The 1971 Nobel Prize for Physiology or Medicine

The Nobel Prize for Physiology or Medicine for the year 1971 has been awarded to Earl W. Sutherland, Jr., for his "discoveries concerning the mechanisms of action of hormones." Dr. Sutherland's studies culminated in the discovery of cyclic 3′,5′-adenosine monophosphate (cyclic AMP), a unique molecule that mediates the action of many hormones and regulates important activities in almost every cell.

Sutherland, who is now professor of physiology at Vanderbilt University School of Medicine in Nashville, began his investigations on hormone action at Washington University in St. Louis in the laboratory of Carl Cori. The Nobel-prizewinning work of Carl and Gerty Cori and that of others had already resulted in the identification of the enzymes involved in glycogen breakdown, and Sutherland began to investigate how the hormone epinephrine (adrenaline) stimulated the degradation of glycogen in liver and muscle. The first point to establish was which step in the pathway of glycogen breakdown was stimulated by epinephrine or by glucagon, another hormone that enhanced glycogen breakdown. By measuring the levels of various intermediates in the glycogen degradative pathway, Sutherland established that the initial step in glycogen breakdown was the one affected. That step was catalyzed by the enzyme phosphorylase, and he then showed that the activity of phosphorylase was increased in liver cells that had been exposed to epinephrine.

Next, along with a move to Western Reserve University School of Medicine in Cleveland, Sutherland began to study the enzyme phosphorylase in detail and found that in liver extracts there was a second enzyme which could convert active phosphorylase to an inactive form. This modification was accompained by a release of inorganic phosphate and represents one of the most important examples of how enzyme activity is regulated by relatively minor changes in an enzyme molecule.

Sutherland, joined about that time by Theodore Rall, then found that the inactive form of phosphorylase could be converted back to the active form by another enzyme present in liver extracts. This activation was accompanied by the incorporation of phosphate back into the phosphorylase molecule. A similar enzyme was simultaneously discovered in muscle by Krebs and Fischer and came to be known as phosphorylase kinase when it was shown that adenosine triphosphate (ATP) served as the phosphate donor in the phosphorylation of phosphorylase.

Once it was established that phosphorylase could be activated and inactivated, it was clear that the degradation of a glycogen was controlled by the relative amounts of active and inactive enzyme. Shortly thereafter, Sutherland and his co-workers showed that, in cell-free extracts, both epinephrine and glucagon promoted the accumulation of the active form of phosphorylase. This was the first demonstration of a physiologically significant effect of a hormone in a cell-free extract and destroyed the major barrier to the understanding of how hormones act. In Sutherland's own words, "The discovery of phosphorylase activation and the discovery of the chemical nature of the change when phosphorylase activity changed were probably equally important landmarks —but not as exciting as finally establishing hormone effects in broken cell systems."

Accumulating in the cell-free extracts of liver after epinephrine treatment was a small heat-stable molecule later identified as cyclic AMP. It was this molecule that promoted the conversion of inactive phosphorylase to the active form, and it is the common intermediate in the action of about half of the known hormones that control the activity of animal cells. Cyclic AMP did not accumulate, however, if the cell membrane fraction was removed from the extracts. Later studies showed that epinephrine and many other hormones acted on the outside of the cell membrane to promote the synthesis of cyclic AMP; on the inner surface of the cell membrane cyclic AMP was released.

At this stage, several formidable problems existed. One was to identify the chemical structure of cyclic AMP. Because the compound was present in extremely small amounts in cells, it was difficult to accumulate enough to characterize it. Finally, Sutherland obtained evidence that it was a nucleotide with unusual properties and sent his results to Leon Heppel, then at NIH. Heppel had previously received a letter from David Lipkin describing a nucleotide he had prepared chemically as a result of treating ATP with barium hydroxide. One day, while clearing his desk, Heppel ran across both letters and realized that both workers were probably studying the same compound. Heppel put the two investigators in communication with each other, and the structure of the heat-stable factor was established as cyclic AMP. Perhaps equally as important was that the chemical synthesis gave a way of preparing sufficient amounts of cyclic AMP for biochemical studies and indicated its probable route of biosynthesis. Sutherland already knew that ATP was required to make the nucleotide in homogenates.

