Tracing Hormone Action in the Cell

During his 30-year research career, Alfred Gilman has helped to clarify how hormones produce their effects in cells, an achievement now recognized by a Lasker Award

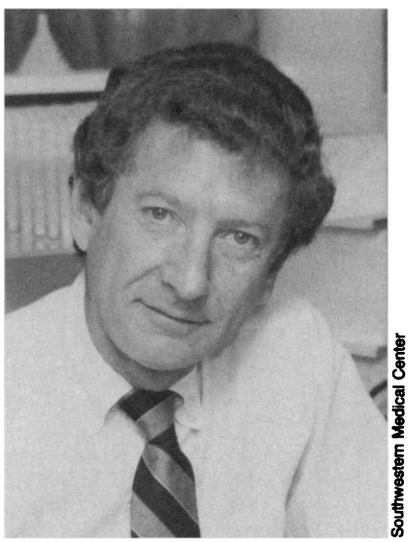
THE AVERAGE MAN OR WOMAN on the street would no doubt draw a blank if confronted with the term "G protein." But in the 10 years since the first G protein was discovered, researchers have found that the proteins are a vital part of the intricate pathways that enable cells to respond to messages from other cells. They have also found that disruptions in G protein function can help cause such serious diseases as cholera, whooping cough, and even cancer.

No wonder then that the Lasker Foundation has honored the G protein's discoverer, Alfred Gilman of the University of Texas Southwestern Medical Center at Dallas, with its award for basic medical research. He shares the award with three other scientists who have made their own prominent contributions to understanding how cells receive and respond to incoming signals (see box on opposite page).

"What's so interesting about their work is that it turns out to be central to all areas of biology," says Michael Brown, a colleague of Gilman at Dallas and himself a winner (with Joseph Goldstein) of the Lasker and the Nobel Prize. "Development, cancer, disorders of metabolism—everything seems to lead back to receptors and intracellular signaling. It's equal to the study of genetics in terms of its pervasiveness in biology."

Gilman has also been mentioned as a prominent candidate for the Nobel Prize. For instance, in its 2 October issue, *The Scientist* selects him as one of 20 scientists of "Nobel Class" on the basis of the number of citations his papers have received and the scientific prizes he has already won. And G protein research has just moved into seventh place on the list of "science's hottest fields," according to the Institute for Scientific Research in Philadelphia.

Earlier this month, *Science* visited Gilman in his Dallas laboratory to talk with him about his still highly active research program. As chairman of the department of pharmacology at Dallas, Gilman no longer works at the bench himself but relies instead on the postdocs and graduate students whom he recruits. "I'm better off talking to people than bumbling around with my own hands," Gilman says. "I've profited over the years from having a nice mixture of people with different backgrounds." His group currently includes ten postdocs and one graduate student.



Southwestern Medical Center

G-man Alfred Gilman. *He discovered a key protein needed for hormone action.*

The ability to recruit good people and then direct their efforts productively is one of Gilman's strengths, says Elliott Ross, who participated in the discovery of G proteins as a postdoc and has remained at Dallas as a faculty member in the pharmacology department. "By giving people their heads, while aiming them at specific goals, he's been very successful," Ross comments. "He's able to be very encouraging and supportive, but critical at the same time."

Gilman has also been able to move with the times during a career that spans nearly three decades. "Our work started with physiological observations and then biochemical observations over decades," he notes. About 5 years ago, he moved into the field of gene cloning, first cloning two G protein genes. And just this summer, Gilman and his colleagues reported that they had achieved a long-sought goal—the cloning of the gene for adenylyl cyclase, the enzyme that makes a chemical known as cyclic AMP (adenosine 3',5'-monophosphate).

Cyclic AMP was discovered 40 years ago by Earl Sutherland and Theodore Rall, who worked at what was then Case Western Reserve University in Cleveland. At the time, researchers had long wondered how hormones, which act at the cell membrane, could transmit their signals to the cell interior. Sutherland and Rall found that some hormones do this by stimulating the synthesis of cyclic AMP, which serves as a "second messenger" for carrying out the hormones' orders inside the cell.

The enzyme that makes the cyclic AMP is therefore a critical component of hormonal signaling pathways, but adenylyl cyclase proved to be extremely difficult to isolate. "The cyclase has been a first-class stinker," Gilman says. "We have been trying to solve it since 1977 and had only one publication in all that time."

Henry Bourne of the University of California, San Francisco, cites the cloning of the cyclase gene as one example of the drive that has enabled Gilman to succeed. "He's intelligent, but there are lots of clever scientists," says Bourne, who has known Gilman for many years. "He just lays out what he wants to do and then pursues it in a nonflashy way."

The discovery of the G protein was at least as difficult as the cloning of the cyclase. Gilman became interested in hormonal signal transmission early on. He joined Rall's laboratory at Case Western as a joint Ph.D.-M.D. student in 1962, shortly after cyclic AMP was identified. Then, in 1969, Gilman became a postdoctoral fellow with Marshall Nirenberg at the National Institutes of Health in Bethesda, Maryland. While at NIH, he developed a new and much improved method for determining cyclic AMP concentrations. "That assay really launched my career because everyone was desperate for it," Gilman recalls.

After leaving N.I.H. in 1971, Gilman joined the faculty of the University of Virginia in Charlottesville, where he decided to continue his investigations into cyclic AMP synthesis. In his research there, he found evidence suggesting that hormones that stimulate the production of the chemical do not act directly on adenylyl cyclase. Rather the hormones appeared to bind to a separate membrane molecule, known as the receptor, and the receptor in turn activates the enzyme.

