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Gastrointestinal Hormones

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Abstract

Solomon A. Berson, M.D., the first Murray M. Rosenberg Professor and Chair of the Department of Medicine at Mount Sinai from 1968 until his death in 1972, and Rosalyn S. Yalow, Ph.D., 1977 Nobel Laureate in Medicine or Physiology and Solomon A. Berson Distinguished Professor-at-Large, brought meticulous quantitation and new vistas to all of clinical medicine and biomedical science through the application of their technique of radioimmunoassay. I was fortunate to know and work with them for many years. In 1972, while I was an NIH Fellow in gastroenterology at Mount Sinai, Dr. Berson suggested that I pursue my research in their laboratory at the Bronx Veterans Administration Hospital. Dr. Berson died one month after I began my research in the Bronx. Yalow and Berson had already discovered big gastrin (G-34), but much work with gastrin remained to be done. Challenging work with secretin, cholecystokinin, and a host of other gut peptides, would keep the Mount Sinai group at the forefront of this exciting field. **Key Words:** Radioimmunoassay, gastrointestinal hormones, regulatory peptides, gastrin, secretin, cholecystokinin.

“Ros Yalow and Sol Berson were the Toscaninis of the field. . . . Most others were, if not organ-grinders, followers. . . .”

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Introduction

IN 1902, conceptual and practical endocrinology began in London when Bayliss and Starling discovered secretin in the duodenal mucosa of a dog. They coined the term “hormone,” suggesting that there were more chemical messengers to be found. Within a year, Eddins discovered gastrin in the mucosa of the gastric antrum. This was a major advance in medical knowledge. And nearly sixty years later, a discovery made by members of

the Mount Sinai community would revolutionize endocrinology, as well as gastroenterology, hematology, virology, clinical pharmacology, oncology, and virtually every other area of medicine and biomedical science.

Berson and Yalow

The technique of radioimmunoassay (RIA) was introduced in 1959 by Solomon A. Berson, M.D., and Rosalyn S. Yalow, Ph.D. It is a method that can detect and measure extremely low concentrations of virtually any substance. They applied it first to the study of insulin, demonstrating that patients with Type 2 diabetes are resistant to its action. Subsequently, they and their younger colleagues studied many hormones and made the first RIA to detect an antigen, then known as Australian antigen, and now known to be a component of Hepatitis B virus. During their long association with Mount Sinai, their work was carried out in the Radioisotope Service of the Bronx Veterans Administration Hospital (VA).

Solomon Berson completed his residency training in internal medicine at the Bronx VA in 1950, and after a brief sojourn in private practice, he joined Rosalyn Yalow in the Radioisotope

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Service during the same year. Rosalyn had established the service in 1947. She was a nuclear physicist and had never taken a course in biology. At that time, Sol had scant background in research, but by 1968, he was appointed to serve as the Murray M. Rosenberg Professor and Chair of the Department of Medicine at the Mount Sinai School of Medicine. His death in 1972 ultimately cut short a brilliant career and eligibility for the Nobel Prize. In 1977, Dr. Yalow was awarded the Nobel Prize in Medicine or Physiology.

The history of gastrointestinal hormones at Mount Sinai is the story of Berson and Yalow, and the following is a brief summary (2). As this is a historical rather than a scientific review, the emphasis is on the major figures within the context of Mount Sinai. Technical reviews of the work involving gastrointestinal hormones, especially the contributions of members of the Mount Sinai community, can be found elsewhere (3, 4).

