

## Radioimmunoassay <sup>[1]</sup>

By: Craer, Jennifer R. Keywords: Berson <sup>[2]</sup> Yalow <sup>[3]</sup> RIA <sup>[4]</sup> insulin <sup>[5]</sup>

Radioimmunoassay (RIA) is a technique in which researchers use radioactive isotopes as traceable tags to quantify specific biochemical substances from blood samples. Rosalyn Yalow and Solomon Berson developed the method in the 1950s while working at the Bronx Veterans Administration (VA) Hospital in New York City, New York. RIA requires small samples of blood, yet it is extremely sensitive to minute quantities of biological molecules within the sample. The use of RIA improved the accuracy of many kinds of medical diagnoses, and it influenced [hormone](#) <sup>[6]</sup> and immune research around the world. Before the RIA was developed, other methods that detected or measured small concentrations of biochemical substances required large samples of blood—often too large for researchers to collect. With the development of RIA, researchers could use a single drop of blood to detect and measure the concentration of some biochemical substances. By 1970 doctors used RIA to measure follicle stimulating and luteinizing [hormones](#) <sup>[7]</sup> to diagnose and treat [infertility](#) <sup>[8]</sup> in women. Further developments led to neonatal screening programs for hypothyroidism.

Berson, a doctor of internal medicine, and Yalow, a nuclear physicist, began working together in 1950 in the laboratory of Radioisotope Service, later called the Solomon A. Berson Research Laboratory at the Bronx VA Hospital. Berson and Yalow's research focused on nuclear medicine and they planned to develop medical applications for radioactive isotopes, especially for insulin. Early in their work at the Radioisotope Service, Berson and Yalow used the RIA to measure the volume of red blood cells (RBCs) in circulation within the human body. They injected human subjects with a serum containing radioactive tags that attached to specific structures—radioactive iodine attached to albumin, a protein found in the blood; and radioactive potassium or phosphorus attached to RBCs. Berson and Yalow measured the number of RBCs with radioactive tags and validated their RIA-based calculation of RBCs with the blood cell-to-plasma ratio, or hematocrit, measured from collected blood. This step enabled Berson and Yalow to verify their methods. They then focused on substances that had never before been measured in living [humans](#) <sup>[9]</sup>.

Berson and Yalow initially developed the RIA method to measure insulin—a small peptide [hormone](#) <sup>[6]</sup> needed to metabolize carbohydrates and fats—which is generally present in low concentrations within the human body. When bodies struggle to produce or to respond to insulin, those bodies exhibit diabetes. Though doctors had treated diabetes with animal-derived insulin since the 1920s, researchers in the 1950s still worked to develop tests to detect insulin levels in the blood to identify the causes of the disease and the side effects of treatment.

Berson and Yalow had to refine the sensitivity of their radioactive labeling method to study insulin in the body. They found that the human body responded to beef and pork insulin as foreign substances, called antigens, and developed antibodies for the insulin as a defensive mechanism. These antibodies then blocked the receptor sites of the insulin, and the blockage inhibited the [hormone](#) <sup>[6]</sup> from decomposing. At that time, scientists assumed that insulin was

too small to trigger antibody production. The discovery that animal-derived insulin mounted an immune response in [humans](#) [9], described in Berson and colleague's article "Insulin-I<sup>131</sup> Metabolism in Human Subjects: Demonstration of Insulin Binding Globulin in the Circulation of the Insulin Treated Subject," enabled researchers to detect small biochemical substances, such as molecules of insulin. Berson and Yalow recognized that their radioisotope labeling method could be further developed to label and trace nearly any biochemical substance of interest. In 1960 Berson and Yalow published a paper describing the RIA technique, titled "Immunoassay of Endogenous Plasma Insulin in Man." Within a year of the development of the RIA, researchers expanded its application beyond the measurement of [hormones](#) [7], using it to study microscopic organisms, medicines, and cancers.

Researchers using the RIA method require an antigen that has been labeled, or bound to a radioactive marker, and an antigen-specific antibody that will bind to the antigen. For Berson and Yalow, the labeled antigen was insulin bound to radioactive iodine (I<sup>131</sup>), and the antibody was insulinase, which is insulin-specific. To complete the insulin RIA, researchers first mix known quantities of the insulin-I<sup>131</sup> and the insulinase. These bind, producing a specific amount of insulin-I<sup>131</sup>-insulinase complexes. Then, researchers introduce a small biological sample, such as blood, to the mix and incubate the mixture for anywhere from several hours to multiple days.

During the incubation period, the insulin-I<sup>131</sup> and any unlabeled insulin in the biological sample come to an equilibrium, or balance, in the number of molecules of each that are bound to the antibody. When two or more antigens, such as labeled and unlabeled insulin, compete for the same binding site on an antibody molecule, the process is called competitive binding. Due to competitive binding, the unlabeled insulin present in the biological sample will displace a portion of the labeled insulin in the insulin-I<sup>131</sup>-insulinase complexes. The radioactively labeled antigens that have been misplaced from their complexes can then be removed, and the bound, labeled antigen can be measured with a [radiation](#) [10] counter. Because the labeled and unlabeled antigens come into equilibrium, the amount of unlabeled insulin that did not bind will be equal to unbound insulin-I<sup>131</sup>. If researchers know the starting concentration of insulin-I<sup>131</sup> and the binding capacity?the percentage of antigen that will, at any time, remain unbound in a saturated solution?they can calculate the amount of bound and unbound unlabeled insulin from the sample. Though RIA methods were established using antigen-antibody binding, antigens may also bind to other proteins, such as albumin, which binds to and carries some [hormones](#) [7] in the blood plasma. Researchers use binding agents, such as albumin, that are non-specific to immune function, to apply this method to detect or measure levels of drugs, viruses, and other compounds or biological substances.

In the United States, research on applications of radioimmunoassay proliferated. Hypothyroidism, a condition in which the body produces low levels of thyrotropin (TSH), can, among other effects, impair the mental development of infants with the condition. The RIA for TSH, developed in 1965 by Robert Utiger at the [Washington University School of Medicine](#) [11] in St. Louis, Missouri, and that of two other thyroid [hormones](#) [7], triiodothyronine and thyroxine, developed in 1971 by Inder Chopra and colleagues at the University of California, Los Angeles and the Harbor General Hospital in Torrance, California, enabled doctors to screen for and treat neonatal hypothyroidism. During that time, Brij Saxena and colleagues at [Cornell University](#) [12] Medical College in New York City, New York, used RIA to diagnose [infertility](#) [8] in women by measuring concentrations of human follicle stimulating and luteinizing [hormones](#) [7] in plasma.

Yalow received the [Nobel Prize in Physiology or Medicine](#) [13] in 1977 for the development of RIA. Berson didn't share the prize, as he died in 1972 and the Nobel committee doesn't award posthumous prizes. Later RIA techniques enabled researchers to measure multiple biochemical substances simultaneously. To reduce the use of radioactive substances, researchers used enzymes and fluorescents to mark target substances.

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## Subject

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