The 1988 Nobel Prize for Physiology or Medicine

Three researchers are honored for developing drugs that combat some of mankind's most common diseases

THE 1988 NOBEL PRIZE for Physiology or Medicine has been awarded to two Americans and a British researcher for "their discoveries of 'Important Principles for Drug Treatment.'" Gertrude Elion and George Hitchings, currently scientists emeritus at Wellcome Research Laboratories of Burroughs Wellcome Company in Research Triangle Park, North Carolina, were honored for work that led them to produce drugs for treating cancer, gout, malaria, and viral infections such as herpes. James Black of King's College Hospital Medical School in London was cited for developing drugs for treating heart disease and peptic ulcers.

In awarding this year's prize to Elion, Hitchings, and Black, the Nobel Assembly at the Karolinska Institute in Stockholm specifically noted that the researchers' drug discoveries grew out of the better understanding of cell biochemistry and physiology generated by their investigations. "While drug development had earlier mainly been built on chemical modification of natural products, they introduced a more rational approach based on the understanding of basic biochemical and physiological processes," the Nobel citation says.

Elion and Hitchings went right to the heart of the cell, to see how nucleic acid synthesis in normal human cells compared with that in cancer cells and in pathogenic bacteria or viruses. Any differences that were found could serve as a point of attack for drugs that would selectively kill the cancer cells or the pathogens without destroying normal cells.

Black, in contrast, focused on the cell surface receptors to which hormones and other physiological agents must bind to exert their effects on their target organs. Under some circumstances, as in heart disease or high blood pressure, the actions of the hormones may become harmful. The idea was to design drugs that bind to the receptors and prevent the hormones from attaching, thereby blocking their effects.

The collaboration of Elion and Hitchings began more than 40 years ago. Hitchings, now 83 and still active as a consultant for Burroughs Wellcome and in philanthropy in the Triangle Park area, began working at the company in 1942. Elion joined his research team a few years later, having been hired by Burroughs Wellcome in 1944. The original group also included Elvira Falco, who subsequently married and now runs a small vineyard near Penobscot, Maine.

When she was hired, Elion notes, companies were reluctant to employ women scientists, but the shortage of men during World War II gave women new opportunities to work in the laboratory. Currently, the busy schedule of the 70-year-old Elion includes consulting for Burroughs Wellcome and serving on the National Cancer Advisory Board.

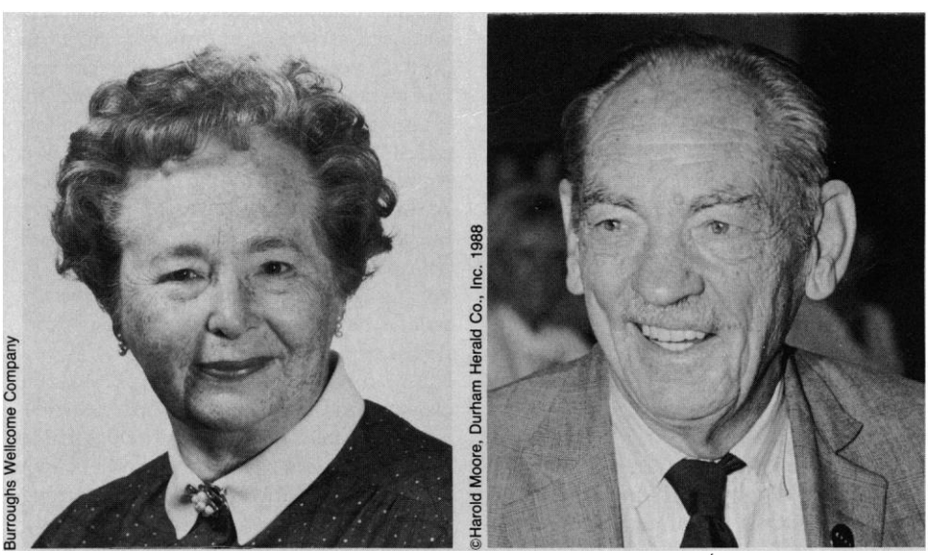
In their research, Elion and Hitchings concentrated on the pathways by which the nucleic acid building blocks, called nucleotides, are synthesized. They made compounds, related in structure to those in the pathways, that interfere with nucleotide synthesis and therefore with that of DNA.

