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SOLOMON A. BERSON

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A Biographical Memoir by

J. E. RALL

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BY J. E. RALL

SOLOMON A. BERSON was born April 22, 1918, in New York City. His father, a Russian émigré who studied chemical engineering at Columbia University, went into business and became a reasonably prosperous fur dyer and the owner of his own company. He was a competent mathematician, enjoyed chess, and played duplicate bridge sufficiently well to become a life master.

Solomon Berson—Sol to his many friends—was the eldest of three children: Manny, the second, became a dentist; Gloria, the youngest, married Aaron Kelman, a physician and a friend of Sol's. In 1942 Sol married Miriam (Mimi) Gittleson. They had two daughters whom Sol adored, and a happy, warm family life.

Sol discovered a taste and aptitude for music early in life. He played in chamber music groups in high school and developed into an accomplished violinist. My impression has always been that he liked the presto movements best—he clearly led his entire life at a presto pace. He also played chess in high school and became sufficiently expert to play multiple games blindfolded. In 1934 he entered the City College of New York and, in 1938, received his degree.

At that time Sol decided he wanted to study medicine. He applied to twenty-one different medical schools but was turned down by every one. Instead, he went to New York University, where he earned a Master of Science degree (in 1939) and a fellowship to teach anatomy at the NYU Dental School, where his brother, Manny, was a student. He was finally admitted to New York University Medical School in 1941 and, a member of Alpha Omega Alpha honorary medical fraternity, received his M.D. degree in 1945. Sol interned at Boston City Hospital from 1945 to 1946, then joined the Army. Serving from 1946 to 1948, he went from first lieutenant to captain. He spent 1948 to 1950 at the Bronx Veterans Administration Hospital for further training in internal medicine, then decided to go into research.

In the spring of 1950, Rosalyn Yalow, assistant chief of the Radioisotope Service in the Radiotherapy Department at the Bronx V.A. Hospital, was looking for a physician qualified in internal medicine and asked Bernard Straus, Chief of Medicine, to recommend someone. He suggested Solomon Berson, though Sol had already arranged to go to the V.A. Hospital in Bedford, Massachusetts. Straus nevertheless encouraged Yalow to interview Berson, and, during the interview, Sol presented her with a series of mathematical puzzles. Since Ros Yalow is not a bad mathematician and has a sense of humor, she offered Sol the position, and he accepted. So began a collaboration that lasted until Sol's death in 1972.

For about a year, while working full-time in the Radioisotope Service, Sol "moonlighted" in the private practice of medicine. He found clinical practice gratifying and his patients adored him, but his work at the V.A. became too engrossing and he gave up his practice. In 1954 when the Radioisotope Service became independent of Radiotherapy, Sol became its chief. The Radioisotope Service was the forerunner of the modern Nuclear Medicine Service, and the thyroid clinic he established there in 1950 continues even now to function as he planned it.

One of Berson and Yalow's early papers in thyroid physiology exemplifies the method that would characterize their research for the next few decades. The research was clinical, involving both normal and diseased subjects; it was mathematically and logically precise; it went beyond specification of the technical requirements of the study to make assumptions inherent in the measurements explicit.

In this early study, Berson and Yalow answered precisely the question of what the human thyroid's so-called "uptake" of radioactive iodine represents. To do this they focused on the quantity of iodide the thyroid clears from the blood per unit of time, having first determined that this was the only physiological constant they could measure that also described one of the functions of the thyroid. In 1952 they published their classic paper on the subject, which is still quoted. It is particularly remarkable that Berson, who lacked extensive formal training in mathematics and physical chemistry, used both—to such good effect—in his research.

About this time Berson and Yalow decided that an excellent way to investigate the metabolism of a variety of biologically interesting compounds was to label them with a radioactive isotope. They were among the first to label serum albumin with radioactive iodine to study its metabolism. This work, reported in 1953, was one of the earliest studies to show how long albumin lasted in the circulation and the kinetic processes governing its synthesis and degradation.

Shortly thereafter the two researchers used insulin labeled with radioactive iodine to test the hypothesis that diabetes of the maturity-onset type was due to an excessively rapid degradation of normally-secreted insulin. They found that when labeled insulin was given to subjects who had been treated with insulin either for diabetes or as shock therapy for schizophrenia, it disappeared more slowly than did insulin administered to normal subjects. They surmised that this was due to the formation of soluble antigen antibody complexes that were metabolized more slowly than free insulin. Analyzing serum by paper electrophoresis, they showed that in subjects previously treated with insulin, labeled insulin added later was found in the B-γ region of serum proteins rather than as free insulin.

This observation, published in 1956, led Berson and Yalow to consider the reversible equilibrium between a binding protein and a ligand, and they soon realized that a method using binding equilibria could be developed to measure very small amounts of material. They then developed the general method of radioimmunoassay on the theory that—if a substance (in their early work, an antibody) can be produced that binds a ligand—the following situation obtains:

$$\mathrm{P} + \mathrm{L} \leftrightarrows \mathrm{PL}$$
$$\mathrm{P} + \mathrm{L}' \leftrightarrows \mathrm{PL}'$$

One must be able to separate bound ligand (PL + PL′) from free P (protein or antibody) and free ligand, L (in this case, insulin). The actual assay is performed with the experimental solution containing a small but unknown amount of ligand, to which an extremely small amount of radioactively labeled ligand (L′) is added. After attaining equilibrium and after electrophoretic separation, the bound and free amounts of radioactivity are measured. A series of standard reactions containing labeled ligand and progressively increasing amounts of unlabeled ligand is prepared simultaneously exactly as above. With increasing amounts of unlabeled ligand, progressively increasing amounts of labelled ligand will be displaced from the antibody. Interpolation of the experimental results on the standard curve then permits accurate estimation of the amount of ligand in the experimental solutions.

