

This Week's Citation Classic

Clark F & Horn D B. Assessment of thyroid function by the combined use of the serum protein-bound iodine and resin uptake of ¹³¹I-triiodothyronine. *J. Clin. Endocrinol. Metab.* **25**:39-45, 1965. [Depts. Med. and Clin. Chem., Med. Sch., Univ. Newcastle upon Tyne and Royal Victoria Infirmary, Newcastle upon Tyne, UK]

A comparison was made of the diagnostic accuracy of the PBI, the resin uptake of ¹³¹I-T3 and their mathematical product: the free thyroxine index. The latter was shown to give the better diagnostic discrimination in patients with thyroid disease and corrected for variations in protein binding of thyroid hormones seen in certain conditions, e.g., pregnancy. [The SC® indicates that this paper has been cited over 250 times since 1965.]

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"This work evolved out of the investigation of the use of the red cell and resin up-take test of labelled thyroid hormones as a test of thyroid function following upon the earlier studies by Hamolsky, *et al.*,¹ Mitchell, *et al.*,² and Tabachnick.³ Following the observations of Osorio, *et al.*,⁴ in 1961 that the red cell uptake of ¹³¹I triiodothyronine was inversely related to the unsaturated or free binding sites on thyroxine binding proteins in plasma (FTB-P), and their subsequent demonstration that an assessment of free thyroxine (FT4) in plasma (the generally accepted determinant of the thyroid status of an individual) could be obtained from the relationship between plasma proteinbound iodine (PBI) and the red cell uptake (Osorio, *et al.*,⁵), we decided to examine the diagnostic reliability of the PBI, of the resin uptake of ¹³¹I triiodothyronine (resin uptake ratio RUR), and of their mathematical product the 'free thyroxine' index (FTI) which is an arbitrary figure assumed to be proportional to the concentrations of free thyroxine in the blood: FT 4 + FTBP = TBPT4.

At equilibrium: $\frac{(FTBP)(FT4)}{(TBPT4)} = K$ or
 $1/K FT4 = \frac{TBPT4}{FTBP}$ assuming that
 $FTBP = K' \frac{1}{RUR}$ and $TBPT4 = PBI$
 $1/K' FT4(FTI) = PBI \times RUR$.

"The derived free thyroxine index so obtained correlated well with the clinical thyroid status of the patient (confirmed when necessary by supplementary tests) and in addition offered for better diagnostic discrimination than the PBI or resin uptake test alone. Furthermore in those subjects whose total thyroid hormones concentration was altered because of a change in the concentration of thyroid hormone binding protein (pregnancy, nephrotic syndrome) and was therefore misleading, the free thyroxine index largely corrected for the disparity.

"The original premise appears to have been borne out and we presume that this is the reason for the frequency of quotation. In addition the concept has been used to evaluate the binding of ligands to plasma proteins in other fields, e.g., clinical pharmacology.

"The work was carried out in the department of medicine and department of clinical biochemistry, University of Newcastle upon Tyne, by myself (as senior Luccock research fellow) and D.B Horn largely during 1963 and owes much to the encouragement of Sir George A. Smart, professor of medicine, and A.L. Latner, professor of biochemistry at that time. Our particular thanks are due to the constant help and advice of S.G. Owen, former reader in medicine, University of Newcastle upon Tyne (presently at the Medical Research Council, London). The paper was submitted solely to the *journal of Clinical Endocrinology and Metabolism* in May 1964 and was accepted by the editor after minor amendments and published in January of the following year. Horn is currently at the department of clinical chemistry, Western General Hospital, Edinburgh, Scotland."

- Hamolsky M W, Stein M & Freedberg A S.** The thyroid hormone-plasma protein complex in man. II. A new *in vitro* method for study of "uptake" of labelled hormonal components by human erythrocytes. *J Clin Endocrinol. Metab.* **17**:33-44, 1957. (Citation Classic. *Current Contents/Clinical Practice* (461:18. 17 November 1980.)
- Mitchell M L, Harden A B & O'Rourke M E.** The *in vitro* resin sponge uptake of triiodothyronine ¹³¹I from serum in thyroid disease and in pregnancy. *J. Clin. Endocrinol. Metab.* **20**:1474-83, 1960.
- Sterling K & Tabachnick M.** Resin uptake of ¹³¹I triiodothyronine as a test of thyroid function. *J. Clin. Endocrinol. Metab.* **21**:456-64, 1961.
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-The assessment of free thyroxine in plasma. *Clin. Sci.* **23**:525-30, 1962.