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EARL W. SUTHERLAND

*1915—1974*

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*A Biographical Memoir by*

CARL F. CORI

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*Biographical Memoir*

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*Earl W. Suiterland*

## EARL W. SUTHERLAND

*November 19, 1915–March 9, 1974*

BY CARL F. CORI

EARL WILBUR SUTHERLAND, JR., was born in Burlingame, a small agricultural community in eastern Kansas, on November 19, 1915, the fifth child of a family of six. His father was born in Wisconsin, went to Grinnell College for two years, and was a farmer in New Mexico and Oklahoma for about ten years. After that he was a merchant for forty years in Burlingame, where he ran a dry goods business. Earl's mother, Edith M. Hartshorn, came from Missouri and completed her higher education at a "ladies' college" and had some practical nursing training. She and all of the children assisted in the operation of the family store. Earl had an older half brother—from a previous marriage of his father—who became a Unitarian minister, three older sisters, and a younger brother, Dr. John Bennet Sutherland, who became a professor of chemical engineering at the University of Missouri. The family was prosperous at first and lived in a large comfortable house, but the depression in the thirties brought hard times.

### THE FORMATIVE YEARS

The family was strongly oriented toward education. Earl's mother had probably the most influence on his early development. She recognized and encouraged his interest in science and also brought him up to be very independent. After teaching him

to swim at the age of five, she let him fish in the nearby Dragoon River by himself. By the time he was eight he was out in the fields and woods with his own shotgun, hunting rabbits and squirrels. There can be little doubt that his love of the outdoors and his lifelong passion for fishing and gardening stem from that early period.

Sutherland enjoyed participating in all sports, playing football and basketball in high school and excelling particularly in tennis. He entered Washburn College in Topeka, Kansas, in 1933, but found it necessary to support himself through college, working as an orderly in a hospital. The austerity he experienced left a mark on him and almost made him decide to practice medicine rather than become a scientist which in those days meant more austerity. In 1937 he graduated from Washburn College with a B.S. degree and married Mildred Rice of Topeka, Kansas. He then entered Washington University Medical School in St. Louis, where I first got to know him. I was then teaching a course in pharmacology in the second year and his performance as a student impressed me so that I offered him a student assistantship in the department. Although the pay was minimal, Earl needed the money badly, since he had a growing family to support.

One might reflect here briefly what it means growing up in the Middle West in the heartland of the country. The Middle West was then and still is a great reservoir of talent from which the rest of the country can draw. In fact, there has been a sort of brain drain going on to the East as well as the West. There is probably more of a challenge to ambition growing up away from big cities. There is a feeling in the Middle West of a lack of sophistication and that bigger opportunities exist elsewhere. However this may be, Earl Sutherland gave the impression of being a Middle Westerner all his life, in his outlook, his sense of humor—he was a specialist in a form of light banter—in his interpersonal relationships, in his conviviality and in his aver-

sion to big-city life. He was very honest and direct in dealing with people and if he held back it was due to some innate suspicion of the motives of others. It was not that he lacked sophistication, but rather that he preferred the simplicity and informality of his early upbringing. On meeting Sutherland as a young man it was not apparent at first that he was quite above the ordinary. Certain personality traits that were probably essential for his success as a scientist were still latent. He was uncertain in which direction he should go.

THE ST. LOUIS PERIOD: WASHINGTON UNIVERSITY,  
1940-1942 AND 1945-1953

The job as student assistant gave Sutherland a chance to try his hand at research. His first two papers with S. P. Colowick who was then a graduate student in the department were concerned with polysaccharide synthesis from glucose by means of purified enzymes. Among other new findings, these papers dealt with the reversibility of the phosphoglucomutase reaction, glucose-1-P  $\rightleftharpoons$  glucose-6-P, which has its equilibrium far to the right. In order to pull the reaction with phosphorylase, barium ions were added which precipitated the inorganic P formed from glucose-1-P, thereby allowing polysaccharide synthesis to take place. It was the study of the phosphorylase system that led Sutherland to the discovery of adenosine-3',5'-phosphoric acid (cyclic AMP), but this was fifteen years later after he had gone to Cleveland as head of the Department of Pharmacology.

After receiving his M.D. degree in 1942, Sutherland served for one year as intern at Barnes Hospital and continued his research in the department. There were some complaints on the part of his clinical teachers because of his frequent absence, but I defended him thinking that he had the making of a good research worker.

Here we meet an old conflict that existed then as now and that is difficult to resolve. In contrast to the Ph.D. student, the

young M.D. generally has had no chance to try his hand at research and cannot find out whether he is good at it until he has served as intern or resident. This is a considerable handicap for a future career in research. On the other hand, early contact with research often leads the prospective M.D. entirely away from the practice of medicine. Sutherland had this to say about the subject in his Nobel Lecture delivered in December 1971:

When I returned to St. Louis after Medical Service in World War II\* I was undecided as to whether I should enter medical practice or go into research. Cori convinced me, not so much by anything he said so much as by his example, that research was the right direction for me to take. Although I have occasionally felt an urge to see patients, I have never really regretted this decision to stay in the laboratory.

Sutherland stayed in the Biochemistry Department of Washington University Medical School in St. Louis from 1945 to 1953 and advanced from instructor to associate professor. During that period he came in contact with a number of investigators who worked there for a time. Among these were Kalckar, Ochoa, Leloir, Arthur Kornberg, Edwin Krebs, Victor Najjar, Rollo Park, T. Z. Posternak, C. DeDuve, and others. Sutherland had this to say about this period in his Nobel Lecture:

I believe that kind of stimulating environment, with the necessary critical mass of young and talented investigators, with the opportunity for the free exchange of ideas, is an important ingredient in the making of scientific progress.

Sutherland collaborated with some of these outside workers. With DeDuve he published a paper on the origin and distribution of a hyperglycemic-glycogenolytic factor present in commercial insulin preparations and concluded that it came from the  $\alpha$ -cells of the islands of Langerhans, thereby establishing its hormone nature. This factor, later renamed glucagon, played a

\* Earl was a battalion surgeon in Patton's army and later served in a hospital in Germany for a total period of two years.

great role in Sutherland's later work. With Posternak he worked on the mechanism of the phosphoglucomutase and phosphoglyceric mutase reactions. Posternak at a later date synthesized various derivatives of cyclic AMP, among them the widely used dibutyryl derivative which is not split by phosphodiesterase.

Sutherland by this time had developed into an independent worker of great potential. Two parallel lines of development came together here that were to be of decisive importance for his later work. The first was an intensive study of the enzyme phosphorylase which initiates the breakdown of glycogen in liver and muscle, and the second was how epinephrine and glucagon stimulated the release of glucose from glycogen in the liver.

Phosphorylase had been isolated from muscle in two forms, one active per se and the other inactive unless adenylic acid was present. There were separate enzymes involved in the conversion of one form into the other, but the nature of the interconversion reaction had not been discovered. Liver phosphorylase had not been extensively purified, but it was shown in work with Sutherland that liver also contains an enzyme system that keeps a balance between an active and inactive form of phosphorylase.

Liver slices had proved to be a convenient test system for the action of glucagon and epinephrine, since these agents increased the glucose output when added *in vitro*. Half-maximal response was obtained with epinephrine in a dilution of 1 : 20 million. Other catecholamines also acted on this system in proportion to their activity as hyperglycemic agents in the intact animal. An analysis of the rate-limiting step of glucose formation in liver slices identified the phosphorylase system as the slow step making it probable that glucagon and epinephrine acted on this system, presumably by promoting the conversion of the inactive to the active form of phosphorylase. This idea could be demonstrated directly by measuring the phosphorylase activity in homogenates prepared from preincubated liver slices. In a con-

trol incubation the phosphorylase activity of liver slices showed a large drop. When at this point epinephrine or glucagon was added, the phosphorylase activity was restored within four minutes. A critical experiment that seemed to make further analysis difficult was the following. When liver slices were first frozen and thawed in order to disrupt cell structure, an effect of epinephrine or glucagon on the phosphorylase system could no longer be demonstrated. The idea that an intact cell structure was required for the action of these hormones was reinforced by the observation that all attempts to demonstrate an action on liver extracts or semipurified liver phosphorylase preparations had failed.