The researchers had to solve several additional problems, however, before their method could be accepted as both sensitive and accurate. Most scientists at that time believed that insulin did not produce antibodies, though Berson and Yalow, building on the work of others, had demonstrated that animal insulins used for the treatment of diabetes did, in fact, produce antibodies in man. (In guinea pigs they had observed specific, high-affinity antibodies to animal insulins that reacted well with human insulin.) It was also important to label the insulin so that there were no degradation products and it could be separated out as a clean component after labeling. When, in 1959, these procedures were finally perfected, Berson and Yalow were able to report the success of their method for measuring insulin concentration in human plasma.

This accomplishment led to a series of studies on insulin secretion and the effect of human diabetes on insulin concentration in plasma. It had been known for many years that there were differences between individuals who developed diabetes as youngsters—who were more likely to go into ketoacidosis—and older diabetics with a tendency to obesity, who rarely went into ketoacidosis. The younger group of patients generally exhibited greatly reduced quantities of insulin in the pancreas and bloodstream and were, therefore, insulin deficient. By radioimmunoassay of insulin, Berson and Yalow showed that many older diabetics had normal or even elevated levels of insulin in the bloodstream. The defect, therefore, was not in the secretion of insulin but in some subsequent step. A complicating factor in all these measurements are the antibodies most patients treated with insulin develop to it (as Berson and Yalow had demonstrated), and precisely where the defect occurs in what is now called "Type II" diabetes is still not completely understood.

The high degree of specificity of the immune system makes radioimmunoassay capable of distinguishing closely related compounds such as thyroxine and triiodothyronine, or cortisol and corticosterone that differ only in a single hydroxyl group. The general principle, furthermore, can be extended to any system in which a specific binding material is available, such as thyroxine-binding globulin for the measurement of thyroxine, or intrinsic factor for measurement of vitamin B_{12}.

Over the next few years, the Radioisotope Service at the Bronx VA Hospital saw an enormous burst of activity as Berson and Yalow adapted radioimmunoassay to the analysis of parathyroid hormone, growth hormone, ACTH, and gastrin, which were until then impossible to measure in blood with any degree of accuracy. In 1963, for example, Berson and Yalow showed for the first time that the secretion of growth hormone was acutely regulated by stimuli such as hypoglycemia and exercise. They also found parathyroid hormone in the blood in several forms that could be differentiated by antibodies with different specificities. They measured gastrin, then a newly-discovered hormone that stimulates secretion of stomach acid, and showed that it existed in several forms of varying size in human plasma. Radioimmunoassay has since been adapted to the measurement of literally hundreds of different substances, ranging from steroids, to thyroid hormones, to the hepatitis B surface antigen, and the tubercle bacilli. The possibility of radioimmunoassay analysis of substances present in concentrations of 10^{-9} to 10^{-13} molar has enormously accelerated progress in many fields of biomedical research.

Dr. Berson received numerous awards for this work, including the 1971 Gairdner Award, the 1971 Dickson Prize, the 1965 Banting Memorial Lecture and Banting Medal of the American Diabetes Association, the 1960 William S. Middleton Medical Research Award, and the American Diabetes

Association's first Eli Lilly Award in 1957. In 1977, five years after his death, Dr. Rosalyn Yalow received the Nobel Prize for the "development of radioimmunoassays of peptide hormones."

Drs. Berson and Yalow patented neither the general concept of radioimmunoassay nor any of the procedures they had developed to make it so precise and sensitive an assay. But while numerous commercial laboratories made large sums of money for performing radioimmunoassays, Berson remained unconcerned. His salary at the Veterans Administration was anything but munificent. Yet, wrote Dr. Jesse Roth, one of Berson's early postdoctoral fellows, ". . . Seymour Glick and I didn't have any travel grants included in our fellowships, nor did the laboratory provide any travel funds, so our meeting expenses were paid for out of Dr. Berson's pocket."

Dr. Berson continued his research at the Radioisotope Service until his death, but in 1968 accepted the professorship and chairmanship of the Department of Medicine, at the Mount Sinai School of Medicine of the City University of New York. In this position, he influenced many medical students and house staff. When he had an argument with the administration at Mount Sinai and threatened to resign, the entire house staff on the medical service agreed to resign *en masse* if he were to leave. Needless to say, the dispute was adjudicated and both Dr. Berson and the house staff stayed on. In spite of the heavy demands of being professor of medicine and chairman of the department in a large medical school, Dr. Berson retained close ties with Dr. Yalow and their laboratory, and the productivity of their scientific collaboration continued unabated.

As is the case with many great and busy scientists, Dr. Berson was on the editorial boards of numerous journals to which he gave a surprising amount of time, carefully and thoughtfully reviewing articles. He was a member of many boards and advisory councils, several with the National Institutes of Health.

In April 1972, the month he was elected to the National Academy of Sciences, Sol Berson died while attending a meeting of the Federation of the American Societies for Experimental Biology in Atlantic City.

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