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Rees Smith B & Hall R. Thyroid-stimulating immunoglobulins in Graves' disease. *Lancet* 2:427-31, 1974.
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This paper described a radioreceptor assay for the measurement of autoantibodies to the thyrotropin (TSH) receptor. The method was based on the ability of the antibodies to inhibit ^{125}I-labelled TSH binding to TSH receptors in thyroid membranes. Analysis of sera from patients with different thyroid diseases suggested that the system was sensitive and specific. [The *SCI*® indicates that this paper has been cited in over 430 publications since 1974.]

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Hyperthyroidism in Graves' disease is due to autoantibodies to the thyrotropin (TSH) receptor. The antibodies interact with the receptor in such a way as to trigger the same series of membrane-associated events as the natural ligand TSH.[1] Originally, the receptor antibodies were measured by an *in vivo* bioassay system first involving guinea pigs[2] and later mice.[3] The bioassay was technically difficult, time consuming, imprecise, insensitive, and involved large numbers of experimental animals (at least five animals per determination). Anyone who has worked with this technique will have longed for a better method, and this was very much on my mind when I joined Reg Hall's Endocrine Unit in Newcastle toward the end of 1972.

In the early 1970s, the first TSH receptor assay systems based on ^{125}I-labelled TSH were being described, particularly by the laboratories of Manley[4] in Brisbane and Lissitzky in Marseilles.[5] Using the receptor assay, several groups of investigators, including our own, were able to show that IgG from patients with Graves' hyperthyroidism inhibited ^{125}I-labelled TSH binding to the TSH receptor, thus providing the first direct evidence for the existence of TSH receptor autoantibodies.

A combination of my own expertise in protein chemistry with Hall's exceptional knowledge of clinical thyroidology enabled us to develop quickly a receptor assay for the receptor antibodies that was suitable for use in specialist research laboratories. This was principally possible through the great generosity of John Pierce (UCLA), who provided many laboratories with his highly purified TSH.

The original assay enabled a range of important clinical studies to be carried out and these provided compelling evidence for a pathogenic role of TSH receptor antibodies in Graves' disease. Furthermore, relatively precise measurement of the antibody levels in serial samples was possible for the first time, and studies of changes in TSH receptor antibody levels during treatment by surgery, radioiodine, or antithyroid drugs showed that these forms of therapy had marked effects on receptor antibody synthesis as well as a direct action on thyroid follicular cells.[1]

Although the original assay was valuable, it had many technical problems and was unsuitable for use outside specialist research laboratories. Recently, however, the original procedure has been greatly improved so as to provide a simple, rapid, sensitive, and precise method for TSH receptor antibody measurement,[6] and this is now in routine use in many laboratories throughout the world.

The eight years spent in Newcastle with Hall were immensely rewarding and enjoyable. The original paper was the first in a whole series of studies in which scientists and clinicians worked together successfully. It was also catalytic in terms of stimulating major investigations into the nature of the TSH receptor and the mechanisms involved in the development of thyroid autoimmunity in man.

1. **Rees Smith B.** Thyrotropin receptor antibodies. (Lefkowitz R J, ed.) *Receptor regulation.* London: Chapman and Hall, 1981. p. 215-44.
2. **Adams D D & Purves H D.** Abnormal responses in the assay of thyrotrophin. *Proc. Univ. Otago Med. Sch.* 34:11-12, 1956. (Cited 235 times.)
3. **McKenzie J M.** Delayed thyroid response to serum from thyrotoxic patients. *Endocrinology* 62:865-8, 1958. (Cited 165 times.)
4. **Manley S W, Bourke J R & Hawker R W.** The thyrotrophin receptor in guinea-pig thyroid homogenate: general properties. *J. Endocrinology* 61:419-36, 1974. (Cited 95 times.)
5. **Verrier B, Fayet G & Lissitzky S.** Thyrotrophin binding properties of isolated thyroid cells and their purified plasma membranes. *Eur. J. Biochem.* 42:355-65, 1974. (Cited 85 times.)
6. **Southgate K, Creagh F, Teece M, Kingswood C & Rees Smith B.** A receptor assay for the measurement of TSH receptor antibodies in unextracted serum. *Clin. Endocrinol.* 20:539-43, 1984.

