy in the minds of physicians. But those drugs were all for infectious diseases. Cancer, the disease that comes from within, was another matter, and in the 1930s the only available treatments for it were surgery and radiation.

The first chemotherapeutic agent for cancer came from warfare. Mustard gas was first used in World War I as a weapon, but in 1942 Alfred Gilman and Fred Phillips administered it first to mice and then to a person with lymphoma. The patient showed some improvement, and chemical relatives of mustard gas were developed and used to treat various cancers.

For leukemia, mustard gas and radiation were of little use, and surgery was impossible because leukemia is a disease of the blood and bone marrow. The disease was first described in 1845 by Rudolf Virchow, a remarkable man involved in medicine, anthropology, public health, and politics. What Virchow saw when he looked at the blood of leukemia patients was a huge proliferation of white blood cells at the expense of both the red blood cells, which carry oxygen, and the platelets, which are needed for blood clotting. The leukemia patient often has intense bone pain as the white blood cells proliferate furiously in the bone marrow, but it is uncontrolled bleeding or infection that is usually the fatal event.

The most voracious of the leukemias, acute lymphocytic leukemia, occurs almost exclusively in children. Without treatment, the children seldom survive beyond 3 months after diagnosis. This rapid decline led many to see childhood leukemia as a lost cause, a problem not worth tackling. Luckily, a few scientists and doctors saw the severity of the disease as an advantage for testing their new treatments. With no other prospects, the children with leukemia had nothing to lose. This gave researchers an opportunity to see whether chemotherapy would work against cancer. Their jumping-off point was interference with the building blocks that make up DNA.

A Leap of Faith

We now know that DNA is the stuff from which genes and chromosomes are made. But the study of DNA had a rather messy start, when in 1868 Friedrich Miescher, working in Tübingen, Germany, isolated nuclei from the pus cells in discarded bandages. Miescher found that the nuclei, which we now know as the cell compartments that hold the DNA, contained an unusual phosphorus-containing chemical. Over the next 50 years, scientists isolated the bases and sugars that make up DNA and determined their structures (the arrangements of their atoms). There are four bases: the two purines called adenine (A) and guanine (G), and the two pyrimidines called cytosine (C) and thymine (T). Long strings of these bases are linked together by intervening sugar and phosphate molecules to make up DNA, and each of our chromosomes is formed from one enormously long DNA molecule.

In 1942, George Hitchings set out to design and synthesize antimetabolites based on the DNA bases.

Curing Childhood Leukemia—A Chronology of Selected Events

This timeline shows the chain of basic research that led to the discovery of a cure for childhood leukemia.

1845
Rudolf Virchow describes leukemia as a disease of the blood.

1878
W. Kühne names the agents from living cells that direct chemical reactions "enzymes."

1894
Emil Fischer proposes the lock-and-key hypothesis for enzyme action.

1908
Paul Ehrlich outlines his concept of chemotherapy: chemicals can be used to selectively interfere with the growth of infectious agents.

1926
James Sumner purifies the enzyme urease, and demonstrates that enzymes are proteins.

1935
Gerhard Domagk discovers the antibacterial action of the sulfonamide, Prontosil.

1940
D. D. Woods and Paul Fildes propose that sulfonamides work as antimetabolites.

1942
Alfred Gilman and Fred Phillips achieve a partial remission after administering mustard gas to a human with lymphoma.

1948
Sidney Farber reports temporary remissions in several cases of childhood leukemia after treatment with aminopterin.

1948
Gertrude Elion and George Hitchings make 2,6-diaminopurine, and Joseph Burchenal uses it to get two remissions in adults with leukemia.

Remarkably little was known about DNA. Hitchings did not know any details of the pathways that he was proposing to block (the production lines that make the DNA bases). Not until 2 years later was DNA shown to be the cell's information store; and the double-helix structure of DNA, which made it clear how the DNA could be "unzipped" to be read or copied, was not to be discovered until 1953, by James Watson and Francis Crick. (For additional information about this and other related discoveries, see "Human Gene Testing" posted on the *Beyond Discovery* website.) All Hitchings knew was that cells needed DNA to divide; therefore, if he could block the cells from making new DNA bases or cause the cells to include defective bases in their DNA, the cells should be unable to reproduce themselves.

