**Radioimmunoassay** [1]


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 [6] 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 [7] to diagnose and treat infertility [8] 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 [9].

Berson and Yalow initially developed the RIA method to measure insulin—a small peptide hormone [6] 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 1950 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 [8] 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-[131] 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^{131}), and the antibody was insulinase, which is insulin-specific. To complete the insulin RIA, researchers first mix known quantities of the insulin-I^{131} and the insulinase. These bind, producing a specific amount of insulin-I^{131}-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^{131} 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
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Yalow received the Nobel Prize in Physiology or Medicine 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.

**Sources**


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