THE CLEVELAND PERIOD:  
WESTERN RESERVE UNIVERSITY,  
1953-1963

This was roughly the state of affairs when in 1953 Sutherland moved to Cleveland to accept the chairmanship of the Department of Pharmacology at Western Reserve (now Case Western Reserve) University. He was much more convinced than I that an *in vitro* test system for epinephrine and glucagon consisting of purified enzymes could be developed, and it was the systematic pursuit of this idea that led to the discovery of cyclic AMP. What we see at work here is a sort of hunch or secret insight plus tenacity, the ability of differentiating between important and unimportant observations, absolute reliance on the accuracy of one's results and a prodigious memory—all qualities that characterize the successful bench scientist and that Sutherland possessed in large measure.

Sutherland's last experimental paper from St. Louis was a preliminary note on the purification of liver phosphorylase. Then there is a gap of several years until things started moving again. During this period Sutherland and Wosilait had purified dog liver phosphorylase in its active form and they found



another enzyme, a phosphatase, that inactivated phosphorylase by splitting off inorganic phosphate. Krebs and Fischer, at the University of Washington in Seattle, had meanwhile been studying the reactivation of inactive rabbit muscle phosphorylase and had shown that this occurred with adenosine 5'-triphosphate (ATP) and  $Mg^{2+}$  or  $Mn^{2+}$  and that a special enzyme, a kinase, was necessary for this reaction. Independently, Sutherland and collaborators had found, by means of radioactive ATP, that phosphate became incorporated when inactive liver phosphorylase was reactivated.

It was thus established that the dynamic equilibrium, inactive  $\rightleftharpoons$  active phosphorylase, which had been demonstrated in liver and muscle was a phosphorylation-dephosphorylation reaction of a serine residue of phosphorylase catalyzed by two separate enzymes. With this information in hand Sutherland and Rall began to add hormones to inactive liver phosphorylase preparations in the presence of ATP and  $Mg^{2+}$ . They observed activation of phosphorylase by epinephrine and glucagon if they used relatively crude liver homogenates, but if they centrifuged the extracts to remove cellular debris, the hormone action disappeared, only to reappear again if they added back the particulate fraction. This proved to be a decisive experiment, because they were then able to show that if the particulate fraction alone was first incubated with hormones, a heat-stable, dialyzable factor was produced that could in turn activate phosphorylase when added to the supernatant fraction. In this manner the hormone response was separated into two consecutive reactions.

The next step was to isolate and identify the heat-stable factor. This proved to be a difficult task, since the maximal concentration of the compound in the tissues, as was found later, rarely exceeds  $10^{-6}$  M and since it is rapidly destroyed by a special phosphodiesterase. The final identification was accelerated by the fact that Cook, Lipkin, and Markham, quite independently, had isolated the same compound from a barium hydrox-

ide digest of ATP and had proposed the same structure. An exchange of samples established the identity of the two compounds and the results of the two groups were published simultaneously in preliminary reports in July 1957 in the *Journal of the American Chemical Society*.\*

This is, in brief, the history of the discovery of adenosine-3', 5'-phosphoric acid, generally referred to as cyclic AMP. Sutherland undoubtedly knew that he had found something of great importance, but even he, I think, could not have foreseen how far-reaching this discovery would turn out to be. In fact, even our present knowledge is still very incomplete and years of future work may be required to unravel the full significance of cyclic AMP for biological processes.

Sutherland's later work at Cleveland, aided by an increasing number of young collaborators, has been summarized in *The Harvey Lecture Series* for 1962.† Adenylate cyclase, the enzyme which in the presence of  $Mg^{2+}$  catalyzes the reaction,  $ATP \rightarrow$  cyclic AMP + inorganic pyrophosphate, was found in practically all tissues of a variety of mammalian species, with the highest concentration being present in each case in the central nervous system. The enzyme is found in a particulate fraction of the cell that sediments at low centrifugal speed and that was suspected to be derived from the cell membrane. When this became firmly established through work by Sutherland and Davoren on pigeon erythrocytes, it opened up a whole new field of isolation and characterizations of cell surface receptors. This development was also foreshadowed by the demonstration by Sutherland and collaborators that detergent-solubilized preparations of brain

\* Dr. Leon Heppel acted as an intermediary since both groups had asked for one of his enzymes to be used in the characterization of an unknown nucleotide, and it was his discernment that had brought the two groups together.

† The collaborators mentioned by Sutherland were Walter Wosilait, Theodore Rall, Gene Riley, Walter Henion, Richard Makman, R. W. Butcher, Ferid Murad, and Maynard Makman. J. Berthet, P. R. Davoren, and T. Posternak were visitors from abroad.

retained their ability to form cyclic AMP and to respond to epinephrine.

There were two additional findings made during this period that were of great importance for future development. One was that hormones other than epinephrine and glucagon could activate adenylate cyclase, for example, adrenocorticotrophic hormone and thyroid-stimulating hormone acting on their respective target organs. The other was that cyclic AMP acted on enzyme systems other than phosphorylase, for example, UDPG-glycogen glucosyl transferase, and that the action could be stimulatory or inhibitory. It was also shown that the level of the cyclic nucleotide was controlled by a specific phosphodiesterase that was competitively inhibited by methyl xanthines. This explained an old observation made long before cyclic AMP, namely, that methyl xanthines enhanced the action of hormones on liver slices.

A rather startling discovery was made toward the end of this period, when it was found by R. S. Makman and Sutherland that *Escherichia coli* produces cyclic AMP in response to glucose depletion. Cyclic AMP, up to this point, was known to function as a mediator of certain hormones in multicellular organisms. Here one finds the cyclic nucleotide functioning in a precaryotic organism which suggests that its role as regulator of cellular processes arose very early in the scheme of evolution.

At this time Sutherland was beset by troubles, partly personal because he was involved in a divorce from his first wife and partly professional because Western Reserve was undergoing rapid changes, particularly in its curriculum at the Medical School. Lecturing did not come easy to Sutherland and he was not happy about administration. Furthermore, he wanted to devote himself fully to an exploration of his discovery of cyclic AMP. I remember having a long talk with Sutherland at that time, trying to persuade him to stay on. He listened politely, but he had already made up his mind. What enabled

him to move to Vanderbilt University was the possibility of obtaining a Career Investigatorship of the American Heart Association, which would give him the freedom he needed at that particular time. In this he was successful.\* At Vanderbilt he found many old friends from the St. Louis days—Rollo and Janie Park, Colowick, Najjar and others—and in this congenial environment his work came to full fruition.

Shortly before moving to Vanderbilt he married Dr. Claudia Sebeste with whom he shared many interests, not the least his passion for fishing. In a film made by Swedish television at the time he was awarded the Nobel Prize one sees Earl and Claudia launching their boat as they are setting out on a fishing trip. Sutherland claimed that some of his best scientific thoughts came while on the water.

THE NASHVILLE PERIOD: VANDERBILT UNIVERSITY,  
1963-1973

Of the many review articles Sutherland has written, one that appeared in *Pharmacological Reviews* for 1966 (with G. A. Robison) is of special interest. In it there is a critical discussion of the question whether cyclic AMP mediates the effect of epinephrine and other catecholamines on the force of myocardial contraction. Evidence for such an effect was first presented by Sutherland and collaborators in 1962, but in the meantime a large literature had grown up around the subject. Sutherland concluded that all of the available evidence was in favor of this hypothesis. He also pointed out that there was no direct connection between the positive inotropic effect of epinephrine and the activation of the cardiac phosphorylase system. This review is also noted for the first diagrammatic representation of the second-messenger concept.