The first thing that Hitchings needed was a way to test potential new drugs simply and cheaply. The solution, developed in his laboratory by Elvira Falco, was a test system using *Lactobacillus casei* (*L. casei* for short). This bacterium would grow on milk or in a synthetic medium as long as it was supplied with either a liver preparation called "*L. casei* factor," or both a purine (A or G) and thymine (T).

Gertrude Elion joined Hitchings' group in 1944, one of the few women finally gaining access to the male-dominated arena of chemistry. She started synthesizing an astonishing array of chemicals that were similar, but not identical, to the purines in DNA. By 1951, Elion had made and tested over 100 of these modified purines. Some of them slowed or stopped the growth of *L. casei*, and Elion could then test which production line they were jamming by adding an excess of thymine or one of the purines. In sufficient quantities, these "true" metabolites could overwhelm the effect of an antimetabolite on a given enzyme, or supply the final product of a pathway, thus making early blockages irrelevant.

Once Elion had identified chemicals that slowed down *L. casei*, she was ready to try them out on a human disease. Hitchings had begun the research program with the idea that rapidly dividing cells would have a more urgent need for DNA than sluggish cells and would therefore be hit harder by drugs that restricted the supply of the DNA building blocks. Now he had only to select his targets from among the types of cells that grow speedily: bacteria, protozoa, and cancer cells. Leukemia was one of the first targets, both because there were no existing therapeutic options for patients and because a mouse model of the disease was available for initial drug testing.

Although Hitchings and Elion began their antimetabolite program earlier, the first leukemia remission was achieved by another group of workers. Sidney Farber, of Boston's Children's Hospital, tested the effect of the vitamin folic acid on cancer and concluded that it made matters worse. His conclusion is now in doubt (and the rationale for testing folic acid has died with him), but it inspired chemists at Lederle Pharmaceuticals to make antimetabolites resembling this molecule that would block the action of folic acid. An early attempt, aminopterin, was rushed into clinical

1953
The US National Cancer Institute (NCI) is founded.

1953
The US Food and Drug Administration approves 6-mercaptopurine (6-MP), made by Elion and Hitchings two years earlier.

1957
At the NCI, Emil Frei and Emil Freireich start a double-blind clinical trial using 6-MP and methotrexate in combination.

1959
The NCI team tries continuing chemotherapy during remission.

1960
Roy Calne uses 6-MP for kidney transplants in dogs.

1963
NCI trial of methotrexate in the spinal cord reduces recurrence of childhood leukemia.

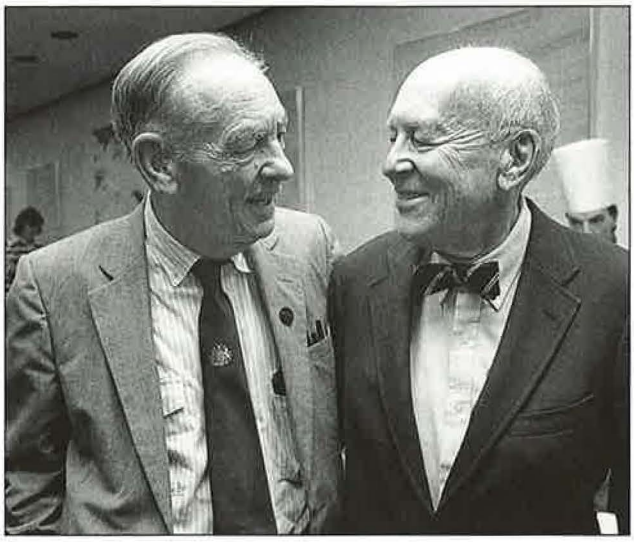
1963
Allopurinol used in leukemia trial reduces amount of uric acid; soon after allopurinol is used to treat gout.

1970
Five year survival for childhood leukemia increases to 50%.

1978
Burroughs Wellcome team makes acyclovir, an effective treatment for genital herpes, cold sores, shingles, and chicken pox.

1988
Gertrude Elion and George Hitchings awarded the Nobel Prize in Physiology or Medicine.

1994
In a study using four intensive treatment regimens, 95% of childhood leukemia patients were disease free after four years. Treatment of the general population is not yet this successful.



