The 1977 Nobel Prize in Physiology or Medicine

It is doubtful that any two discoveries in the last 40 or more years have had as great an impact on basic and clinical endocrinology as the development of radioimmunoassays (RIA's) and the discovery that the hypothalamic region of the brain secretes hormones that control the secretion of hormones by the anterior pituitary gland. In recognition of these achievements, the 1977 Nobel Prize for Physiology or Medicine has now been awarded to Rosalyn Yalow for her contribution to the development of RIA's and to Roger Guillemin and Andrew Schally for their work on the hypothalamic hormones.

The two discoveries are related since the development of RIA's has permitted the isolation and chemical characterization of hypothalamic hormones to proceed at a much faster pace than would be possible by bioassays, which are much less sensitive. RIA's can detect hormones in nanogram or picogram quantities and therefore can be used to measure hormones in the blood, which was not possible by earlier bioassay methods. RIA's also have become increasingly important in biology and medicine in the measurement of such diverse substances as peptide and steroid hormones, digitoxin, cyclic AMP (adenosine 3′,5′-monophosphate), morphine, and, most recently, the endogenous brain opiates. Future possibilities for additional uses of RIA's seem limitless.

The increasing use of these RIA's has led to new technological developments in gamma counters, scintillation counters, pipetting devices, and other equipment used in this technique. At the present time many hospitals use RIA's routinely for diagnosis of thyroid diseases, diabetes, growth disorders, hypertension, reproductive failures, hormone-secreting cancers, and other endocrine-related disorders.

Unlike bioassays that measure hormones by the physiological response of a tissue to a hormone, RIA's are based on the competition between radioactive and native hormones for high affinity antibody binding sites. The labeled hormone (^{125}I or ^{131}I) competes with unlabeled hormone (the hormone to be assayed) for binding sites on the specific antibody.

It is impossible to write about the work of Rosalyn Yalow without also writing about Solomon Berson, since they worked together as a team until the untimely death of Berson in 1972 at the age of 54. Beginning in the early 1950's, while investigating the causes of insulin resistance in diabetics, Berson and Yalow discovered that diabetics treated with insulin had antibodies to insulin. When they first attempted to publish this important observation, it was rejected on the belief that insulin was incapable of inducing antibodies. Berson and Yalow then established that the addition of increasing amounts of unlabeled insulin (under in vitro conditions) to a mixture of insulin antibody and labeled insulin resulted in displacement of the labeled insulin. This discovery formed the basis for the first RIA, that of insulin. Since then, RIA's have been developed for other hormones and have become a practical tool in basic and clinical research. Berson and Yalow also fully developed the theoretical and mathematical principles underlying RIA's.

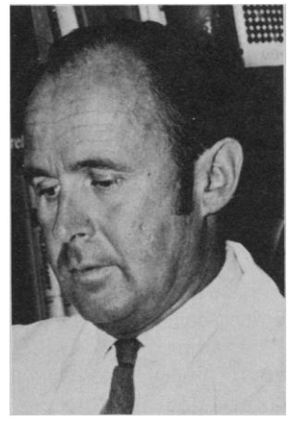
Yalow was born and raised in New York City, and received a Bachelor's degree at Hunter College. She earned a Ph.D. in physics at the University of Illinois, where she also met and married a physicist. The Yalows returned to New York, and Rosalyn took a position as a physicist in the Radioisotope Service of the Veterans Administration Hospital in the Bronx. There she began her collaborative work with Solomon Berson, also a native New Yorker who obtained his M.D. degree from New York University College of Medicine. Both were brilliant and critical investigators and complemented each other in many ways—Berson with his vast clinical knowledge and Yalow with her extensive knowledge of physics, mathematics, and chemistry.

Yalow is now Senior Medical Investigator at the Veterans Administration Hospital and Research Professor in the Department of Medicine at Mount Sinai School of Medicine. Although her two chief preoccupations are her family (she has two children) and her work, she is also a gifted and incisive lecturer, is an adviser to important committees in the medical sciences, and is a member of the editorial boards of several journals. Together with Berson she was responsible for training and advising many investigators throughout the world in the use of RIA's. She has received many honors prior to the award of the Nobel Prize.

