Discovery of Insulin Antibodies in the 1950s Led to Radioimmunoassay

NUCLEAR MEDICINE PIONEER AWARD CONFERRED ON ROSALYN S. YALOW AND SOLOMON A. BERSON

Rosalyn S. Yalow, PhD, and the late Solomon A. Berson, MD, worked in partnership for 22 years at the Bronx Veterans Administration (VA) Hospital and revolutionized an entire phase of laboratory medicine.

They began working in 1950 on radionuclide methods to determine blood volume, and followed a path that led them to measurements of infinitesimal amounts of hundreds of substances in blood and other body fluids with the radioimmunoassay (RIA) technique.

The Society of Nuclear Medicine (SNM) will honor that discovery this month at the 33rd Annual Meeting in Washington, DC, where Dr. Yalow and Mrs. Miriam Berson will accept the Georg Charles de Hevesy Nuclear Medicine Pioneer Award.

[Immediately following the award ceremony at the formal opening and plenary session, Dr. Yalow will teach a continuing education course on endocrine evaluation using RIA and multiple imaging modalities (Sun., June 22, 10:30–12:00, Rm. 38).]

From studies designed to test a hypothesis that diabetes in the adult was attributable to abnormal degradation of insulin, Drs. Yalow and Berson found that the slowed disappearance of radiolabeled insulin was attributable to the presence of insulin-binding antibodies in insulin-treated subjects.

Despite the accepted belief that insulin did not produce antibodies, Drs. Yalow and Berson published these results in 1956 (*1*).

Drs. Berson and Yalow's paper convinced the scientific community to accept the idea of a soluble antigen-antibody complex. They demonstrated that equilibrium (or affinity) constants were several orders of magnitude lower than the accepted constants based on theoretical analysis.

This paper also contained a description of all the essential phenomena that the Berson-Yalow team would later integrate to create the RIA—the first recognized competitive binding assay (*2,3*).

These papers demonstrated, for the first time, how insulin could be measured in humans, and provided the basis for extending the methodology to other substances.

The RIA technique enabled Drs. Berson and Yalow to quantify insulin in a small volume of unextracted plasma at concentrations in the nanogram/milliliter range.

Insight into Function

"The exquisite sensitivity, specificity, and comparative ease of RIA, especially now that instrumentation and reagents are so readily and universally available have permitted assay of biologically significant materials where measurements were otherwise difficult or impossible.

"Only if we can detect and measure can we begin really to understand, and herein lies the major contribution of RIA as a probe for insight into the function and perturbations of the fine structure of biologic systems," said Dr. Yalow (*4*).

RIA Principle

These findings formed the basis for the RIA, where an antigen is added to a solution of a radioantigen-antibody complex, and the cold antigen competes with the labeled antigen to bind with the antibody.

Rosalyn S. Yalow, PhD, in Stockholm accepting her Nobel Prize in 1977 for the development of radioimmunoassay.

The unbound antigen is later separated from the complexes, and the radioactivity in both portions is measured with a gamma counter. By determining the ratio of labeled bound antigen to labeled free antigen, and comparing that ratio to standard measurements of known samples, the concentration of antigen in the unknown sample can be determined.

RIA "has provided virtually all

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the information now known about the regulation of hormonal secretion and the interrelationships among hormones, and has contributed greatly to our understanding of the mechanisms of hormonal release, and or hormonal physiology in general," said Dr. Yalow.

The technique has been further developed to measure non-hormonal substances, such as drugs, vitamins, enzymes, viruses, serum proteins, and tumor antigens, and binding agents other than antibodies have been used for "radioligand" assays. (Other markers, such as enzymes covalently bound to antigen, have also been used in place of radioactive labels, but with decreased sensitivity.)

In the late 1950s, Drs. Yalow and Berson and their research fellows ran courses to introduce the RIA methodology to other investigators, many of whom became leaders in the field of endocrinology. By 1975 over 4,000 hospitals and clinical laboratories in the United States performed RIAs—almost double the number of the early 1970s (5). A screening test for the hepatitis virus in blood banks is only one of a myriad RIA applications.

RIA is also used extensively in developing nations. In August 1985, Dr. Yalow spoke on the use of RIA at an international symposium in Vienna, Austria, on nuclear medicine in developing countries, sponsored by the International Atomic Energy Agency (IAEA).

Giving her views on how to maximize the use of RIA in developing countries, Dr. Yalow said, "The diagnosis of active infectious disease is of great importance in areas of the world where these diseases are major causes of morbidity and mortality, and RIA can make important contributions in this field." (6)

Solomon A. Berson, MD, and Rosalyn S. Yalow, PhD, at the University of Pittsburgh to receive the Dickson Prize in 1971, one of numerous awards. Bernard Straus, MD, chief of the Bronx VA Medical Service in 1950, brought the two investigators together, and later said that Dr. Berson contributed his brilliance in biology to the team while Dr. Yalow provided the mathematic muscle. "Sol was something of a romantic. Ros was keen and scientific, and certainly a steadying influence," he added.