In the 1940s, George Hitchings (left) pioneered the design and synthesis of antimetabolites, the class of drugs that could be used to destroy cancer cells. Joseph Burchenal (right) of Memorial Sloan-Kettering Hospital in New York City administered these drugs to leukemia victims and succeeded in inducing cancer remissions in some cases. (Memorial Sloan-Kettering Cancer Center)

trials just a year after the structure of folic acid had been reported. In 1948, the Farber team reported that treatment with aminopterin had resulted in temporary remissions in several cases of childhood leukemia. The remissions were rare and brief, but an encouraging start. Another variant of folic acid, called methotrexate, was developed within a year, and this antimetabolite became a mainstay of leukemia chemotherapy.

Elion's first success came in 1948 with a chemical called 2,6-diaminopurine, which had two amine groups protruding from the normal purine structure. In tests with the *L. casei* bacterium, it blocked the conversion of adenine into a DNA building block. Elion and Hitchings sent 2,6-diaminopurine to Joseph Burchenal at the Memorial Sloan-Kettering Hospital in New York City for testing, initially in mice. Burchenal succeeded in getting two remissions in adults who had leukemia, but for most patients the drug was too toxic: the nausea and vomiting were intolerable.

To make the successful antimetabolite, 6-mercaptopurine or 6-MP, Elion replaced an oxygen atom on the purine ring with a sulfur atom. This chemical not only had antitumor activity in mice, but it produced remissions, without undue toxicity, in children who had acute leukemia. In the few days after news of the clinical success with 6-MP broke, Hitchings received over 600 phone calls. The excitement about 6-MP was so great that the US Food and Drug Administration approved its use late in 1953—only 10 months after clinical trials began, and 7 months before all the data supporting its effectiveness were made public.

Systematic Medical Research

The two drugs that would cure Debbie Brown in 1954 were now established. But for most patients and their doctors, this was only the beginning. With the combined use of methotrexate and 6-MP, the average survival time for childhood leukemia had been extended from just 3 months to a year. For much of the extra time, the children were in remission, showing no external signs of the disease. Early in these studies, the scientists, doctors, and patients hoped that the children were permanently cured. But almost inevitably the cancer came back. And when it came back it was usually resistant to the drugs that had been used the first time.

The great success of antibiotics had set the tone for medical treatment in this period. Everyone expected "a magic bullet," a single drug that could eliminate all signs of disease. Gradually, the researchers and doctors saw that no one drug would be enough for childhood leukemia. They would have to carry out more precise clinical trials to determine exactly which combination, dose, and frequency of drugs would be best.

The focus for the next stage was the US National Cancer Institute (NCI) in Bethesda, Maryland, which was founded in 1953. In an extraordinary confluence

Gertrude Elion received the Nobel Prize in Physiology or Medicine in 1988, together with George Hitchings, for their work on the design of drugs to cure childhood leukemia and other diseases. (Photo courtesy of Reportagebild, Stockholm, Sweden)

of talent and names, Emil Frei III and Emil J. Freireich joined the NCI in 1955 to lead leukemia-drug trials. The conciliatory Frei and the confrontational Freireich worked together with their chief, C. Gordon Zubrod, to modernize chemotherapy trials. Before their work, drug trials were often anecdotal and usually inconclusive. The first step for the NCI doctors was to define a "remission." Rather than trying to assess some vague measure of a patient's well-being, the doctors counted the number of leukemic cells in bone-marrow samples. They then initiated trials in which all patients were given the same treatment program. Other doctors believed that treatment should be customized for each patient, but with this approach the results of any study would always be confusing. Frei and Freireich also devised the concept of a double-blind study, in which neither patient nor doctor knows who is getting which treatment. This was essential to avoid any bias that might creep in if the doctor or patient hoped that a particular treatment would be better.

In one of the early trials, the NCI doctors showed that transfusing patients with fresh supplies of blood platelets could prevent serious bleeding. That kept the patients alive for long enough to reap the benefits of new drugs—drugs from varied sources, including plants. With the new drugs, obtaining remissions became almost routine. But still the cancer would return in most cases. What did the doctors need to do to wipe out the cancer once and for all? Frank Schabel and Howard Skipper, working at the Southern Research Institute, used mice to show that a single leukemic cell was all that was needed to start a fatal process. The task was thus defined: to wipe out every last leukemic cell. That led the doctors to try continuing chemotherapy past the time when all signs of the disease had disappeared. And mathematical modeling by Schabel and Skipper of the growth of the cells gave the doctors an estimate of how hard, how often, and for how long they would have to hit the cancer. Knowing that a number of their drugs had different, nonoverlapping side effects, the doctors took another critical step: they began to use new combinations of drugs, hitting the cancerous cells from several directions at once.