The foundation for the isolation and structural determination of some hypothalamic hormones, for which Roger Guillemin and Andrew Schally each were awarded the Nobel Prize, was established by an English anatomist, Geoffrey Wingfield Harris, who died in 1971 at the age of 58 years. More than anyone else, Harris made the original contributions and assembled the evidence that established that the hypothalamic portion of the brain controlled pituitary function. It is via the nervous connections to the hypothalamus that external and internal environmental stimuli can influence pituitary hormone secretion.

The hypothalamus lies at the base of the brain and is attached to the pituitary gland by a stalk. Although the posterior lobe of the pituitary is nervous tissue and is part of the brain, the anterior and intermediate lobes of the pituitary originate from the roof of the mouth. The anterior pituitary (AP), which secretes at least six important hormones, has no sig-

Roger Guillemin



Andrew Schally

Rosalyn Yalow

nificant nervous connections to the brain, and the only pathway between the two is the network of portal blood vessels by which blood flows to the pituitary from the hypothalamus (Fig 1).

Harris and his collaborators showed that if the portal vessels were sectioned and a plate was inserted between the cut ends to prevent regeneration, there was a marked depression of AP function. From this he developed the portal vessel "chemotransmitter hypothesis," which stated that the hypothalamus secreted neurohormones that traversed the portal vessels to regulate secretion of AP hormones.

Harris's publications had a profound influence on endocrinologists and other scientists. A few were inspired to tackle the formidable problem of isolating those putative hypophysiotropic hormones from the hypothalamus. Among them were Roger Guillemin and Andrew Schally. The first of these substances to be demonstrated in the hypothalamus was corticotropin releasing factor (CRF), first reported by Saffran and Schally, and independently by Guillemin in 1955. CRF stimulates release of adrenocorticotropin (ACTH) from the AP, which in turn promotes adrenal cortical function.

It was Saffran and Schally who named the first putative hypothalamic hormone "corticotropin releasing factor," and since then the terms "releasing factor" or "release inhibiting factor" have been applied to chemically uncharacterized hypothalamic hypophysiotropic substances. The terms "releasing hormone" or "release inhibiting hormone" have been reserved mainly for those hypothalamic factors of known chemical structure. Evidence for the existence of the other hypothalamic factors that control AP hormone secretion was forthcoming in the 1960's.

The chemical identification of the hypothalamic releasing and inhibiting factors has been and remains a laborious task, and to date only the structures of three of these are known. One explanation for this is that these factors are present in the hypothalamus in only nanogram amounts. In order to collect a sufficient amount of hypothalamic tissue to extract these small quantities of hormones, it was necessary for Guillemin and Schally to enlist the cooperation of numerous slaughterhouses. They quickly removed the brains from freshly slaughtered sheep and swine, and rapidly dissected the hypothalamus from the brains before the labile hormones degraded. This represented a problem of organization, logistics, and a considerable expenditure of research funds.

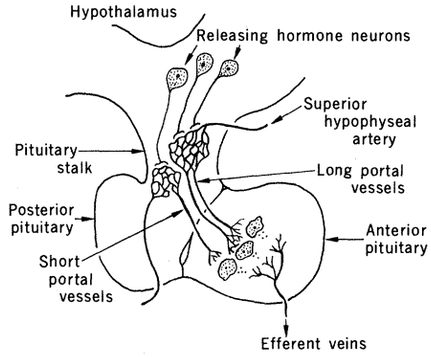


Fig. 1. Diagrammatic illustration of neural control of the anterior pituitary gland.

From hundreds of thousands of swine and sheep hypothalami weighing many kilograms, Schally and Guillemin were able to extract only a few milligrams of partially purified hormone. From these minute quantities of hormone, they made structural determinations. Guillemin has estimated that, on the basis of weight, the cost of isolating the first milligram of pure sheep thyrotropin releasing hormone (TRH) was two to five times more expensive than a kilogram of moon rock carried to earth from the Apollo 13 mission. The costs for the research by these two men were met mainly by the National Institutes of Health and the Veterans Administration.