\* Actually, he did not apply for this investigatorship until he had established himself at Vanderbilt and in the meantime he supported himself with grants from the National Institute of Health.

In the diagram, the hormone, released by various stimuli, acts as the first-messenger by changing the activity of the membrane-bound adenylate cyclase. The cyclic AMP then acts as a second messenger, influencing various intracellular processes, the nature of which depends on the particular function of the target cells. The scheme was amplified later to provide specific binding sites for various hormones acting on adenylate cyclase. Thus, the second-messenger concept could explain how glucagon, a protein, and epinephrine, a small molecule, could have qualitatively the same effect on liver cells and how, for example, vasopressin acting on the toad bladder could alter sodium ion permeability. The scheme also left room for other cyclase systems giving rise to different second messengers such as guanosine 3',5'-cyclic monophosphate.

Some criteria that Sutherland and collaborators found useful in deciding whether a given system followed the above mechanism were the following. First, a stimulation of adenylate cyclase by a given hormone should be demonstrable on intact tissues as well as broken cell preparations. Second, the concentration of cyclic AMP in the tissues should show a dose-response curve when the amount of added hormone was varied and should show a proper time relationship to the action of the hormone. Third, drugs that inhibit the specific phosphodiesterase, such as theophylline, should act synergistically with a hormone operating via the adenylate cyclase system. Finally, it should be possible, at least in theory, to mimic the hormone effect by adding cyclic AMP or one of its more lipophilic derivatives to tissue preparations, but such experiments are often defeated by the low permeability of tissues for cyclic AMP.

Each of these four criteria was fulfilled in the case of catecholamine activation of phosphorylase in liver and of lipase in fat tissue. Further work on fat tissue showed that the antilipolytic effect of insulin was associated with a marked decrease in the tissue level of cyclic AMP. Prostaglandin  $E_1$  was likewise

antilipolytic; in a concentration of  $0.004 \mu M$  it neutralized 50 percent of the effect of  $5.5 \mu M$  epinephrine on cyclic AMP. A new development in this area is the demonstration that fat cells when exposed to lipolytic agents produce an antagonist that acts as a feedback inhibitor of cyclic AMP formation. Several posthumous articles dealing with this problem have appeared.

In the course of a few years, more and more physiological processes were being discovered in different tissues and in different animal species that were influenced by the concentration of cyclic AMP. Sutherland in his Nobel Lecture lists thirty-six such processes, but since that time some more have been added. In the majority of cases the effect of cyclic AMP was to increase the rate of the process, but there were at least nine instances in which cyclic AMP had the opposite effect. In this respect, the simultaneous increase in phosphorylase activity and decrease in glycogen synthetase activity produced by catecholamines has special regulatory significance, since it prevents futile cycling of glucose-1-phosphate. Here substantial progress has been made by Krebs and collaborators by showing that the target of cyclic AMP is a protein kinase. This enzyme by transferring a phosphate group from ATP activates phosphorylase (via a second kinase) and inactivates glycogen synthetase. Protein kinases are widely distributed, some responding to cyclic AMP and some not, but this is an area still being investigated.

One of the regulatory effects of cyclic AMP is to cause the release of a number of hormones, including insulin, thyroid hormone, steroid hormones and anterior pituitary hormones. Although Sutherland suggested that these hormones might be thought of as "third messengers," he later gave up this terminology since it would create semantic difficulties. This may be illustrated by the thyroid system. The thyrotropin-releasing hormone of hypothalamic cells stimulates adenylate cyclase in the thyrotropic cells of the anterior pituitary. This causes the release of thyroid-stimulating hormone which stimulates adenylate cyclase in the thyroid, the end result being the release of triiodo-



thyronine and related products. A similar chain of sequential hormone release, each involving cyclic AMP, is operative in steroidogenesis. Thus, the various relationships in the endocrine system cannot all be explained by the second-messenger concept.

In 1971 G. A. Robison, R. W. Butcher, and Sutherland published a comprehensive monograph on cyclic AMP in which they not only summarized the then existing literature, but also discussed the many unsolved problems. They point out that no general principle has emerged that would explain the multifarious actions of cyclic AMP on enzyme induction, permeability, enzyme secretion (salivary gland), tension (smooth muscle), contractility (cardiac muscle), aggregation (slime mold), proliferation (thymocytes), Lac mRNA synthesis (*E. coli*), and many others. It seems possible that all of these effects are initially the result of an alteration in the activity of some enzyme, but this has not been proved. As they express it:

In a very real sense, our ignorance regarding the mode of action of cyclic AMP reflects our ignorance of the nature of basic cell processes in general.

Most of Sutherland's research in his last years centered around cyclic GMP (guanosine 3',5'-cyclic monophosphate), the only other cyclic nucleotide discovered so far that occurs naturally. This nucleotide is widely distributed in mammalian tissues and is also present in lower phyla. Its concentration is generally one-tenth that of cyclic AMP. The cyclase that makes cyclic GMP is different in several respects from the one that makes cyclic AMP and differences have also been noted in the phosphodiesterases that hydrolyze the two compounds. In particular, hormones that stimulate the formation of cyclic AMP had no effect on the level of cyclic GMP. Both cyclic nucleotides are found in the plasma and are excreted in surprisingly large amounts in the urine. A number of intriguing observations were made about factors that changed the excretion of these two nucleotides in the urine and an effect of calcium ions on tissue

levels of cyclic GMP was discovered, but a biological role for this nucleotide has not been established. As Sutherland commented on one occasion, he and his group spent about a third of their time working on methods. Better and better methods were essential for progress in this difficult field.

Sutherland maintained his interest in medical problems and pointed out that because cyclic AMP had such a widespread regulatory function it would seem likely that a variety of disorders may be related to defects in the formation or action of this nucleotide. One genetic aberration of this nature has been discovered in rats. Several drugs already in use appear to act by way of cyclic AMP by inhibiting phosphodiesterase. Perhaps the most dramatic recent discovery in the medical field is that cholera toxin exerts its effect by prolonged activation of adenylate cyclase in the intestinal epithelium.

Another recent development is the relationship of the adenylate cyclase system to diabetes. One of the basic experiments was carried out by Sutherland and his group when they showed that the injection of anti-insulin serum in normal rats causes an immediate rise in the cyclic AMP level of the liver. Apparently, under normal physiological conditions the glucose output of the liver depends on a balance between hormones which increase the level of cyclic AMP—principally glucagon and catecholamines—and insulin which decreases it. In alloxan diabetes, as might be expected, the cyclic AMP level is increased and injection of insulin promptly lowers it but not below a certain baseline level. Sutherland expressed the opinion that most of the known effects of insulin on the liver can be explained by its ability to lower the intracellular level of cyclic AMP. The mechanism by which insulin produces this effect is not known. It should also be mentioned that the increased glucose transport produced by insulin in muscle and other tissues is apparently not related to a change in the cyclic AMP level.

Since cyclic AMP is involved not only in some of the actions of insulin but also in insulin release from the pancreas, an appli-



cation of this information to diabetes seems warranted. It now seems clear, based mainly on studies of diabetes in laboratory animals, that many of the metabolic disturbances are due to the increased level of cyclic AMP in adipose and hepatic tissue. The excessive mobilization of fatty acids leads to ketosis, and the stimulation of glycogenolysis and gluconeogenesis leads to hyperglycemia. To this may be added a disturbance in the insulin-releasing mechanism in prediabetes which has been observed by other authors. There is here ample opportunity to make use of basic information in trying to explain the pathogenesis of a prevalent human disease.