By the late 1940s and early 1950s some of the DNA synthesis inhibitors, known as antimetabolites, were showing promise as anticancer drugs. Clinical trials that were conducted at Sloan-Kettering Institute (now Memorial Sloan-Kettering Cancer Center) in New York City showed that one of these agents, 6-mercaptopurine, had anticancer effects in leukemia patients. "With 6-mercaptopurine we knew we had to be on the right track," Elion says. This drug and thioguanine, which was also produced by Elion and Hitchings, remain in use today for treating acute leukemias.

Inhibitors of nucleic acid synthesis are effective for cancer chemotherapy because cells need to duplicate their DNA to divide, and agents that prevent this are toxic. Rapidly dividing cancer cells are particularly sensitive to the drugs' effects.

Although this is easy to see now, in the 1940s when Hitchings and Elion began their investigations very little was known about the nucleic acids. DNA was just beginning to be accepted as the carrier of the genetic information. Moreover, there was then little experience with cancer chemotherapy, notes Vincent DeVita, Jr., who is leaving his position as director of the National Cancer Institute to become physician-in-chief at Memorial Sloan-Kettering. "At the time they did this work it was very insightful and it has had great durability," DeVita says. "I'm tickled to death [about the Nobel Prize]. It couldn't have happened to nicer people."

The other drugs produced by Elion and Hitchings include azathioprine, a modified form of 6-mercaptopurine. "This was the first immunosuppressive agent that allowed kidney and other transplants," says Paul Calabresi of Brown University School of Medicine. Although newer immunosuppressive drugs, particularly cyclosporine, have come on the scene, azathioprine is still used to fight transplant rejection and for treating diseases, such as rheumatoid arthritis, that may be caused by the immune



Gertrude Elion and George Hitchings *share the Nobel Prize for developing drugs against cancer and other diseases.*

system attacking the body's own tissues.

Allopurinol, another modified form of 6-mercaptopurine that was produced during the 1960s, turned out to be a good inhibitor of uric acid synthesis. It is used to prevent excess uric acid buildup, which can lead to kidney damage, in patients undergoing treatment for leukemias or lymphomas. The uric acid is produced as a by-product of cancer cells killed during therapy. Moreover, allopurinol became a standard drug for treating gout, which is characterized by uric acid deposition in the joints.

By exploiting the differences between nucleic acid synthesis in normal human cells and that in lower organisms, Elion and Hitchings were also able to develop drugs for treating a wide range of infectious diseases. Pyramethamine, for example, is effective against the malaria parasite, a protozoan, whereas trimethoprim is used for bacterial infections, particularly of the urinary and respiratory tracts.

The 1970s saw the development by the Burroughs Wellcome researchers of acyclovir, now widely used for treating herpes virus infections. Although the AIDS drug AZT (azidothymidine) was not synthesized by Elion and Hitchings, it, too, works by the principles they formulated. Moreover, the pneumonia frequently suffered by AIDS patients is treated with trimethoprim in combination with a sulfa drug.

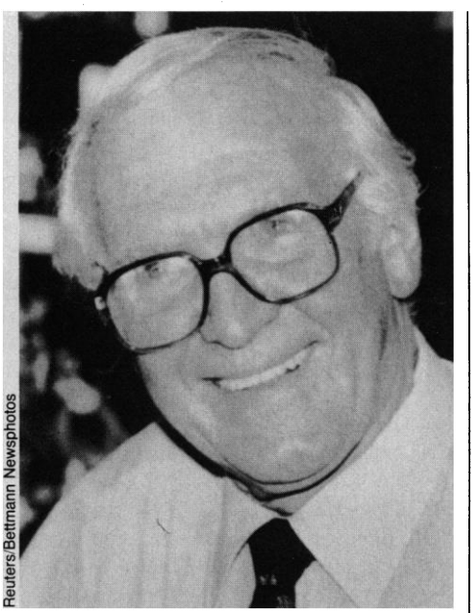
"Here are two people who in the course of the last 40 years have developed a method of designing drugs that specifically block key enzymes in the nucleic acid pathway and have thereby produced benefits in some of the major areas of human diseases," says Calabresi of Elion and Hitchings.