TRH Structure Determined

After 7 years of work on the structural analysis of CRF (its structure is still unknown), Schally and Guillemin decided to turn their attention to the isolation of thyrotropin releasing factor (TRF), the substance that stimulates release, from the AP, of thyrotropin, which in turn regulates release of the thyroid hormones. After 7 or 8 years of additional work they were successful in this endeavor, and in the latter half of 1969, Burgus, Guillemin, Schally, and collaborators announced the structure of TRH. TRH was found to be a simple tripeptide amide, pyroglutamylhistidinylprolyl amide. By 1966, Schally had found that his purified TRF preparation consisted of three amino acids in equimolar amounts—histamine, proline, and some form of glutamic acid. The final chemical identification of TRH represented a dramatic milestone in the history of neuroendocrinology, and essentially proved the validity of Harris's "chemotransmitter hypothesis." Indeed, Harris was thrilled to hear of this discovery and warmly congratulated both men.

Synthetic TRH has the same potency as endogenous TRH. TRH has been shown to have the same structure in all species tested to date, including man, and is active orally as well as by injection. Also, TRH has proved to be useful for testing pituitary and thyroid functions in human patients, without producing serious side effects. TRH was found by A. H. Tashjian of Harvard to release prolactin and in some cases growth hormone. The other hypothalamic hormones of known structure, luteinizing hormone releasing hormone (LHRH) and somatostatin, similarly have been shown to release more than one AP hormone. Although TRH is more concentrated in the hypothalamus, it is present throughout the brain. There is evidence that TRH may serve as a neurotransmitter and thereby influence behavior.

The knowledge gained from the work on TRH made it possible to determine the structure of LHRH, identified by Schally and his colleagues in 1971 and shortly thereafter in Guillemin's laboratory. LHRH is a decapeptide and, like TRH, the amino-terminal is a pyroglutamic acid residue, and the carboxyl-terminal has a substituted amide group. S. M. McCann and Harris independently reported the first evidence for the presence of luteinizing hormone releasing factor (LRF) in 1960. In 1964 M. Igarashi and McCann, as well as J. C. Mittler and J. Meites, independently published the first evidence for follicle stimulating hormone (FSH) releasing factor (FRF).

Until the isolation of the decapeptide LHRH, it was believed that there were separate factors controlling LH and FSH release. However, no separate releasing hormones for the two gonadotropins have been demonstrated thus far. LHRH, acting on the pituitary, causes the release of both LH and FSH from the AP to control the functions of both the ovaries and testes. Therefore, LHRH participates in the regulation of the menstrual cycle in primates and the estrous cycles in other mammals. It also indirectly controls spermatogenesis and male sex hormones (for example, testosterone) secretion by the testes. Like TRH, LHRH acts rapidly when administered to man and animals to release LH and FSH. Many analogs of LHRH have been synthesized, some of which are more potent than the native LHRH. A few analogs that inhibit LH and FSH release have been synthesized. These may prove useful as contraceptive agents. There also are reports that LHRH, like TRH, influences behavior.

The third hormone of the hypothalamus to be isolated in pure form was growth hormone release inhibiting factor (GIF), first demonstrated to be present in

the hypothalamus by L. Krulich and McCann in 1968. Guillemin and his colleagues determined the structure of GIF to be a tetradecapeptide in 1973 and named it somatostatin. There also is a growth hormone releasing factor (GRF) in the hypothalamus, first reported by R. Deuben and Meites in 1963–64, but its structure has not been determined. Somatostatin inhibits the ability of TRH to release thyrotropin, and surprisingly enough, to inhibit glucagon and insulin secretion by the pancreas, and gastrin and HCl secretion by the stomach. There is evidence that somatostatin is also produced in the pancreas and gastrointestinal tract. There is great interest in the possibility that somatostatin may be useful for treating diabetes and peptic ulcers as well as some growth disorders.

Guillemin was born in 1924 in Dijon, France. He earned the M.D. degree and served in the French Resistance during the German occupation in World War II. In 1948, after hearing a lecture by Hans Selye on stress, he asked Selye whether he could work in his laboratory. Selye agreed and Guillemin went to Montreal in 1948 and there he collaborated with Claud Fortier, who is now at Laval University in Quebec City, on control of ACTH release. In Selye's laboratory, Guillemin learned the fundamentals of experimental endocrinology. After receiving the Ph.D. degree in 1952, he accepted a position in the Department of Physiology at Baylor University Medical School, where he remained for almost 20 years and did the work that culminated in the isolation and structural characterization of TRH.

