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A sensitive immunoradiometric assay for serum thyroid-stimulating hormone
A first-line investigation for thyroid function

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Summary
The value of a highly sensitive immunoradiometric assay for thyroid-stimulating hormone (TSH) in distinguishing between hyperthyroid patients and normal controls is discussed. The assay has a sensitivity of 0.3 μIU/ml and correctly categorised all patients in this study as either hyperthyroid or euthyroid. An approach to thyroid function testing using this sensitive TSH assay as a first-line investigation is presented.

Subjects and methods
Fasting TSH concentrations from the sera of 76 normal subjects (51 women aged 19 - 57 years, 25 men aged 22 - 58 years) and 148 untreated thyrotoxic patients (130 women aged 20 - 74 years, 18 men aged 25 - 66 years) were measured. Thyrotoxicosis was diagnosed on the basis of clinical symptoms and signs and elevated serum free thyroxine (fT₄) and free tri-iodothyronine (fT₃) concentrations.

The Serono TSH Maiaclone is a solid phase immunoradiometric assay (IRMA) employing three distinct high affinity monoclonal antibodies, two of these labelled with iodine-125 and the third with fluorescein isothiocyanate (FITC). The three monoclonal antibodies are premixed as a single liquid reagent. The fT₄ and fT₃ were measured by Amerlex Kit radio-immunoassays (Amersham International, UK).

Results
The analytical sensitivity, calculated by analysing the zero standard in replicate (20 times) and determining the two-standard deviation value, was 0.3 μIU/ml. The intra- and interassay coefficients of variation of three controls run in 7 assays are shown in Table I. TSH concentrations were less than 0.5 μIU/ml in the sera of all 148 thyrotoxic patients tested, and less than the analytical sensitivity (0.3 μIU/ml) in 130 (88%). All euthyroid patients in the reference group had a TSH concentration > 0.6 μIU/ml. The range of TSH concentrations in the reference group was 0.6 - 4.1 μIU/ml, with a mean (± SD) of 1.82 ± 0.89 μIU/ml.

Discussion
The Serono TSH Maiaclone assay is a solid phase IRMA employing three high affinity monoclonal antibodies and magnetic separation technology. This study demonstrates that this rapid, sensitive TSH IRMA assay, with an analytical sensitivity of 0.3 μIU/ml, can distinguish between the low TSH found in hyperthyroid patients and TSH concentrations found in normal controls. Although TSH was not undetectable
in all hyperthyroid patients, TSH values were <0.5 μU/ml in all hyperthyroid patients and ≥0.6 μU/ml in all normal controls. The TSH assay thus offers an extremely sensitive and specific test in the diagnosis of hyperthyroidism. Similarly excellent discrimination between hyperthyroid and euthyroid patients has been reported by other workers using sensitive TSH assays, but not uniformly so, overlap between hyperthyroid and euthyroid patients has been noted. The assay described here is rapid and easy to perform, while many of the sensitive TSH assays previously described are time consuming or not ideal for routine use.

As well as being useful in the diagnosis of hyper- and hypothyroidism, TSH measurements are useful in assessing thyroid status in non-thyroidal illnesses - in patients with antibodies to T4 and T3 and in familial dysalbuminaemic hyperthyroxinaemia; all these conditions cause changes in levels of thyroid hormones, but little change in TSH levels. Low TSH levels together with low fT3 levels are suggestive of hypopituitarism, but it must be noted that TSH concentrations may be within the reference range in this condition.

Despite the ease and convenience offered by a sensitive TSH assay, results should be carefully interpreted to avoid incorrect diagnosis. In particular, TSH levels may be within the reference range in patients with the rare syndrome of inappropriate TSH secretion and may not accord with thyroid status in patients on T3 therapy.

Keeping the above caveats in mind, we suggest — as Caldwell et al. recently did — that a sensitive TSH assay be used as a first-line investigation in assessing thyroid status. If TSH is undetectable or below the reference range, an fT4 estimation should be done and, if this is raised, the diagnosis of hyperthyroidism is confirmed, while if fT4 is low the probable diagnosis is hypopituitarism. However, if fT4 is normal, fT3 should be measured for the diagnosis of T3 intoxicosis. If TSH is elevated, again an fT4 estimation should be performed: if fT4 is low the diagnosis is hypothyroidism, while if fT4 is normal the patient has subclinical hypothyroidism.

Greater experience with this assay in a much larger number of patients will inform us whether TSH measurement by a sensitive IRMA will live up to the promise it appears to offer. The assay can be further improved by the use of a lower standard.

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