The second obstacle was the question of how to measure cyclic AMP. The fact that cyclic AMP could activate phosphorylase and stimulate glycogen breakdown provided the basis for Sutherland and his co-workers to assay cyclic AMP, although this assay was difficult to perform and constituted a major technical obstacle for a number of years. Nevertheless, Sutherland proceeded to make a number of fundamental observations that created a revolution, first in endocrinology and later in all of biology, for cyclic AMP turned out to be present in almost all cells.

Since glycogen is mainly found in liver and muscle, the cyclic AMP in the other tissues seemed likely to control other processes. When Sutherland examined cyclic AMP accumulation in other hormonally dependent tissues, he found that many hormones increased cyclic AMP synthesis in their target tissues; steroid hormones, however, do not appear to act through the cyclic AMP system. The various hormones acted by increasing the ac-

tivity of the enzyme adenyl cyclase, thereby increasing cyclic AMP synthesis. The name of the game became cyclic AMP, and many workers realized that cyclic AMP might explain how their particular pet hormone might work.

As unicellular organisms evolved into the greater complexity of multicellular life, individual cells began to communicate with each other by chemical signals, such as hormones, and also by developing a nervous system. One problem that has occupied many endocrinologists is how hormones instruct their target tissues to perform their specialized functions. One of Sutherland's contributions is that he has made possible a unifying concept of the mechanism of hormone action. Hormones could be considered as first messengers leaving their site of synthesis and circulating to their target tissues, where they are recognized by specific receptors. Sutherland suggested that, after the hormone combined with receptor, the activity of adenyl cyclase present in the cell membrane increased and the common "second messenger" cyclic AMP was generated inside the cell, where it could stimulate cyclic AMP-sensitive enzymes already present in the tissue to carry out their specialized functions.

Sutherland established a set of criteria to be met to show that a hormone worked through the cyclic AMP system. He indicated that a hormone should increase cyclic AMP levels in tissue, that it should increase the activity of adenyl cyclase, and finally that cyclic AMP itself added to the tissue should mimic the action of the hormone. Unfortunately, cyclic AMP does not readily enter many cells. Theodore Posternak, while visiting Sutherland's laboratory, synthesized a number of cyclic AMP analogs. The most famous of these is dibutyryl cyclic AMP, which appears to enter cells more readily than cyclic AMP itself, because its lipophilic nature allows it to penetrate cell membranes. Thus, if cells treated with dibutyryl cyclic AMP show the same response as cells treated with an appropriate hormone, then this is strong evidence that the hormone works through the cyclic AMP system.

Earl W. Sutherland, Jr.

Cyclic AMP has been found to explain many puzzling biological phenomena. Cyclic AMP acts directly at the gene level in *Escherichia coli* and other bacteria to promote synthesis of many inducible enzymes and even flagella, and the well-known ability of glucose to repress the synthesis of various inducible enzymes in *E. coli* is due to its ability to lower cyclic AMP. Cyclic AMP is a signal for amoebas to aggregate in what constitutes a primitive form of differentiation; cyclic AMP controls the activity of brain cells; and alterations in cyclic AMP metabolism appear to be responsible for some of the altered properties of cancerous connective tissue cells.

One of the most impressive aspects of Sutherland's contribution is that it is truly unique. Today, important discoveries are often made simultaneously in different laboratories. In the case of Earl Sutherland, the rest of us were years behind.

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RESEARCH TOPICS

Global Meteorology (II): Numerical Models of the Atmosphere

Weather in much of the Northern Hemisphere is now routinely forecast for periods up to 72 hours, and fortunately so, because modern man is increasingly dependent on weather information. And while forecasts are often imperfect, they and the computer models on which they are based do predict the weather more accurately than was possible before their advent. Reliable long-range forecasts (from a few days to 2 weeks) would be even more useful, and understanding of average weather patterns on the still longer time scale of several years might help to resolve the question of whether man is inadvertently altering the climate.

Meteorologists have been developing sophisticated models of the atmosphere as one method of coming to grips with these problems, and in recent years they have been conducting numerical experiments with these models to investigate the feasibility of long-range prediction of the weather and simulation of the climate. They have already obtained some interesting results. But achievement of these goals seems to await a better theoretical understanding of meteorological processes, more detailed observational data on the weather, and still faster computers.

Numerical modeling of the weather has always been intimately involved with electronic computers. Among the earliest applications of the first modern computer—built at the Princeton Institute for Advanced Study and completed in the early 1950's—was to the problem of weather prediction. Despite the use of a very simplified atmospheric model, these early attempts—by John von Neumann and Jule Charney—proved so successful that operational use of the technique for weather fore-