It will not be possible here to review all the ramifications of Sutherland's work, because much of it lies in the future. It may well turn out as Peter Reichard said in his presentation address at the Nobel ceremony in Stockholm that cyclic AMP is involved in the regulation of essentially all life processes.

#### THE UNIVERSITY OF MIAMI: 1973-1974

Sutherland's decision to move to the University of Miami in July 1973 was surprising, but was probably motivated to a large extent by his failing health. In March 1974, following a massive esophageal hemorrhage, he came down with an intractable infection which ended his life prematurely, when he was still at the height of his productivity.

#### EPILOGUE

Within too short a life span Earl Sutherland was singularly successful in fulfilling his scientific mission. Having made a scientific discovery of paramount importance, he had the satisfaction of developing a large part of this new field himself, of seeing it grow ever more in importance and of receiving universal recognition. He also had the faculty of choosing able and devoted young people as collaborators with whom he shared his ideas and in whose development he took great interest.

It may be appropriate here to say something about the qual-

ities that Earl Sutherland possessed and that made him such an outstanding scientist. First and perhaps foremost he had the gift of intuition. He could set up the right experiment at the right time without necessarily knowing why. Secondly, his intuition was strong enough to generate a remarkable degree of tenacity. He held on to the idea that the action of a hormone could be demonstrated in a cell-free system *in vitro*. Thirdly, he was an excellent worker in the laboratory who could recall any of the experiments he and his associates had carried out in the past. Fourthly, Sutherland was highly original in his concepts and did not follow current lines of thought. He had ambition, a powerful drive, and an intensity and singularity of purpose that was most remarkable. He carried his laboratory problems constantly in his head, and other interests, except his passion for fishing, provided little competition.

Sutherland clearly expressed his motivation for doing scientific work when he received the Lasker Award in 1970. He said:

Let me confess here, lest I leave a false impression, that I did not have the welfare of future generations primarily in mind when I began my research on the hyperglycemic action of glucagon and the catecholamines. Rather, my motivation was primarily directed to satisfying my curiosity about how these hormones acted.

Sutherland was very honest with himself and this enabled him to turn a dispassionate eye on his own research and to avoid wishful overevaluation. Perhaps his final summing up in his Nobel Lecture expresses what he felt: "A life in research can be a most enjoyable life with many frontiers to explore."

Earl Sutherland was such an explorer.

I AM INDEBTED to the following persons for information: Dr. John B. Sutherland (courtesy of Dr. R.-J. Ho), Dr. Claudia Sebeste Sutherland, Dr. Rollo Park, Dr. W. J. Whelan, and Ms. Ilene Scheinbaum,

## BIBLIOGRAPHY

## KEY TO ABBREVIATIONS

Ann. N.Y. Acad. Sci. = Annals of the New York Academy of Sciences

Biochim. Biophys. Acta = Biochimica et Biophysica Acta

Clin. Res. = Clinical Research

Fed. Proc. = Federation Proceedings (Publications of the Federation of American Societies for Experimental Biology)

J. Biol. Chem. = Journal of Biological Chemistry

J. Clin. Invest. = Journal of Clinical Investigation

Mol. Pharmacol. = Molecular Pharmacology

Pharmacol. Rev. = Pharmacological Reviews

Proc. Natl. Acad. Sci. USA = Proceedings of the National Academy of Sciences of the United States of America

## 1941

With Sidney P. Colowick and Carl F. Cori. The enzymatic conversion of glucose-6-phosphate to glycogen. *J. Biol. Chem.*, 140: 309-10.

## 1942

With Sidney P. Colowick. Polysaccharide synthesis from glucose by means of purified enzymes. *J. Biol. Chem.*, 144:423-37.

## 1947

With C. F. Cori. Influence of insulin on glycogen synthesis and breakdown in liver slices. *Fed. Proc.*, 6:297.

## 1948

With Carl F. Cori. Influence of insulin preparations on glycogenolysis in liver slices. *J. Biol. Chem.*, 172:737-50.

With Christian DeDuve. Origin and distribution of the hyperglycemic-glycogenolytic factor of the pancreas. *J. Biol. Chem.*, 175: 663-74.

With C. DeDuve. A glycogenolytic factor from pancreas. *Fed. Proc.*, 7:195.

## 1949

With T. Z. Posternak and C. F. Cori. Activation of phosphoglucosutase. *Fed. Proc.*, 8:1.

With T. Z. Posternak and Carl F. Cori. The mechanism of action of phosphoglucomutase and phosphoglyceric acid mutase. *J. Biol. Chem.*, 179:501-2.

With Carl F. Cori, Robert Haynes, and Norman S. Olsen. Purification of the hyperglycemic-glycogenolytic factor from insulin and from gastric mucosa. *J. Biol. Chem.*, 180:825-37.

Activation of phosphoglucomutase by metal-binding agents. *J. Biol. Chem.*, 180:1279-84.

With Mildred Cohn, Theodore Posternak, and Carl F. Cori. The mechanism of the phosphoglucomutase reaction. *J. Biol. Chem.*, 180:1285-95.

With Theodore Posternak and Carl F. Cori. Mechanism of the phosphoglyceric mutase reaction. *J. Biol. Chem.*, 181:153-59.

## 1950

Effect of the hyperglycemic factor of the pancreas and of epinephrine on glycogenolysis. *Recent Progress in Hormone Research*, 5:441-63.

## 1951

The effect of the hyperglycemic factor and epinephrine on enzyme systems of liver and muscle. *Ann. N.Y. Acad. Sci.*, 54:693-706.

The effect of the hyperglycemic factor and epinephrine on liver and muscle phosphorylase. In: *Phosphorus Metabolism*, ed. Wm. D. McElroy and Bentley Glass, vol. 1, pp. 53-66. Baltimore: The Johns Hopkins Press.

With Carl F. Cori. Effect of hyperglycemic-glycogenolytic factor and epinephrine on liver phosphorylase. *J. Biol. Chem.*, 188:531-43. Purification of liver phosphorylase. *Fed. Proc.*, 10:256.

## 1952

The effect of epinephrine and the hyperglycemic factor on liver and muscle metabolism *in vitro*. In: *Phosphorus Metabolism*, ed. William D. McElroy and Bentley Glass, vol. 2, pp. 577-97. Baltimore: The Johns Hopkins Press.

Factors affecting liver and muscle phosphorylase. In: *A Symposium on the Clinical and Biochemical Aspects of Carbohydrate Utilization in Health and Disease*, ed. V. A. Najjar. Baltimore: The Johns Hopkins Press.

## 1955

- Polysaccharide phosphorylase, liver. In: *Methods in Enzymology*, ed. Sidney P. Colowick and Nathan O. Kaplan, pp. 215-22. New York: Academic Press.
- Hormonal regulatory mechanisms. In: *Proceedings of the Third International Congress of Biochemistry*, pp. 318-27. New York: Academic Press.
- With Walter D. Wosilait. Inactivation and activation of liver phosphorylase. *Nature*, 175:169-70.
- With W. D. Wosilait and T. Rall. Effect of epinephrine and glucagon on activation of liver phosphorylase. *Fed. Proc.*, 14:289.