Influenced by Curie and Fermi

Dr. Yalow was born in New York City in 1921, and was the first physics major at Hunter College of the City University of New York.

At age 17 the biography of Marie Curie made an indelible impression on her, and she recalls hearing Enrico Fermi a year later lecturing at Columbia University on the discovery of nuclear fission.

"In the late 1930s, when I was in college, physics—and, in particular, nuclear physics—was the most exciting field in the world," she said.

Although she was told that a woman would not be given an assistantship in physics, and that she should work as a professor's secretary so she could take graduate courses, Dr. Yalow did receive an assistantship from the University of Illinois (the first woman to do so since 1917), where she earned her PhD in physics in 1945. (She is currently the recipient of 37 honorary doctorates.)

Dr. Yalow returned to New York City and worked as an electrical engineer at the Federal Telecommunications Laboratory and taught physics at Hunter College. Her engineering skills came in handy at the Radioiso-

tope Service of the Bronx VA Hospital in the late 1940s, since she equipped the laboratory and designed the radiation counters.

In 1950 Dr. Yalow decided to work full-time at the Radioisotope Service, and was joined by Dr. Berson, who completed his residency that year in internal medicine at the Bronx VA.

Also a native of New York City, Dr. Berson was born in 1918, and received his MD from New York University in 1945. His research work with Dr. Yalow on blood volume, thyroid physiology, and eventually the RIA of insulin, human growth hormone, parathyroid hormone, adrenocorticotropin hormone (ACTH), and glucagon were recognized as major contributions to biomedical science.

He received many honors and became a senior medical investigator at the Bronx VA hospital.

Dr. Berson took an official leave of absence from the Bronx VA in 1967 to become chairman of the Department of Medicine at the Mount Sinai School of Medicine in New York. During that time, he also returned to his lab at the Bronx VA several nights a week, continuing his research in the measurement and physiology of peptide hormones and other substances.

"Sol Berson aspired to revolutionize medical education and, had he lived, he might have succeeded," said Dr. Yalow in the memorial issue of the *Mount Sinai Journal of Medicine* (40:261–297, 1973) dedicated to Solomon Berson.

In the same publication, a former Mount Sinai medical student remembered his first Berson lecture on the thyroid gland. "I recall sitting for about an hour quite dumbfounded as an energetic, enthusiastic, incredibly knowledgeable man gave the best lecture I ever heard. I had heard rumors about Dr. Berson, but after that lecture, I knew that I had been exposed to the greatest intellect of my educational career."

Other students felt the same way. Five out of 22 graduate students showed up for Dr. Berson's first lecture in a course on endocrine physiology, given at 7:00 a.m. For the second class, the room was filled with everyone registered for the course as well as about 30 graduate students from Queens, Brooklyn, Hunter, and City Colleges.

Gifted Educator

The educational atmosphere in the Bronx VA Radioisotope Service was just as intense. During a memorial service for Solomon Berson held on June 23, 1972, at the Fourth International Congress of Endocrinology in Washington, DC, a former research fellow said that Dr. Berson always regretted that the Bronx VA did not offer the breadth of science courses provided at larger research centers.

"He singlehandedly provided us with formal didactic courses in differential equations, advanced calculus, vector analysis, biochemistry, and physics, as well as extensive practical and theoretical teaching in radioisotopes," said Jesse Roth, MD, chief of the Diabetes Section at the National Institute of Arthritis and Metabolic Diseases (*8*).

The editor of the journal *Diabetes* recalled that, no matter how busy Dr. Berson was, he would always accept requests to review papers, and rewrote them carefully so as not to insult the authors.

RIA opened the door to multiple vistas for the Berson-Yalow team, whose collaborative effort resulted in about 250 papers and book chapters on topics ranging from insulin and diabetes to studies of several hormones, hepatitis antigens, and gastrin secretion. Several of their projects in the 1960s clarified various aspects of glucose tolerance, insulin secretion, and the etiology of diabetes. In the years since Dr. Berson's death, the number of publications from that laboratory has more than doubled.

Stanley J. Goldsmith, MD, president of the SNM, worked as a research fellow in the Berson-Yalow laboratory from 1968 to 1970. "They worked day and night at 90 miles-an-hour and I would leave them at 2:00 a.m. because I had to sleep, and they would be back to work before 8:00 a.m. the same morning when I returned," recalled Dr. Goldsmith, who is also director of the Department of Physics-Nuclear Medicine at the Mount Sinai Medical Center in New York.

