

This Week's Citation Classic®

Evered D C, Ormston B J, Smith P A, Hall R & Bird T. Grades of hypothyroidism. *Brit. Med. J.* 1:657-62, 1973.

[University Depts. Medicine and Clinical Biochemistry, Royal Victoria Infirmary, Newcastle upon Tyne, and Dept. Haematology, Newcastle upon Tyne General Hospital, England]

Hypothyroidism is a graded phenomenon that can be classified by its clinical features and a range of laboratory techniques. This classification provides a useful framework for the study of the natural history of this disorder. [The SC¹ indicates that this paper has been cited in over 200 publications.]

David C. Evered
CIBA Foundation
41 Portland Place
London W1N 4BN
England

June 1, 1987

Major advances in our understanding of the physiology and pathophysiology of the endocrine system have taken place over the last 30 years. These can be attributed directly to three factors. The first was the development of radioimmunoassay procedures for the protein and polypeptide hormones and, later, for low-molecular-weight compounds. These highly sensitive techniques made it possible to assay directly many hormones in the blood for the first time, and the assays were accurate, precise, fast, and inexpensive. The second factor was the isolation, purification, and synthesis of the hypothalamic releasing hormones, the first of which was thyrotrophin releasing hormone (TRH), which became available for use in 1970. The third major factor directly relevant to these studies was the recognition that most thyroid disease, in the absence of iodine deficiency, is due to autoimmune processes.

I moved to Newcastle upon Tyne in 1970 and, although we worked on different medical units, established an alliance and friendship with Reg Hall that continues to flourish today. At that time, Hall had already established a sensitive thyrotrophin assay¹ in his laboratory. With my previous experience in developing radioimmunoassays of low-molecular-weight compounds, I quickly established assays for thyroxine and triiodothyronine. It was with these techniques that we set out to reappraise the pathophysiology of hypothyroidism.

Tests of thyroid function fell into three distinct categories: direct tests of thyroid function involving thyroid hormone assay or dynamic tests (using radionuclides of iodine), tests reflecting the resultant disturbances of peripheral tissue function, and tests demonstrating secondary perturbations of the hypothalamic-pituitary-thyroid axis (to these were added those techniques used to identify the cause of the thyroid disease).

In our earlier paper² we had stated that hypothyroidism was a graded phenomenon resulting from suboptimal circulating levels of one or both thyroid hormones and that the grades of hypothyroidism could be classified conveniently on the basis of clinical and laboratory features. This paper reported the observations that confirmed this hypothesis. The study was carried out with Brian J. Ormston, a research fellow who had been involved in some of the early clinical studies on TRH; Percy A. Smith, who carried out the lipid and lipoprotein estimations; and Tom Bird, who had set up microtitre techniques for the assay of thyroid autoantibodies.

The paper proved to be of considerable value to our group since it provided a framework for further studies, in particular, a large-scale community survey led by W. Michael Tunbridge that clearly showed the high prevalence of thyroid disease in an unselected population.³ The terminology that we used provoked some debate at the time, but the classification has since been widely adopted. This study introduced the concept of, and focussed attention on, the most minor degree of thyroid failure—subclinical hypothyroidism. It also indicated that this stage did not inevitably progress to more severe degrees of failure; indeed, as we later demonstrated, it can regress. The study also raised the question of whether a minor degree of biochemical thyroid failure was associated with any biological disadvantage and, in particular, if it was a significant risk factor for coronary artery disease. Our later surveys indicated that this was almost certainly not the case,⁴ but many studies addressing this question were carried out in the 1970s with conflicting results. [For a recent review on thyroid disease see reference 5.]

1. Hall R, Amos J & Ormston B J. Radioimmunoassay of human serum thyrotrophin. *Brit. Med. J.* 1:582-5, 1971. (Cited 235 times.)
2. Evered D C & Hall R. Hypothyroidism. *Brit. Med. J.* 1:290-3, 1972. (Cited 50 times.)
3. Tunbridge W M, Evered D C, Hall R, Appleton D, Brewis M, Clark F, Evans J G, Young E, Bird T & Smith P A. The spectrum of thyroid disease in a community: the Wickham Survey. *Clin. Endocrinol.* 7:481-93, 1977. (Cited 210 times.)
4. ———. Lipid profiles and cardiovascular disease in the Wickham area with particular reference to thyroid failure. *Clin. Endocrinol.* 7:495-508, 1977.
5. Ladenson P W. Diseases of the thyroid gland. *Clin. Endocrinol. Metab.* 14:145-73, 1985.

CC/GM