## 1956

- With T. Rall and J. Berthet. Effect of epinephrine and glucagon on the reactivation of phosphorylase in liver homogenates. *Fed. Proc.*, 15:1.
- With J. Berthet and M. H. Makman. Observations on the action of certain sulfonylurea derivatives. In: *Symposium on Clinical and Experimental Effects of Sulfonylureas in Diabetes Mellitus*, ed. R. Levine and G. G. Duncan. New York: Grune and Stratton. Also in: *Metabolism*, 5:768-74.
- With W. D. Wosilait and T. W. Rall. The action of glucagon on liver phosphorylase. In: *Ciba Foundation Colloquia on Endocrinology (Proceedings)*, vol. 9, pp. 179-93. London: J. and A. Churchill.
- With Walter D. Wosilait. The relationship of epinephrine and glucagon to liver phosphorylase. I. Liver phosphorylase; preparation and properties. *J. Biol. Chem.*, 218:459-68.
- With W. D. Wosilait. The relationship of epinephrine and glucagon to liver phosphorylase. II. Enzymatic inactivation of liver phosphorylase. *J. Biol. Chem.*, 218:469-81.
- With T. W. Rall and W. D. Wosilait. The relationship of epinephrine and glucagon to liver phosphorylase. III. Reactivation of liver phosphorylase in slices and in extracts. *J. Biol. Chem.*, 218:483-95.
- With T. W. Rall and W. D. Wosilait. The interconversion of phosphorylase *a* and phosphorylase *b* from dog heart muscle. *Biochim. Biophys. Acta*, 20:69-76.

1957

- With T. W. Rall and Jacques Berthet. The relationship of epinephrine and glucagon to liver phosphorylase. IV. Effect of epinephrine and glucagon on the reactivation of phosphorylase in liver homogenates. *J. Biol. Chem.*, 224:463-75.
- With Wallace F. Henion. Immunological differences of phosphorylases. *J. Biol. Chem.*, 224:477-88.
- With Jacques Berthet and T. W. Rall. The assay of glucagon and epinephrine with use of liver homogenates. *J. Biol. Chem.*, 229:351-61.
- With T. W. Rall. The properties of an adenine ribonucleotide produced with cellular particles, ATP,  $Mg^{++}$ , and epinephrine or glucagon. *Journal of the American Chemical Society*, 79:3608.

1958

- With M. H. Makman and R. S. Makman. Measurement and characterization of a glucagon-like material in human and dog blood. *Fed. Proc.*, 17:1542.
- With T. W. Rall. Formation of a cyclic adenine ribonucleotide by tissue particles. *J. Biol. Chem.*, 232:1065-76.
- With T. W. Rall. Fractionation and characterization of a cyclic adenine ribonucleotide formed by tissue particles. *J. Biol. Chem.*, 232:1077-91.
- With M. H. Makman and R. S. Makman. Glucagon in human plasma. In: *Hormones in Human Plasma*, ed. H. N. Antonaides, pp. 119-37. Boston: Little, Brown and Co.
- With Maynard H. Makman and Richard S. Makman. Presence of a glucagon-like material in blood of man and dog. *J. Biol. Chem.*, 233:894-99.

1959

- With T. W. Rall. Action of epinephrine and norepinephrine in broken cell preparations. Symposium on Catecholamines. *Pharmacol. Rev.*, 2:464-65.
- With T. W. Rall. Mechanism of glycogenolytic action of epinephrine. *Pharmacologist*, 1:41-42.
- With R. W. Butcher, Jr. Enzymatic inactivation of adenosine 3',5'-phosphate by preparations from heart. *Pharmacologist*, 1:63.

## 1960

- With F. Murad and T. W. Rall. Formation of adenosine 3',5'-phosphate by particular preparations. *Fed. Proc.*, 19:1.
- With T. W. Rall. The relation of adenosine-3',5'-phosphate and phosphorylase to the actions of catecholamines and other hormones. *Pharmacol. Rev.* 12:265-99.
- With Tag E. Mansour, T. W. Rall, and Ernest Bueding. The effect of serotonin (5-hydroxytryptamine) on the formation of adenosine 3',5'-phosphate by tissue particles from the liver fluke, *Fasciola hepatica*. *J. Biol. Chem.*, 235:466-70.
- With T. W. Rall. Enzymes concerned with interconversion of liver phosphorylases. In: *Methods in Enzymology*, vol. 5, ed. S. P. Colowick and N. O. Kaplan, pp. 377-91. New York: Academic Press.
- With R. C. Haynes, Jr., and T. W. Rall. The role of cyclic adenylic acid in hormone action. In: *Recent Progress in Hormone Research*, vol. 16, ed. G. Pincus, pp. 121-38. New York: Academic Press.
- With T. W. Rall. Formation of adenosine 3',5'-phosphate (cyclic adenyate) and its relation to the action of several neurohormones or hormones. *Acta Endocrinologica*, 34:171-74.
- With R. W. Butcher and T. W. Rall. Measurement of adenosine 3',5'-phosphate (cyclic 3,5-AMP) activity in heart, other tissues and urine. *Pharmacologist*, 2:66.

## 1961

- With T. W. Rall. The regulatory role of adenosine 3',5'-phosphate. Cold Spring Harbor Symposia on Quantitative Biology, 26: 347-54.

## 1962

- The biological role of adenosine 3',5'-phosphate. In: *The Harvey Lecture Series*, vol. 57, pp. 17-33. New York: Academic Press.
- With Th. Posternak and W. F. Henion. Derivatives of cyclic 3',5'-adenosine monophosphate. *Biochim. Biophys. Acta*, 65:558-60.
- With T. W. Rall and Tara Menon. Adenyl cyclase. I. Distribution, preparation, and properties. *J. Biol. Chem.*, 237:1220-27.
- With T. W. Rall. Adenyl cyclase. II. The enzymatically catalyzed



- formation of adenosine 3',5'-phosphate and inorganic pyrophosphate from adenosine triphosphate. *J. Biol. Chem.*, 237:1228-32.
- With F. Murad, Y.-M. Chi, and T. W. Rall. Adenyl cyclase. III. The effect of catecholamines and choline esters in the formation of adenosine 3',5'-phosphate by preparations from cardiac muscle and liver. *J. Biol. Chem.*, 237:1233-38.
- With L. M. Klainer, Y.-M. Chi, S. L. Freidberg, and T. W. Rall. Adenyl cyclase. IV. The effects of neurohormones on the formation of adenosine 3',5'-phosphate by preparations from brain and other tissues. *J. Biol. Chem.*, 237:1239-43.
- With R. W. Butcher. Adenosine 3',5'-phosphate in biological materials. I. Purification and properties of cyclic 3',5'-nucleotide phosphodiesterase and use of this enzyme to characterize adenosine 3',5'-phosphate in human urine. *J. Biol. Chem.*, 237:1244-50.

## 1963

- With Peter R. Davoren. The effect of L-epinephrine and other agents on the synthesis and release of adenosine 3',5'-phosphate by whole pigeon erythrocytes. *J. Biol. Chem.*, 238:3009-15.
- With Peter R. Davoren. The cellular location of adenyl cyclase in the pigeon erythrocyte. *J. Biol. Chem.*, 238:3016-23.
- With R. S. Makman. Presence of cyclic 3',5'-adenosine phosphate in *E. coli*. *Fed. Proc.*, 22:470.

## 1964

- With I. Øye, R. W. Butcher, and H. E. Morgan. Epinephrine and cyclic 3',5'-AMP levels in working rat hearts. *Fed. Proc.*, 23:2762.
- With R. W. Butcher, R. J. Ho, and H. C. Meng. Cyclic 3',5'-AMP levels and free fatty acid (FFA) release. *Proceedings of International Congress of Biochemistry*, 6:715.
- With P. R. Davoren and R. S. Makman. The cellular location of adenyl cyclase and adenosine-3',5'-phosphate in *Escherichia coli*. In: *Ciba Foundation Symposium on Control of Glycogen Metabolism*, ed. W. J. Whelan and M. P. Cameron, pp. 233-43. London: J. and R. Churchill.
- With P. R. Davoren. The formation of adenosine 3',5'-phosphate. In: *Biochemical Aspects of Hormone Action*, ed. A. B. Eisenstein, p. 149. Boston: Little, Brown and Co.