For a period of 3 years, from 1960 to 1963, Guillemin served as Associate Director of the Laboratory for Experimental Endocrinology at the College de France under the chairmanship of Robert Courrier, commuting between Paris and Houston. While in France he managed to collect several million fragments of sheep hypothalami and published papers in French and English journals dealing with work on TRF and other hypothalamic factors. The principal chemist who collaborated with Guillemin at Baylor was Roger Burgus, who has remained with him to the present time. Guillemin left Baylor in 1972 for the Salk Institute at La Jolla, California, where he is now associate director. He now lives with his wife and children in a home filled with a large collection of artifacts from Mexico and other Latin American countries, and is known as a connoisseur of wines and good food.

Schally was born in Wilno, Poland, in 1926. He and his family fled from Poland to England in 1939. Schally received a Bachelor's degree from the University of London and obtained his first research experience at the prestigious National Institute for Medical Research in Mill Hill, London, between 1949 and 1952. From there he went to McGill University in Montreal, where he earned a Ph.D. degree in biochemistry with Murray Saffran working on the extraction of CRF from the hypothalamus. After obtaining his degree in 1957, Schally moved to Baylor University in Houston to collaborate with Guillemin on the chemical identification of CRF. After 5 years he left to work independently at the Veterans Administration Hospital in New Orleans, and became a Senior Medical Investigator there in 1973. He has at the same time been on the staff of the Department of Medicine at Tulane University School of Medicine since 1962 and is now a professor.

Among the most prominent collaborators of Schally in New Orleans have been Akira Arimura, Abba Kastin, and Cyril Bowers of Tulane University School of Medicine and the Veterans Administration Hospital. Schally is a person of ambition and dedication, and has set an example for long and hard work in his laboratory that would be difficult to match. He and his colleagues have published more than 850 papers since 1962, and he has received many honors prior to the announcement of the Nobel Prize. Proficient in Spanish and Portuguese, Schally is a popular lecturer in Latin America and Spain. His wife is a physician from Brazil who has collaborated with him in clinical testing of hypothalamic hormones.

Finally, it is regrettable that there is no provision for awarding Nobel Prizes posthumously, to recently deceased, outstanding investigators, such as Berson and Harris, who have contributed greatly to an area recognized by the Nobel Committee. Possibly in such cases a medal or certificate could be presented to the institute in which they worked, which would be forever cherished by their families, colleagues, friends, and benefactors.

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Protein Degradation: Putting the Research Together

For many years, biologists have studied how proteins are synthesized and how cells control which proteins are made. The other side of the coin, however, is the breakdown of proteins—a subject whose importance is only slowly coming to be appreciated. Within the past few years, researchers have begun to realize that the regulation of protein breakdown in cells has important implications for problems in genetics, cell biology, endocrinology, and clinical medicine. They are now laying the foundation for studies of how and why proteins are degraded. Of particular interest are discoveries at several laboratories that suggest there may be more than one way to control the breakdown of proteins.

Nearly all proteins are broken down and resynthesized many times within the life of a cell. The average rates at which a cell's proteins are degraded, however, vary with physiological conditions. And different proteins last for vastly different lengths of time before they are destroyed. Some are degraded after minutes, some after hours, and some after days. Evidence is accumulating that cellular controls of average breakdown rates and of the rates at which individual proteins are degraded are both biologically and clinically important.

Since 1951, it has been known that protein degradation is tied to growth control in bacteria. When *Escherichia coli* cells are rapidly growing, they degrade proteins very slowly. When the cells are starved for essential nutrients, their growth nearly ceases and their rates of protein degradation increase severalfold. Moreover, it seems that bacteria use the same signals to cease their growth and to increase their rates of protein degradation. Now it seems likely that correlations between rates of growth and protein degradation are not limited to bacteria. Within the past few years, a number of investigators have found that changes in average breakdown rates are a crucial part of growth control in mammalian cells, tissues, and organs.

Michael Warburton and Brian Poole of Rockefeller University recently reported that there is a high inverse correlation