But there were other indications that the

Lasker Award Goes to Four Signal Scientists

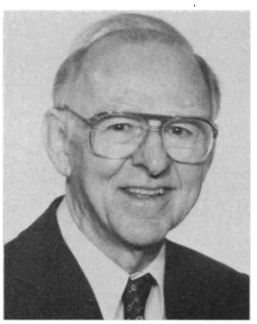
An international group of three scientists shares this year's Lasker Award for Basic Medical Research with Alfred Gilman. The other winners are Michael Berridge of the University of Cambridge, England, Edwin Krebs of the Howard Hughes Medical Institute at the University of Washington School of Medicine in Seattle, and Yasutomi Nishizuka of Kobe University School of Medicine in Japan.

The researchers were honored for their contributions, made over a 40-year period, toward understanding the biochemical pathways that enable cells to respond to hormones, growth factors, and other environmental signals. Their work, the Lasker Foundation says, "is helping other scientists to understand the origins of major health problems such as psychiatric disorders, hypertension, and cancer, and is already guiding the development of highly specific new drugs and therapeutic approaches to these crucial medical conditions."

Berridge and Gilman have both focused on the earlier stages in signal transmission and in particular on the generation of the "second messengers" that carry hormonal signals into the cell interior. Berridge found that a group of membrane compounds known as the polyphosphoinositides mediate the increased concentrations of calcium ions that serve as second messengers for many hormones. Before his work the importance of the polyphosphoinositides had been under appreciated—at best. Berridge once told *Science* that his early findings had been greeted with a great deal of skepticism, but in the past 5 years research on the compounds has exploded.

Krebs and Nishizuka were cited for their discoveries of key enzymes whose activities are altered by the second messengers, thereby producing the cell's responses. In the 1950s, Krebs recognized that the addition of phosphate groups to proteins, which is carried out by enzymes known as kinases, can profoundly affect the target proteins' functions. He suggested then that such phosphorylations might play a general role in cell regulation. Then, in the early 1980s, Nishizuka discovered protein kinase C, a critical component of the signal pathways for growth factors. He also showed that certain cancer-causing chemicals known as tumor promoters work by activating this kinase, another indication of the importance of signal transmission to the cell. ■ **J. L. M.**

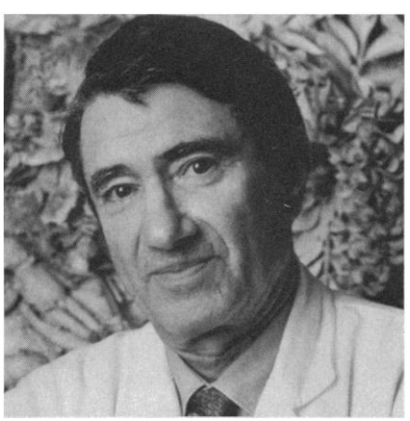
Michael Berridge



Edwin Krebs

Yasutomi Nishizuka

signaling pathway might be still more complicated. In particular, Martin Rodbell's group at N.I.H. had found that hormones could not activate cyclic AMP synthesis unless another cell chemical, namely guanosine triphosphate (GTP), was also present. The question was why was the GTP required?



Baulieu too: Etienne-Emile Baulieu, the University of Paris, wins the Clinical Lasker Award for work on steroid hormones and the "contragestive" drug RU 486 (*Science*, 22 September, pp. 1319 and 1351).

Gilman, Ross, and their colleagues ultimately provided the answer during the mid- to late 1970s, when they showed that the signaling pathway includes a third component—the G protein—interposed between the receptor and the adenylyl cyclase. When a hormone binds to its receptor, it first activates the G protein. This step requires the GTP. The active G protein then stimulates the adenylyl cyclase to make cyclic AMP, which induces the appropriate cellular responses. G proteins got their names because they bind guanine nucleotides, not because they were discovered by Gilman.

In the 10 years since Gilman's group identified the first G protein, researchers have uncovered perhaps a dozen more. They work with different receptors, mediating and coordinating responses to dozens of hormones and neurotransmitters.

When they malfunction, the results can be serious. Bourne has recently found, for example, that certain mutations in the gene for the G factor that Gilman discovered can convert it to an oncogene that causes pituitary tumors. Moreover, the proteins produced by the *ras* oncogenes, which have been linked to human cancers, have proved to have some G protein features.

In addition to running an active research group and chairing the pharmacology department, Gilman is the principal editor of *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. Gilman's late father, who was himself a prominent pharmacologist, and Louis Goodman of the University of Utah produced the first edition of the book, which has become known as the bible of pharmacology, back in 1941. When *Science* visited Dallas, Gilman was in the throes of completing the latest revision, a massive task for a book with over 1800 pages.

Gilman was also looking ahead to his laboratory's next projects, however. He noted that he sometimes thinks that the G protein field might be becoming "mature" and that he should be thinking about moving on to something different. But something new in the field always comes along to pique his curiosity.

The cloning of the adenylyl cyclase gene provides a case in point. Quite unexpectedly, the protein that it encodes turned out to have all the earmarks of an ion channel. The finding raises the possibility that the enzyme may transport some substance into or out of cells in addition to making cyclic AMP. Finding out whether that is the case is one of the projects that the Gilman group will be pursuing in the future. ■ **JEAN L. MARX**