The final step in converting remissions to cures was the identification of the brain and spinal cord as an important hideout for the cancer cells. Because the central nervous system is separated from the blood, and thereby protected from bloodborne diseases and toxins, the anti-leukemia drugs were not getting into these areas. The doctors therefore began to inject drugs directly into the spinal-cord canal and to target radiation specifically to the head. The combination of these treatments and the newer drugs has increased the cure rate for childhood leukemia to nearly 80%. But the drugs of choice for maintaining remissions are still 6-MP and methotrexate.

New Horizons

Hitchings had envisioned the antimetabolites as a therapy for any number of diseases; leukemia was merely the first to be tested. The path to the first of two unexpected uses began with Robert Schwartz, of Tufts University. Inspired by the knowledge that the antimetabolites hit certain immune cells in the blood particularly hard, he found that 6-MP could stop the immune system of rabbits from responding to a foreign protein. Roy Calne, of the Royal Free Hospital in London, heard about Schwartz's finding and put the immunosuppresive effect of 6-MP to work. The drug reduced the immune system's rejection of transplanted kidneys in dogs and so lengthened the time that the dogs retained the kidneys. He then tested a pro-drug of 6-MP that Elion had made called Imuran ™ and found it even more effective (a pro-drug is a drug that is administered in one form and then releases the active component, in this case 6-MP, in the body). Imuran remains in use for human kidney transplants today.

Antimetabolites were next used to treat gout, a disease in which the body accumulates too much of a chemical called uric acid. Crystals of uric acid build up in the joints of patients and cause painful arthritis. The treatment for gout, a drug called allopurinol, was first used in a leukemia trial. Elion and Hitchings, in collaboration with Wayne Rundles and hematologists at Duke Medical Center in North Carolina, were using allopurinol to increase the potency of 6-MP by jamming the enzyme that destroys 6-MP in the body. The approach was partially successful, but the combination of 6-MP and allopurinol was not only more effective but also more toxic. The scientists knew that the target for allopurinol was the enzyme that made uric acid, so they looked at how much uric acid the patients in the trial were excreting in their urine. They found that the drug was working: allopurinol was blocking formation of uric acid. Further trials proved that it could reverse the accumulation of uric acid and thus relieve the symptoms of gout—a major medical triumph.

In 1968, Elion and others on the Burroughs Wellcome team decided to look at whether the

In 1989, childhood leukemia survivors staged a reunion at Memorial Sloan-Kettering Hospital in New York City to celebrate the individuals and institutions that played a role in their cure. Without their treatments, it is unlikely that any would have survived to adulthood. (Harry Heleotis, NYC)

antimetabolites they had synthesized could be used to slow down viruses. The last of a series of chemicals that they tried was a version of guanine in which the sugar ring attached to it in DNA was opened and shortened. This chemical, called acyclovir, is now an effective treatment for various herpes virus infections, including genital herpes, cold sores, shingles and chickenpox. Acyclovir is an extremely effective drug; only viruses have enzymes to convert it into a toxic form that then blocks the construction of viral DNA, so the drug is far less toxic to humans than are many other antimetabolites.

In 1988 the Royal Swedish Academy of Sciences awarded Elion and Hitchings the Nobel Prize in Physiology or Medicine for introducing to drug discovery "a more rational approach based on the understanding of basic biochemical and physiological processes." Their approach is now used widely; these days, researchers (who can now determine the exact structure of enzymes) have the help of computers to design defective keys for an enzyme lock. To find more powerful, less toxic drugs, researchers will need to find enzymes that, like the target of acyclovir, are specifically required by the viruses or cells that cause a particular disease. Every year, many potential targets for antimetabolites are being discovered by the basic research that is rapidly unraveling the chemistry of the cell, the same type of research that suggested that antimetabolites could be used to cure childhood leukemia.

No one knows what the next successful drug target will be, nor what type of human suffering it will relieve. But whatever the new cures, the credit for them will belong to more than those who make the final breakthrough. Much credit should also go to the worldwide team of biologists and chemists, each of whom may spend a lifetime teasing out the workings of one or two of the cell's thousands of activities. On the foundations of these discoveries will come great benefits to human welfare. And many scientists will be able to stand with great pleasure among survivors of deadly diseases.

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