On Monday, 17 October, the day that the winners of this year's medicine prize were announced, Hitchings was scheduled to give a lecture at Memorial Sloan-Kettering. He kept that commitment, forgoing the celebration thrown that day at the Burroughs Wellcome laboratory in North Carolina.

At a press conference held at Sloan-Kettering, Hitchings talked about the numerous chance encounters he has had over the years with people who had been cured, or whose family members had been cured, by drugs that he and Elion had produced. "That's more reward than medals and placards and all the rest," Hitchings said.

The drugs developed by Black work on a very different principle from the one on which the drugs produced by Elion and Hitchings are based. Nevertheless, his successes, like theirs, have grown out of a knowledge of the way cells operate.

"Jim Black's real contribution scientifically is that he has a deep understanding of physiological mechanisms. He just doesn't take chemicals off the shelf," says Irving London, who has a joint appointment at Harvard Medical School and the Massachusetts Institute of Technology. London chairs the Bioscience Advisory Committee of the pharmaceutical company Johnson & Johnson Company, which provides support for a private research foundation that Black established in London.



James Black *is recognized for producing drugs for treating heart disease and ulcers.*

Black's research on receptor-blocking drugs has produced propranolol, which is widely used for treating heart disease and high blood pressure, and the antiulcer drug cimetidine, best known in this country by its trade name Tagamet. Alfred Gilman of the University of Texas Southwestern Medical Center at Dallas describes cimetidine as "the salvation of anyone with ulcers."

Propranolol, which was produced by Black in the early 1960s, is one of the "β-blocker" drugs that counter the effects of the hormones norepinephrine and epinephrine on the heart and blood vessels. These hormones had been something of a puzzle because they have opposing actions on the same tissue, causing both the contraction and relaxation of smooth muscle, for example. In the 1940s, however, the late James Ahlqvist recognized that this could be explained if hormones acted through two distinct types of receptors, which were designated α and β.

Propranolol specifically blocks the β type. Although other investigators had made β-blockers before Black produced propranolol, it was the first such drug to become clinically important.

Propranolol was originally used to treat patients with angina pectoris, a heart condition characterized by chest pains, especially during exertion when the heart's demand for oxygen is great. Propranolol effectively relaxes the heart muscle so that its demand for oxygen does not outstrip the supply.

During the late 1970s and early 1980s, a series of studies showed that propranolol also decreases the death rate of heart attack survivors by about 25%. "It demonstrated, perhaps for the first time, that a drug given to heart attack survivors actually saves lives," says Eugene Passamani of the National Heart, Lung, and Blood Institute.

In fact, one study conducted by the NHLBI was stopped several months before its scheduled conclusion because a preliminary analysis of the results showed that propranolol was having a greater than expected effect in reducing mortality in heart attack survivors. The data already justified offering the drug to the study controls—and to other heart attack survivors.

In addition to being used for treating angina pectoris and reducing heart attack mortality, propranolol also lowers high blood pressure. For many years, it was the only β-blocker approved by the Food and Drug Administration, but now there are several of the drugs, with varying spectra of activities, on the market.

The history of cimetidine follows a course similar to that of propranolol. Although histamine release in the stomach causes ulcers by stimulating acid production there, attempts to treat ulcers with the same antihistamines used to combat respiratory allergies were ineffective. Black realized that the problem might be that the histamine receptors of the stomach are different from those of the respiratory tract.

By synthesizing a series of compounds that resemble histamine, he and his coworkers were able to characterize the histamine receptor of the stomach lining, which is called the H_2 receptor. They then produced the drug cimetidine, which blocks that receptor and helps ulcers to heal by preventing stomach acid production.

Before then, stomach ulcers that did not heal often had to be removed surgically. The introduction of cimetidine marked the beginning of a new era in ulcer treatment. Since then several additional drugs that work the same way have been developed.

The Nobel Assembly rarely favors the researchers who develop new drugs with the prize. The last to be so honored was the Italian Daniele Bovet who won in 1957 for his discovery of antihistamines. By awarding this year's medicine prize to Elion, Hitchings, and Black, the Assembly has recognized researchers who have helped to combat many of mankind's most serious diseases. ■ JEAN L. MARX