- With Maynard H. Makman. Use of liver adenyl cyclase for assay of glucagon in human gastro-intestinal tract and pancreas. *Endocrinology*, 75:127-34.
- With M. H. Makman. Glucagon in gastrointestinal tract. *Endocrinology*, 75:127 (Abstract).
- With J. S. Handler, R. W. Butcher, and J. Orloff. Vasopressin and theophyllin on concentration of adenosine 3',5'-monophosphate in the intact urinary bladder of the toad. In: *Proceedings of the 56th Annual Meeting, American Society for Clinical Investigation*, Atlantic City, N.J.

## 1965

- Adenyl cyclase and hormone action. In: *Pharmacology of Cholinergic and Adrenergic Transmission*, ed. G. B. Koelle, W. W. Douglas, and A. Carlsson, pp. 317-18. New York: Macmillan.
- With I. Øye and R. W. Butcher. The action of epinephrine and the role of adenyl cyclase system in hormone action. *Recent Progress in Hormone Research*, 21:623-46.
- With J. M. Marsh, R. W. Butcher, and K. Savard. Stimulatory effect of luteinizing hormone (LH) on adenosine 3',5'-monophosphate (cyclic 3',5'-AMP) accumulation in corpus luteum slices. *Fed. Proc.*, 24:320.
- With Richard S. Makman. Adenosine 3',5'-phosphate in *Escherichia coli*. *J. Biol. Chem.*, 240:1309-14.
- With Joel G. Hardman. A cyclic 3',5'-nucleotide phosphodiesterase from heart with specificity for uridine 3',5'phosphate. *J. Biol. Chem.*, 240:3704-5.
- With R. W. Butcher, R. J. Ho, and H. C. Meng. Adenosine 3',5'-monophosphate in biological materials. II. The measurement of adenosine 3',5'-monophosphate in tissues and the role of the cyclic nucleotide in the lipolytic response of fat to epinephrine. *J. Biol. Chem.*, 240:4515-23.
- With J. S. Handler, R. W. Butcher, and J. Orloff. The effect of vasopressin and of theophylline on the concentration of adenosine 3',5'-phosphate in the urinary bladder of the toad. *J. Biol. Chem.*, 240:4524-26.
- With G. A. Robison, R. W. Butcher, I. Øye, and H. Morgan. Epinephrine relation to cyclic 3',5'-AMP in perfused working rat heart. *Mol. Pharmacol.*, 1:168.

1966

- With E. Bueding, R. W. Butcher, J. Hawkins, and A. R. Timms. The effect of epinephrine on adenosine 3',5'-phosphate and hexose-phosphates in intestinal smooth muscle. *Biochim. Biophys. Acta*, 115:173.
- With I. Øye. Effect of epinephrine and other agents on avian erythrocyte membranes. *Biochim. Biophys. Acta*, 127:347-54.
- With G. A. Robison. The role of cyclic 3',5'-AMP in responses to catecholamines and other hormones. *Pharmacol. Rev.*, 18:145-61.
- With R. W. Butcher, J. G. T. Sneyd, and C. R. Park. Effect of insulin on adenosine 3',5'-monophosphate in the rat epididymal fat pad. *J. Biol. Chem.*, 241:1651-53.
- With Joel G. Hardman and James W. Davis. Measurement of guanosine 3',5'-monophosphate and other cyclic nucleotides. Variations in urinary excretion with hormonal state of the rat. *J. Biol. Chem.*, 241:4812-15.
- With John M. Marsh, R. W. Butcher, and Kenneth Savard. The stimulatory effect of luteinizing hormone on adenosine 3',5'-monophosphate accumulation in corpus luteum slices. *J. Biol. Chem.*, 241:5436-40.
- With J. G. T. Sneyd and R. W. Butcher. The effect of insulin on adenosine 3',5'-phosphate (cyclic AMP) in adipose tissue. *Fed. Proc.*, 25:584.

1967

- With G. A. Robison, J. H. Exton, and C. R. Park. Effect of glucagon and epinephrine on cyclic AMP levels in rat liver. *Fed. Proc.*, 26:257.
- With R. W. Butcher, G. A. Robison, and J. G. Hardman. The role of adenosine 3',5'-monophosphate in hormone action. In: *Wirkungsmechanismen der Hormone*, Eighteenth Mosbacher Colloquium, Germany, ed. P. Karlson, pp. 1-29. Berlin: Springer-Verlag.
- Germany, ed. P. Karlson, pp. 1-29. Springer-Verlag.
- With G. A. Robison and R. W. Butcher. Adenyl cyclase as an adrenergic receptor. *Ann. N.Y. Acad. Sci.*, 139:703-23.
- With R. W. Butcher. The effects of the catecholamines, adrenergic blocking agents, prostaglandin E<sub>1</sub>, and insulin on cyclic AMP

levels in the rat epididymal fat pad *in vitro*. Ann. N.Y. Acad. Sci., 139:849-59.

With R. W. Butcher and J. E. Pike. The effect of prostaglandin  $E_1$  on adenosine 3',5'-monophosphate levels in adipose tissue. Proceedings of Second Nobel Symposium. Also in: *Prostaglandins*, ed. Sune Bergström and Bengt Samuelsson, pp. 133-38. New York: Wiley-Interscience.

With J. G. Falbriard and Th. Posternak. Preparation of derivatives of adenosine 3',5'-phosphate. Biochem. Biophys. Acta, 148:99-105.

With W. F. Henion and Th. Posternak. Effects of derivatives on adenosine 3',5'-phosphate on liver slices and intact animals. Biochem. Biophys. Acta, 148: 106-13.

With E. De Robertis, Georgina Rodriguez De Lores Arnaiz, Martha Alberici, and R. W. Butcher. Subcellular distribution of adenyl cyclase and cyclic phosphodiesterase in rat brain cortex. J. Biol. Chem. 242:3487-93.

With D. G. Grahme-Smith, R. W. Butcher, and R. L. Ney. Adenosine 3',5'-monophosphate as the intracellular mediator of the action of adrenocorticotrophic hormone on the adrenal cortex. J. Biol. Chem., 242: 5535-41.

With R. W. Butcher. Relation of cyclic 3',5'-AMP to hormone action. Seventh International Congress of Biochemistry, Tokyo, Japan.

With Robert C. Haynes, Jr. Increased release of amino acids from rat thymus after cortisol administration. Endocrinology, 80:288-96.

With Robert C. Haynes, Jr. Altered metabolism of DNA in rat thymus, an early response to cortisol. Endocrinology, 80:297-301.

#### 1968

With G. A. Robison and R. W. Butcher. Cyclic AMP. In: *Annual Review of Biochemistry*, vol. 37, ed. P. D. Boyer, pp. 149-74. Palo Alto, Calif.: Annual Reviews.

With G. A. Robison and R. W. Butcher. Some aspects of the biological role of adenosine 3',5'-monophosphate (cyclic AMP). Circulation, 3:279-306.

With J. G. Hardman, R. W. Butcher, and A. E. Broadus. The biological role of cyclic AMP. In: *Progress in Endocrinology*, Proceedings of the Symposium on the Third International Con-

- gress of Endocrinology, Mexico, ed. Carlos Gual, Amsterdam: Excerpta Medica Foundation.
- With R. W. Butcher, J. G. Hardman, and G. A. Robison. The role of cyclic AMP in hormone actions. In: *Advances in Enzyme Regulation*, vol 6, ed. G. Weber, pp. 357-89. Oxford, England: Pergamon Press.
- With L. S. Jefferson, J. H. Exton, R. W. Butcher, and C. R. Park. Role of adenosine 3',5'-monophosphate in the effects of insulin and anti-insulin serum on liver metabolism. *J. Biol. Chem.*, 243: 1031-38.
- With R. W. Butcher and Christine E. Baird. Effects of lipolytic and antilipolytic substances on adenosine 3',5'-monophosphate levels in isolated fat cells. *J. Biol. Chem.*, 243:1705-12.