In 1950, the High Flux Isotope Reactor at Oak Ridge Tennessee was firing neutrons into the nuclei of atoms. It was often said that a physicist looking into the "swimming pool" reactor could see the blue glow of the neutrons streaming out and believe that the intellectual creations of Albert Einstein, Hans Bethe, and Enrico Fermi were the greatest works of art of the century. Nuclear physics had been Ros' first love. Fermi inspired her when she heard him speak in 1939, along with many others "hanging from the rafters in Room 301 of the Pupin Laboratory at Columbia University." However, with her new Ph.D., she joined IT&T, in 1945, working outside the field she loved. Then, when the soldiers returned from the war, she found herself replaced by a man. She took a tip from her husband, Aaron Yalow, who was working as a medical physicist at Montefiore Hospital, and went to work creating a nuclear medicine service at the Bronx VA. But Ros needed a bright physician to work with, and the Chief of Medicine at the VA, Dr. Bernard Straus, suggested Sol Berson. Berson had recently opened a practice on Long Island, which Straus regarded as a mistake. When the young nuclear physicist came looking for a research partner, Straus got Berson and Yalow together and, through his department, funded their early efforts.

Their work first grew from the circumstance of the availability of radioisotopes. When these two individuals, one with no background or knowledge of biology or medicine and the other with no knowledge of research or radioisotopes, joined force, something just "clicked." They worked with an intensity beyond passion, with lit-

tle regard for themselves, and little regard for its effects upon those around them.

Radioimmunoassay

By 1955, Yalow and Berson were already well known and respected for their quantitative work in the areas of iodine and albumin metabolism. Then came their ability to measure peptide hormones, the proteins that act as chemical messengers and regulate body functions. Hormones like insulin, glucagon, growth hormone, parathormone, ACTH, gastrin, secretin, and cholecystokinin (CCK), some of which circulate in the blood at concentrations as low as 10^{-12} M, equivalent to the concentration of one teaspoon of sugar dissolved in a lake which is sixty-two miles long, sixty-two miles wide, and thirty feet deep. This was quite an accomplishment. And they were quick to realize that RIA could be applied to a vast array of endogenous and exogenous substances, because antigenicity, the ability to elicit an antibody response, as they had shown for insulin, was a far more general characteristic of molecules than had previously been thought. The commercial possibilities for RIA were enormous. In fact, RIAs have made fortunes for commercial laboratories and producers of assay kits.

"We never thought of patenting RIA," Yalow once told me, looking down her nose as though a dead fish had been placed before her. "Of course, others suggested this to us, but patents are about keeping things away from people for the purpose of making money. We wanted others to be able to use RIA. Now some people assume that I'm sorry, but I'm not. Anyway, we had no time for such nonsense."

Suddenly, physicians and researchers wanted to go meet and learn from the masters. And they came from everywhere: Guillemin, Rosselin and Assan from Paris; Isidori and Negri from Rome; Samols and Hartog from London; Thomopoulou from Athens; Devlin from Dublin; Gomez-Mont from Mexico; Scott from Auckland; McGarry, McKenzie, Colle and Schucher from Montreal; Beraud from Lausanne; Brauman from Brussels; Pimstone from Capetown; and Jadresic from Santiago de Chile, to mention just a few.

The guests would stay for a few days, or a week, or a month, and leave The Bronx with the secrets of RIA, with hands-on experience using the new method that was changing the world, and with the blessings of the masters. Many also took with them some of Berson and Yalow's precious antisera, the small volumes of guinea pig plasma containing specific antibody molecules, to enable

them to begin to work quickly when they got home; for many it was the gift of a new direction in their work. All returned with stories of what it was like to be around Berson and Yalow, where concepts and approaches to problems flew between them and around the lab like tennis balls. "It was like bouncing ideas around," say many of the people who worked in the laboratory. It was the free exchange of ideas and the opportunity to participate which excited the visitors and fellows alike. Berson and Yalow were overpowering in the defense of their data when controversy arose, but they did not try to stifle the competition. They did not try to sell their antisera, and the suggestion that they patent their methods, as Yalow indicates, was met with frank derision. It truly can be said that they gave of their knowledge and materials and bade the scientific community to go forth and multiply. It is also true that they were intensely competitive, disinclined to collaborate with others, and frequently harsh and unforgiving in their criticism.

Among those who came to visit Berson and Yalow was the outstanding gastrointestinal physiologist and doyen of gastrointestinal hormones, Morton Grossman. Grossman was a good friend of Henry Janowitz and both had studied with Andrew Ivy, the discoverer of cholecystokinin. It was Mort Grossman who influenced Sol to enter the field of gastrointestinal hormones, and he introduced Ros and Sol to Rod Gregory, Michlos Bodansky and Victor Mutt, the researchers who purified gastrin, secretin, and cholecystokinin.

