

This Week's Citation Classic

Karam J H, Grodsky G M & Forsham P H. Excessive insulin response to glucose in obese subjects as measured by immunochemical assay. *Diabetes* 12:197-204, 1963.

This paper shows that obese, non-diabetic subjects had levels of serum immunoreactive insulin three to four times higher than those of non-obese, normal subjects after identical rapid intravenous glucose loads. These findings established the relevance of obesity in interpreting the excessive insulin responses to glucose in early maturity-onset diabetics. [The SC[®] indicates that this paper has been cited over 335 times since 1963.]

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In late 1960, after a year of laboratory research at Hammersmith Hospital in London, I began an endocrinology fellowship in Peter H Forsham's Metabolic Research Unit at the University of California in San Francisco, where a new modification of the radioimmunoassay of insulin had just been developed by Gerold M Grodsky.¹ My interest in the clinical potential of this method derived from two earlier years spent as a resident physician at the Bronx VA Hospital, where Berson and Yalow had initiated the exciting technology of radioimmunoassay and had reported that early maturity-onset diabetics had a greater insulin-secretory response to oral glucose than normal subjects.²

"I was fortunate to be assigned to Jerry Grodsky's lab and was advised to learn the insulin immunoassay by obtaining from a local meat-packing plant some fresh beef pancreas, from which insulin might be extracted and assayed. However, my first harrowing venture into a slaughterhouse so dulled my discriminatory sense that I passively accepted abattoir terminology of 'sweetbreads' for my

requested pancreas. My initial attempts to estimate insulin repeatedly failed. Lventual histological evidence that the frozen tissue was not pancreas at all but thymus (neck sweetbreads), and subsequent recovery of insulin from true pancreas (abdominal sweet breads'), salvaged my research career. confirmed the specificity of the Grodsky-Forsham insulin assay, and, to no one's concern at the time, suggested a lack of immunoreactive insulin in beef thymus gland.

"As my primary interest was in clinical research, I submitted a protocol to compare the effects of intravenous glucose versus galactose in stimulating insulin secretion in humans. To verify that my technical skills were adequate to measure circulating insulin in serum, I administered glucose intravenously to a maturity-onset mild diabetic, and, as reported by Yalow and Berson, confirmed that the insulin response was considerably higher than after a similar dose of glucose given to a normal subject." In discussing this result with Jerry Grodsky and Peter Forsham, I commented that my diabetic subject was markedly obese, weighing 570 lb. Since his extreme obesity far surpassed his mild hyperglycemic disorder, it raised the question of whether obesity itself contributed to the excessive insulin response to glucose seen in our patient as well as in Yalow and Berson's early diabetics, whose weights were not reported but in whom obesity is known to have a high frequency.

"Subsequent findings in 9 of 10 non-diabetic, obese subjects demonstrated that obesity itself was clearly associated with a supra-normal insulin response to glucose. This led to the conclusion that the presence of obesity should be weighed carefully whenever evaluating insulin levels in either the diabetic or the non-diabetic.

"That this finding has achieved the distinction of being one of the most cited papers in its field is most satisfying to the three of us, who have continued close collaboration in a research unit that emphasizes a balanced relationship between basic and clinical research."

1. **Grodsky G M & Forsham P H.** An immunochemical assay of total extractable insulin in man. *J. Clin. Invest.* 39:1070-9, 1960.
2. **Yalow R S & Berson S A.** Plasma insulin concentrations in non-diabetic and early diabetic subjects: determinations by a new sensitive immunoassay technic. *Diabetes* 9:254-60, 1960.