1969

- With R. W. Butcher. The role of cyclic AMP and anti-lipolytic actions of hormones on adipose tissue. In: *Proceedings, International Symposium on Protein and Peptide Hormones*, Liege, Belgium, 1968, ed. M. Margoulies, pp. 150-53. Amsterdam: Excerpta Medica Foundation.
- With R. W. Butcher. The role of cyclic AMP in the steroidogenic actions of ACTH and LH. In: *Proceedings, International Symposium on Protein and Peptide Hormones*, Liege, Belgium, 1968, ed. M. Margoulies, pp. 176-80. Amsterdam: Excerpta Medica Foundation.
- With Joel G. Hardman and James W. Davis. Effects of some hormonal and other factors on the excretion of guanosine 3',5'-monophosphate in rat urine. *J. Biol. Chem.*, 244:6354-62.
- With Joel G. Hardman. Guanyl cyclase, an enzyme catalyzing the formation of guanosine 3',5'-monophosphate from guanosine triphosphate. *J. Biol. Chem.*, 244:6363-70.
- With Eji Ishikawa, Setsuko Ishikawa, and James W. Davis. Determination of guanosine 3',5'-monophosphate in tissues and of guanyl cyclase in rat intestine. *J. Biol. Chem.*, 244:6371-94.
- With Arthur E. Broadus, Robert C. Northcutt, Joel G. Hardman, Neil I. Kaminsky, and Grant W. Liddle. Effects of glucagon on cyclic AMP and cyclic GMP levels in human plasma and urine. *Clin. Res.*, 17:65.

With N. I. Kaminsky, A. E. Broadus, J. G. Hardman, H. E. Ginn, and G. W. Liddle. Effects of glucagon and parathyroid hormone on plasma and urinary cyclic AMP in man. *J. Clin. Invest.*, 48:42a.

With G. A. Robison and J. G. Hardman. Some thoughts on the possible role of cyclic AMP in diabetes. In: *Proceedings of the 1969 Nobel Symposium*, ed. E. Cerasi and R. Luft, pp. 137-54. New York: Wiley.

With G. A. Robison. The role of cyclic AMP in the control of carbohydrate metabolism. (Banting Memorial Lecture.) *Diabetes*, 18: 797.

## 1970

With G. A. Robison. On the relation of cyclic AMP to adrenergic receptors and sympathin. Symposium on Cell Biology and Cytopharmacology, Milan, Italy. (The Sollmann Oration.) *Pharmacologist*, 12:33-37.

With G. A. Robison and R. W. Butcher. On the relation of hormone receptors to adenylyl cyclase. In: *Fundamental Concepts in Drug-Receptor Interactions*, Proceedings of Buffalo-Milan Symposium on Molecular Pharmacology, ed. J. F. Danielli, J. F. Moran, and D. J. Triggle, p. 59. New York: Academic Press.

With J. A. Beavo, N. L. Rogers, O. B. Crofford, J. G. Hardman, and E. V. Newman. Effects of xanthine derivatives on lipolysis and on adenosine 3',5'-monophosphate phosphodiesterase activity. *Mol. Pharmacol.*, 6:597-603.

With Arthur E. Broadus, Neil I. Kaminsky, Joel G. Hardman, and Grant W. Liddle. Kinetic parameters and renal clearances of plasma adenosine 3',5'-monophosphate in man. *J. Clin. Invest.*, 49:2222-36.

With Arthur E. Broadus, Neil I. Kaminsky, Robert C. Northcutt, Joel G. Hardman, and Grant W. Liddle. Effects of glucagon on adenosine 3',5'-monophosphate and guanosine 3',5'-monophosphate in human plasma and urine. *J. Clin. Invest.*, 49:2237-45.

With Neil I. Kaminsky, Arthur E. Broadus, Joel G. Hardman, Douglas J. Jones, Jr., John H. Ball, and Grant W. Liddle. Effects of parathyroid hormone on plasma and urinary adenosine 3',5'-monophosphate in man. *J. Clin. Invest.*, 49:2387-95.

With G. A. Robison and M. J. Schmidt. On the development and

- properties of the brain adenylyl cyclase system. In: *Advances in Biochemical Psychopharmacology*, vol. 3, ed. P. Greengard and E. Costa, pp. 11-30. New York: Raven Press.
- With J. A. Beavo and Joel G. Hardman. Hydrolysis of cyclic guanosine and adenosine 3',5'-monophosphate by rat and bovine tissue. *J. Biol. Chem.*, 245:5649-55.
- With G. A. Robison. Sympathin E, Sympathin I and the intracellular level of cyclic AMP. *Circulation Research*, Supplement I to vols. 26 and 27, pp. 1-147 and 1-161.
- With Roger A. Johnson, Joel G. Hardman, and Arthur E. Broadus. Analysis of adenosine 3',5'-monophosphate with luciferase luminescence. *Analytical Biochemistry*, 35:91-97.
- With J. A. Beavo, N. L. Rogers, O. B. Crofford, J. G. Hardman, and E. V. Newman. Effects of xanthine analogs on lipolysis and on cyclic nucleotide phosphodiesterase activity. *Clin. Res.*, 18:51.
- With A. E. Broadus, N. I. Kaminsky, J. G. Hardman, and G. W. Liddle. Kinetic parameters and renal clearances of plasma cyclic AMP and cyclic GMP in man. *Clin. Res.*, 18:73.
- With J. H. Ball, N. I. Kaminsky, A. E. Broadus, J. G. Hardman, and G. W. Liddle. Effects of catecholamines and adrenergic blocking agents on cyclic nucleotides in human plasma. *Clin. Res.*, 18:336.
- With N. I. Kaminsky, J. H. Ball, A. E. Broadus, J. G. Hardman, and G. W. Liddle. Hormonal effects on extracellular cyclic nucleotides in man. *Clin. Res.*, 18:528.
- With J. P. Gray, J. G. Hardman, and T. Bibring. High guanylyl cyclase activity in sea urchin spermatozoa. *Fed. Proc.*, 29:608.
- With J. A. Beavo and J. G. Hardman. Cyclic GMP and cyclic AMP hydrolysis by phosphodiesterase preparation from beef and rat tissues. *Fed. Proc.*, 29:616.
- With N. I. Kaminsky, J. H. Ball, A. E. Broadus, J. G. Hardman, and G. W. Liddle. Hormonal effects on extracellular cyclic nucleotides in man. *Transactions of the Association of American Physicians*, 83:235-44.
- On the biological role of cyclic AMP. *Journal of the American Medical Association*, 214:1280-88.
- With R. W. Butcher and G. A. Robison. The role of cyclic AMP in certain biological control systems. In: *Ciba Foundation Symposium on Control Processes in Multicellular Organisms*, ed.

