
It's about the Journey, Not the Destination: The Birth of Radioimmunoassay¹

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Featured Article: Yalow RS, Berson SA. Immunoassay of endogenous plasma insulin in man. *J Clin Invest* 1960;39:1157–75.³

They met in 1950. She was a 29-year-old researcher with a PhD in nuclear physics who had been accepted to graduate school only because there was a shortage of male students because of World War II. He was a 32-year-old physician who had collected more than 100 rejection letters over several years before finally being accepted into medical school. Their meeting turned out to be not just a professional match made in heaven, but also the beginning of a journey that led all the way to Stockholm.

In 1921, the same year that Rosalyn Yalow was born, Banting and Best prepared an extract from dog pancreas and showed that a compound in the extract was capable of controlling blood glucose concentrations in dogs whose pancreas had been removed (1). Shortly afterward, they used a more highly purified extract from fetal calves to treat a 14-year-old boy with type 1 diabetes (2). By 1923, bovine insulin was being commercially purified for use in patients.

During her graduate training, Yalow became proficient in the design and use of instrumentation for measuring radioactive substances. By serendipity, she ended up at the Veterans Administration Hospital in the Bronx, which had decided to develop a radioisotope service. Here she met Solomon Berson, who within 4 years was to become chief of the service. Combining their knowledge and backgrounds, they initiated radioisotope studies of thyroid hormone metabolism. Recognizing the importance of diabetes, they soon set their sights on insulin. By now, highly purified insulin was readily available and could be radioiodinated and monitored in their laboratory.

Berson and Yalow focused on type 2 diabetes, asking why patients with this form of diabetes, who appar-

ently could produce insulin, were unable to control blood glucose concentrations. To address this question, they collaborated with 3 other scientists in a study that involved the injection of ¹³¹I-labeled insulin into diabetic and nondiabetic individuals who either had undergone insulin treatment or had never received insulin. Their results, published in 1956 with Berson as lead author (3), showed that insulin clearance from blood was rapid in patients, both diabetic and nondiabetic, who had not been exposed to insulin but was much slower in individuals who had been treated with insulin. Paper and starch radioelectrophoretograms, as well as ultracentrifugation experiments, showed that the insulin in blood from patients treated for months to years with insulin was bound to a γ -globulin protein. They were convinced this protein was an insulin antibody that was produced by immunizing patients with repeated injections of bovine insulin. The experts in the field disagreed, however: It was not possible for a molecule with a molecular weight of 5800 Da to be immunogenic! This work was rejected by *Science* and was initially rejected by the *Journal of Clinical Investigation (JCI)*, only to be accepted after the authors agreed to not use “insulin-binding antibody” in the title but to substitute “insulin-binding globulin.” They were also asked to document that the globulin met the definition of an antibody given in a 1941 textbook. Forty-eight years later, an interesting commentary in *JCI* itself on Berson and Yalow’s contributions included a sentence stating, “For those of us who have been frustrated by how difficult it may be at times to get an article published in the *JCI*, it may be heartening to know that Berson and Yalow sometimes shared that same problem” (4).

Key pieces of information from the insulin-clearance studies laid the foundation for this duo’s future work. First, insulin was indeed immunogenic. Second, antibodies formed against insulin seemed to have enough affinity to be considered useful as a capture technique. Third, ¹³¹I-labeled insulin could be used to monitor the amount of insulin bound to the antibodies. Fourth, unbound ¹³¹I-labeled insulin and ¹³¹I-labeled insulin bound to antibody migrated differently in paper radioelectrophoretograms. Yalow and Berson used this information first to develop an immunoassay for bovine insulin that used human antisera. Although the assay worked, the two learned that human antisera

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³ This article has been cited more than 2460 times since publication.

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produced against bovine insulin had too little affinity to be useful for measuring human insulin. By 1959, they had overcome this obstacle by showing that anti-bovine antisera obtained from immunized guinea pigs possessed the desired properties for use in measuring human insulin at the concentrations found in plasma (5). This was the final missing piece of the puzzle.

Yalow and Berson's seminal 1960 paper finally provided the details of the immunization of guinea pigs, the preparation and purification of ^{131}I -labeled insulin, the principles of the immunoassay, its calibration, and even recovery studies. Although the separation of bound and free insulin required paper electrophoresis, it was possible to run 250–300 strips (samples) per day.

Yalow and Berson realized the potential commercial value for RIA but refused to patent the method. Solomon Berson died from a heart attack in 1972, 5 years before he would have shared a Nobel Prize. Yalow wrote in her autobiography for the Nobel ceremonies in 1977 that the laboratory they shared had been designated the Solomon A. Berson Research Laboratory (6). In her Nobel lecture, she showed the audience a copy of the rejection letter from *JCI*. I guess some things are hard to forget.

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