

# Citation Classics

**Yalow R S & Berson S A.** Immunoassay of endogenous plasma insulin in man.  
*Journal of Clinical Investigation* 39:1157-75, 1960.

**This paper describes in detail an immunoassay for plasma insulin in man, based on the reaction of human insulin added *in vitro* to plasma, which is after recovered and measured for endogenous insulin concentrations. Employing this method, the paper reports plasma insulin concentrations during glucose tolerance tests in nondiabetic and in early diabetic subjects, and plasma insulin concentrations in subjects with functioning islet cell tumors or leucine-sensitive hypoglycemia. [The *SCI*<sup>®</sup> indicates that this paper was cited 1,100 times in the period 1961-1975.]**

Rosalyn S. Yalow, Ph.D.  
Veterans Administration Hospital  
130 West Kingsbridge Road  
Bronx, New York 10468

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"Radioimmunoassay methodology (RIA) has become the method of choice for the determination of the minute concentrations in plasma, other body fluids, or tissue extracts of hundreds of substances of biologic interest such as peptidal and non-peptidal hormones, drugs, enzymes, viruses, etc. It is in use in over 4,000 research and general clinical laboratories in the United States and in thousands of laboratories around the world. For instance, in 1973, a symposium on 'Radioimmunoassay and Related Procedures in Clinical Medicine and Research' was held in Turkey under the auspices of the International Atomic Energy Agency. Participants came from 42 countries, all concerned with the applicability of RIA to clinical problems and biomedical investigation in their own lands. Solution of public health problems such as those requiring increased sensitivity for detection of hepatitis B antigen in blood used for transfusion or

early detection of neonatal hypothyroidism are dependent on RIA. RIA was first used in endocrinology to study the regulation of hormonal secretion and the diagnosis of states of hormonal excess or deficiency but its applications have since extended into virtually all medical specialities. At present RIA is considered so classic a method that relatively few of the scientific papers based on RIA refer to the original detailed description of the methodology presented in this 1960 paper in the *Journal of Clinical Investigation*.

"RIA developed out of our earlier work demonstrating the ubiquitous presence of insulin-binding antibodies in insulin-treated subjects. In that paper we reported that the binding of labeled insulin is a quantitative function of the amount of insulin present when the antibody concentration is kept fixed. This provided the basis for the radioimmunoassay of insulin. However, several years were to pass before we were able to demonstrate the practical application of this principle to the measurement of plasma insulin in man. The 1960 *Journal of Clinical Investigation* paper gives detailed information concerning the problems, practices, and pitfalls in the development of a new RIA as well as presenting what was then new physiologic data on insulin levels in normal and pathologic states and in response to various stimuli.

"Perhaps one should be modest in a commentary on one's own work. However, of the more than 200 publications resulting from my collaborative work with Dr. Solomon A. Berson for the 22-year period before his untimely death in 1972, and the more than 50 papers from my laboratory since, the 1956 paper on the antigenicity of insulin in man and the 1960 paper on the assay of plasma insulin in man remain as the favorites. I am pleased, though not surprised, that the 1960 article has become a highly cited 'classic'."

- 1. Berson S A, Yalow R S, Bauman A, Rothschild M A & Newerly K.** Insulin-<sup>131</sup>I metabolism in human subjects: demonstration of insulin binding globulin in the circulation of insulin-treated subjects. *Journal of Clinical Investigation* 35:170-90, 1956.