Drs. Berson and Yalow were so busy researching that it didn't occur to them to patent RIA, but they still might have chosen to forgo that right. Dr. Yalow once said that she has no desire to work as a consultant to pharmaceutical companies that manufacture RIA kits because "I would not be free to speak my mind on the policies in the use of RIA procedures."

In regard to the role each one played in this synergistic relationship, other scientists have described Dr. Berson as a man who was intermittent and brilliant, painting all the sweeping brushstrokes, while Dr. Yalow was chronic and meticulously drew in the fine details (*7*).

Dr. Berson died of a heart attack at a medical meeting in 1972. Colleagues have described him as infinitely energetic, empathetically dedicated to his patients, and a master of chess, mathematics, history, literature, and the violin.

Nobel Prize in 1977

Subsequently, Dr. Yalow received the Nobel Prize in Physiology or Medicine in 1977 for the RIA technique. At that time, she also emphasized the importance of educational responsibilities to the Berson-Yalow team.

In the biographic essay published by the Nobel Foundation, Dr. Yalow said, "Through the years Sol and I together, and now I alone, have enjoyed the time spent with the 'profes-

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sional children,' the young investigators who trained in our laboratory. The emphasis has been not only in learning our research techniques, but also our philosophy. I have never aspired to have a cadre of investigators-in-training that is more extensive than I can personally interact with and supervise."

She also used her Nobel fame to speak out to newspaper reporters and her congressman for more support within the VA system for research fellows.

During the banquet following the Nobel Prize Awards Ceremony in Stockholm, Sweden, Dr. Yalow was chosen to represent all the laureates in responding to the tribute from the Students of Stockholm.

"Among you students of Stockholm and among other students, at least in the Western world, women are represented in reasonable proportion to their numbers in the community; yet among the scientists, scholars, and leaders of our world, they are not. No objective testing has revealed such substantial differences in talent as to account for this discrepancy," said Dr. Yalow, and she urged female students to believe in themselves "or no one else will."

Dr. Yalow's drive to teach others extends far beyond the Bronx VA. She has spent a month in India, for example, helping researchers develop RIAs for infectious diseases.

And she never gives up trying to educate regulatory agencies and the public on the risks of radiation compared to exaggerated fears. In 1979, when the three commercial low-level radioactive waste disposal sites in the United States threatened to refuse deliveries, she testified before a congressional committee on the amounts of natural radioactivity present in the living adult human body.

"According to the rules of the US Nuclear Regulatory Commission (NRC), if I were a laboratory animal who had received this amount of radioactivity as 'by-product material' and died with this radioactivity still in my body, I could not be buried, burned, or disposed of in the garbage. My carcass would have to be packed into a small can, placed inside a larger can, and transported to a site for disposal of radioactive wastes. There I would needlessly occupy forever space that should be saved for significantly radioactive materials," she stated.

Four years later, testifying before the New York City Council's Committee on Environmental Protection, she again tried to dispel myths about radioactive waste, and she also reported that the NRC had collected data that confirmed her 1979 testimony, and changed its regulations accordingly.

This past April, Dr. Yalow spoke before the American Chemical Society on the inconsistencies that still exist in NRC regulations, and the need to base these rules on more sound scientific reasoning.

The SNM Nuclear Medicine Pioneer Award was established in 1960, and named for Georg Charles de Hevesy, the Hungarian chemist who first used radionuclides as indicators of metabolism (*9*), in 1979. The recipient is selected each year by the SNM president.

The first volume of *The Journal of Nuclear Medicine* in 1960 published an abstract on RIA by Drs. Berson and Yalow (*10*). Since then, the specialty has burst forth in many directions, and this almost legendary partnership serves as an ideal model for the partnership within the nuclear medicine community of basic and clinical scientists.

Linda E. Ketchum

Past Recipients of the Hevesy Nuclear Medicine Pioneer Award

1960	Ernest O. Lawrence
1961	Henri Becquerel and Marie Curie
1962	Joseph Hamilton and Bertram Low-Beer
1963	Enrico Fermi
1964	Lord Rutherford of Nelson
1965	Geoacchino Failla
1966	Otto Hahn
1967	Gilbert N. Lewis
1968	Pioneers of the 1930s
1969	Herrmann L. Blumgart
1970	John J. Lawrence
1971	Glenn T. Seaborg
1972	Frederic and Irene Joliot Curie
1973	Lise Meitner
1974	Hal O. Anger
1975	George V. Taplin
1976	David E. Kuhl
1977	Those who took part in the "Chicago Pile" experiment—12/2/42
1978	Benedict Cassen
1979	Georg Charles de Hevesy
1980	Merrill Bender and Monte Blau
1981	William G. Myers
1982	William H. Beierwaltes
1983	None
1984	Henry N. Wagner, Jr.
1985	Michel M. Ter-Pogossian

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