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This Week's Citation Classic®

Hershman J M & Pittman J A, Jr. Utility of the radioimmunoassay of serum thyrotrophin in man. *Ann. Intern. Med.* 74:481-90, 1971.
[Metabolic Research and Nuclear Medicine Labs., Veterans Admin. Hosp., and Div. Endocrinology and Metabolism, Dept. Med., Univ. Alabama Sch. Med., Birmingham, AL]

This paper describes the application of a thyrotropin (TSH) radioimmunoassay for differentiation of primary hypothyroidism from hypothyroidism due to pituitary disease. Synthetic thyrotropin-releasing hormone (TRH) given intravenously increased serum TSH levels. We showed the clinical utility of the TSH measurement and studied the dynamic aspects of pituitary TSH secretion. [The *SCI*® indicates that this paper has been cited in over 200 publications.]

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The first measurements of serum thyrotropin (TSH) by radioimmunoassay (RIA) were made by Robert Utiger[1] and William Odell and his colleagues[2] in 1965. Both investigators very kindly advised me about the art of RIA of TSH. Jim Pittman and I were both interested in clinical measurements of serum TSH for differential diagnosis of hypothyroidism. When I joined his Division of Endocrinology at the University of Alabama in Birmingham in 1967, he encouraged me to work on the problem.

I had developed a RIA for bovine TSH in 1965, but human TSH did not cross-react in this system. In 1967 the National Pituitary Agency provided the crucial reagents: highly purified human TSH and an antibody to it. My human TSH RIA, like others of the time, had a relatively high "serum blank" and thus overestimated normal values. We defined a normal range of serum TSH based on a study of 173 normal individuals. Patients with clear-cut primary hypothyroidism had greatly elevated TSH values, and patients with hypopituitarism or hyperthyroidism had undetectable levels.

We also measured the biological activity of the serum of myxedematous patients and of human pituitary extracts in the mouse bioassay developed by Max McKenzie and found that the ratio of biologic to immunologic activity was 3.5 for the serum and 2.0 for the pituitaries. The data suggested that some pituitary molecules with biologic activity lacked the determinants detected by the antibody; thus, TSH was a heterogeneous substance. Current work suggests that this is due to heterogeneity of the carbohydrate side-chains in the glycoprotein molecule. With four-hour blood sampling and the lack of precision of our assay in the normal range, we failed to discover the late-evening presleep peak in serum TSH readily found using a more sensitive RIA and sampling of blood every 20 minutes.[3] We showed that acute exposure to cold did not release TSH in human subjects in contrast with our data in rats. Serum TSH levels increased rapidly after birth and declined in the first three days. Important negative findings were the failure of electroconvulsive therapy or vasopressin to increase serum TSH levels.

After Schally and Guillemin came up with the tripeptide structure of thyrotropin-releasing hormone (TRH), Charles Baugh of our biochemistry department in Birmingham synthesized TRH so that we could test its effects in man before Abbott Laboratories had made it widely available. We had reported our preliminary work on clinical studies with TRH the previous year in a rapid publication format.[4] We provided additional data indicating the suppression of TSH secretion in hyperthyroidism, and we showed the use of TRH for evaluation of TSH reserve in patients with pituitary disease. TRH given orally produced a smaller response than one-tenth the dose given intravenously, but the response to oral TRH was more prolonged.

Pittman was a superb clinical investigator. He terminated his research career prematurely to accept the leadership of the VA research program in Washington and then the deanship of the University of Alabama School of Medicine.

Subsequently, my colleagues at UCLA and I improved the TSH assay considerably so that we could define the normal range with precision.[5] Our "highly sensitive" RIA has been joined in the last two years by a slew of commercial kits for ultrasensitive measurement of serum TSH levels. The basis for the interest in this field is the frequency of thyroid disease and the popularity of the TSH measurement.

I think that the paper is highly cited because it was a review of the state of the clinical art at that time and documented the clinical physiology. It summarized three years of work in my laboratory and nowadays would probably be divided into several discrete reports. A recent review of control of TSH secretion is available.[6]

1. **Utiger R D.** Radioimmunoassay of human plasma thyrotropin. *J. Clin. Invest.* 44:1277-86, 1965. (Cited 255 times.)
2. **Odell W D, Wilber J F & Paul W E.** Radioimmunoassay of thyrotropin in human serum. *J. Clin. Endocrinol. Metab.* 25:1179-88, 1965. [See also: **Odell W D.** Citation Classic. *Current Contents/Clinical Practice* 8(43):10, 27 October 1980.]
3. **Parker D C, Pekary A E & Hershman J M.** Effect of normal and reversed sleep-wake cycles upon nyctohemeral rhythmicity of plasma thyrotropin: evidence suggestive of an inhibitory influence in sleep. *J. Clin. Endocrinol. Metab.* 43:318-28, 1976.
4. **Hershman J M & Pittman J A, Jr.** Response to synthetic thyrotropin-releasing hormone in man. *J. Clin. Endocrinol. Metab.* 31:457-60, 1970. (Cited 140 times.)
5. **Pekary A E, Hershman J M & Parlow A F.** A sensitive and precise radioimmunoassay for human thyroid stimulating hormone. *J. Clin. Endocrinol. Metab.* 41:676-84, 1975. (Cited 175 times.)
6. **Hershman J M & Pekary A E.** Regulation of thyrotropin secretion. (Imura H. ed.) *The pituitary gland.* New York: Raven Press, 1985. p. 149-88.