Gastrin

In 1970, Yalow and Berson reported their assay for gastrin and discovered "big gastrin," or G-34, the 34-amino-acid gastrin peptide (5). The major discovery that gastrin is found in tissues and blood in both 17- and 34-amino-acid forms, energized the gastrointestinal hormone research community. They brought both their technical expertise and their cutting edge understanding of hormone physiology to the study of gastrointestinal peptides, and they shared these, along with their gastrin antisera, with many individuals who would advance the field. Indeed, so influential was their finding of heterogeneous forms of plasma gastrin that it inspired some to see "micro-heterogeneity," or a plethora of innumerable gastrin forms. Nonetheless, their view that G-17 and G-34 are the predominant biologically active gastrin peptides mediating meal-stimulated acid secretion prevailed.

Since the major stimulus of gastric acid secretion is the ingestion of a meal, Berson and Yalow performed extensive studies of meal-stimulated

gastrin release. Their findings uncovered a fundamental pathophysiologic mechanism associated with duodenal ulceration. Acidification of the antral portion of the stomach causes "feedback inhibition" of gastrin release. Since groups of duodenal ulcer patients have lower mean fasting gastric pH and higher rates of meal-stimulated acid secretion when compared with normals, they hypothesized that mean fasting plasma gastrin concentrations and integrated meal-stimulated gastrin release should be lower in groups of duodenal ulcer patients. Their observation that groups of duodenal ulcer patients had normal mean fasting gastrin levels and greater integrated meal-stimulated gastrin release indicated that, as a group, duodenal ulcer patients have relatively insensitive acid feedback inhibition of gastrin release (3). They further demonstrated that when acid feedback inhibition becomes grossly insensitive, a patient may display pathophysiology that mimics the autonomous hypergastrinemia of a gastrinoma (3, 6). They called this condition "non-tumorous hypergastrinemic hyperchlorhydria," admittedly a bit of a tongue twister, allowing others to rediscover this pathophysiology and apply the names "hypergastrinemia of antral origin" and "antral G-cell hyperplasia."

Subsequent work with gastrin demonstrated that the hyperchlorhydria resulting from extensive small bowel resection is caused by hypergastrinemia due to the absence of a gastrin release-inhibiting factor (7). In addition, the Mount Sinai group studied the molecular structure of gastrins from a variety of mammalian species, discovered gastrinomas in dogs and cats, traced gastrin-like peptides back to mollusks, and determined the distribution and metabolic fate of heterogeneous gastrin peptides (8–10).

Secretin and Cholecystokinin

With respect to the first hormone, secretin, the Mount Sinai group constructed the first successful assays (11, 12). Secretin had proven difficult to measure because the molecule, lacking a tyrosine, was difficult to label with radioactive iodine, and because it circulates in very low concentration. Nonetheless, methods of labeling the amino-terminal histidine and extraction from plasma using reverse-phase cartridges allowed demonstration of postprandial secretin release and hypersecretinemic states.

The Mount Sinai group played a central role in working out the technical problems in measuring cholecystokinin and in determining its complex heterogeneity and distribution in plasma, gut,

and brain tissues (13–19). This group was the first to demonstrate that CCK is found in neurons of the cerebral cortex, that it is concentrated in synaptosomes, and that it is released by paradigms similar to those for nonpeptide neurotransmitters.

Conclusion

From the discovery of the first hormones, the regulatory peptides of the digestive system and the study of brain-gut peptides have been exciting and productive areas for the understanding of health and disease. We may take pride in the fact that members of the Mount Sinai community have contributed to this crucial area. In addition to Solomon Berson and Rosalyn Yalow, it is also worth mentioning Seymour Glick, Jesse Roth, John Walsh, and John Eng, each of whom has contributed greatly to this field both during and after their association with Mount Sinai. Those of us who have worked in the field are indebted to them all.

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