G. E. W. Wolstenholme and J. Knight, pp. 64-76. London: J. and A. Churchill.

1971

- With W. D. Patterson and J. G. Hardman. Metabolism of cyclic nucleotides in rat blood. *Fed. Proc.*, 30:220.
- With R. A. Johnson. Fluoride inhibition of detergent dispersed brain adenylyl cyclase. *Fed. Proc.*, 30:220.
- With J. H. Exton, Joel G. Hardman, T. F. Williams, and C. R. Park. Effects of guanosine 3',5'-monophosphate on the perfused rat liver. *J. Biol. Chem.*, 246:2658-64.
- With J. A. Beavo and Joel G. Hardman. Stimulation of adenosine 3',5'-monophosphate hydrolysis by guanosine 3',5'-monophosphate. *J. Biol. Chem.* 246:3841-46.
- With J. G. Hardman and G. A. Robison. Cyclic nucleotides. *Annual Review of Physiology*, 33:311-36.
- With G. A. Robison and R. W. Butcher. *Cyclic AMP*. New York: Academic Press.
- With Ren-Jye Ho. Formation and release of a hormone antagonist by rat adipocytes. *J. Biol. Chem.*, 246:6822-27.
- With J. H. Exton, G. A. Robison, and C. R. Park. Studies on the role of adenosine 3',5'-monophosphate in the hepatic actions of glucagon and catecholamines. *J. Biol. Chem.*, 246:6166-77.
- With R. J. Ho. Occurrence of a hormone antagonist in rat epididymal fat cells. *Physiologist*, 14:163.
- With G. A. Robison. Cyclic AMP and the function of eukaryotic cells: An introduction. *Ann. N.Y. Acad. Sci.*, 185:5-9.
- With J. G. Hardman, J. A. Beavo, J. P. Gray, T. D. Chrisman, and W. D. Patterson. The formation and metabolism of cyclic GMP. *Ann. N.Y. Acad. Sci.*, 185:27-35.
- With A. E. Broadus, Joel G. Hardman, Neil I. Kaminsky, John H. Ball, and Grant W. Liddle. Extracellular cyclic nucleotides. *Ann. N.Y. Acad. Sci.*, 185:50-66.
- With J. A. Beavo, N. L. Rogers, O. B. Crofford, C. E. Baird, J. G. Hardman, and E. V. Newman. Effects of phosphodiesterase inhibitors on cyclic AMP levels and on lipolysis. *Ann. N.Y. Acad. Sci.*, 185:129-36.
- With G. A. Robison. On the relation of cyclic AMP to adrenergic receptors and sympathin. In: *Advances in Cytopharmacology*,



vol. 1, ed. F. Clement and B. Ceccarelli, pp. 263-72. New York: Raven Press.

## 1972

- With John H. Ball, Neil I. Kaminsky, Joel G. Hardman, Arthur E. Broadus, and Grant W. Liddle. Effects of catecholamines and adrenergic-blocking agents on plasma and urinary cyclic nucleotides in man. *J. Clin. Invest.*, 51:2124-29.
- Studies on the mechanism of hormone action. (Nobel Lecture.) In: *Les Prix Nobel en 1971*, pp. 240-57. Stockholm: P. A. Norstedt and Soner. Also in: *Science*, 177:401-8.
- With R. J. Ho and J. D. Bomboy. Site of action of a hormone antagonist from adipocytes. *Physiologist*, 15:169.
- With J. H. Exton and G. A. Robison. Glucagon and cyclic AMP. In: *Handbook of Physiology*, p. 425. Washington, D.C.: American Physiology Society.
- With J. G. Hardman, T. D. Chrisman, J. P. Gray, and J. L. Sudath. Guanylate cyclase: Alteration of apparent subcellular distribution and activity by detergents and cations. In: *Proceedings of the Fifth International Congress of Pharmacology*. Basel, Switzerland: S. Karger.

## 1973

- With C. E. Zeilig, R. A. Johnson, and D. L. Friedman. Studies on the role of cyclic AMP in HeLa cells. In: *Proceedings, Fifth International Congress on Pharmacology*, San Francisco, California, ed. George G. Acheson. Basel, Switzerland: Karger.
- With R. J. Ho and J. D. Bomboy. Local feedback regulation of cyclic nucleotides (S1-2). In: *Endocrinology*, ed. R. O. Scow, p. 352. New York: American Elsevier.
- With R. J. Ho, J. D. Bomboy, and H. K. Wasner. Elevation of cAMP levels and subsequent formation of antihormone activity in adipocytes of rat and hamster. *Fed. Proc.*, 535:963.
- With R. A. Johnson and S. J. Pilgis. Properties of detergent dispersed adenylate cyclase from liver plasma membrane. In: *Ninth International Congress of Biochemistry*, Stockholm, p. 258.
- With R. J. Ho, H. K. Wasner, and J. D. Bomboy. A feedback inhibitor of adenylate cyclase. In: *Ninth International Congress of Biochemistry*, Stockholm, p. 355.



- With Andre Peytremann, Wendall E. Nicholson, Grant W. Liddle, and Joel G. Hardman. Effects of methylxanthines on adenosine 3',5'-monophosphate and corticosterone in the rat adrenal. *Endocrinology*, 92:525-30.
- With G. Schultz, J. G. Hardman, K. Schultz, and J. W. Davis. A new enzymatic assay for guanosine 3':5'-cyclic monophosphate and its application to the ductus deferens of the rat. *Proc. Natl. Acad. Sci. USA*, 70:1721-25.
- With G. Schultz, J. G. Hardman, K. Schultz, and C. E. Baird. The importance of calcium ions for the regulation of guanosine 3':5'-cyclic monophosphate levels. *Proc. Natl. Acad. Sci. USA*, 70:3889-93.
- With J. G. Hardman and G. Schultz. Cyclic GMP: Vestige or another intracellular messenger? In: *Cyclic AMP, Cell Growth, and the Immune Response*, ed. W. Braun, L. M. Lichtenstein, and C. W. Parker, pp. 223-36. New York: Springer-Verlag.
- With G. Schultz and J. G. Hardman. Cyclic nucleotides and smooth muscle function: In: *Asthma, Physiology, Immunopharmacology and Treatment*, ed. K. F. Austen and L. M. Lichtenstein, pp. 123-37. New York: Academic Press.
- With Roger A. Johnson. Detergent-dispersed adenylate cyclase from rat brain. *J. Biol. Chem.*, 248:5114-21.
- With C. A. Sutherland, G. Schultz, and J. G. Hardman. Effects of vasoactive agents on cyclic nucleotide levels in pig coronary arteries. *Fed. Proc.*, 32:733.
- With G. Schultz, J. G. Hardman, and L. I. Hurwitz. Importance of calcium for the control of cyclic GMP levels. *Fed. Proc.*, 32:773.
- With R. A. Johnson. Effect of chelators on detergent dispersed brain adenylate cyclase. *Fed. Proc.*, 32:568.
- With R. J. Ho, J. D. Bomboy, and H. K. Wasner. Elevation of cAMP levels and subsequent formation of antihormone activity in adipocytes of rat and hamster. *Fed. Proc.*, 32:535.
- My life and cyclic AMP. (The Fourth Feodor Lynen Lecture, ed. R. Park.) In: *Protein Phosphorylation in Control Mechanisms*, vol. 5, pp. 1-30. New York: Academic Press.

1974

- With W. D. Patterson and J. G. Hardman. A comparison of cyclic nucleotide levels in plasma and cells of rat and human blood.

Endocrinology, 95:325-27.

With R. J. Ho. Inhibition of adenylate cyclase by a factor isolated from human plasma. Fed. Proc., 33:1526.

1975

With R. J. Ho, J. D. Bomboy, and H. K. Wasner. Preparation and characterization of a hormone antagonist from adipocytes. In: *Methods in Enzymology*, vol. 38, ed. S. P. Colowick and N. O. Kaplan, pp. 431-38. New York: Academic Press.

With R. A. Johnson. Preparation of particulate and detergent dispersed adenylate cyclase from brain. In: *Methods in Enzymology*, vol. 38, ed. S. P. Colowick and N. O. Kaplan, p. 135. New York: Academic Press.

With Ren-Jye Ho. Action of feedback regulator on adenylate cyclase. Proc. Natl. Acad. Sci. USA, 72:1773-77.