

# This Week's Citation Classic

**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.  
[Dept. Med., Harvard Med. Sen.; Med. Res. Dept., Yamins Res. Lab.; and Med. Serv., Beth Israel Hosp., Boston, MA]

**A new *in vitro* method is presented, based on the 'uptake' of 1-131 T-3 by red blood cells from whole blood. The simple test accurately differentiates hyper-, hypo-, and euthyroidism, is unaffected by iodine exposure, avoids administration of radioactivity to patients, and indicates several epiphenomena of wide biologic and clinical interest. [The *SCI*® indicates that this paper has been cited over 320 times since 1961.]**

Milton W. Hamolsky  
Department of Medicine  
Brown University  
Rhode Island Hospital  
Providence, RI 02902

October 30, 1980

"Our studies were based on a) the fact that thyroxin (T-4) and triiodothyronine (T-3) molecules are both hydrophilic and lipophilic, and b) the notion that their hormonal action might therefore involve alignment at, and alteration of, the aqueous plasma-lipid membrane interface.

"We found: 1-131 T-4 or 1-131 T-3 passed *in vitro* from buffers to olive or mineral oil, lipid extracts of tissue or cell components, to the rat diaphragm, to foreskin of seven-day old males. Attempts to isolate human white blood cells to study uptakes were premature in 1952, so we turned to human red blood cells —then considered 'simple' sacs of hemoglobin. The addition of increasing amounts of plasma to the buffer solution progressively decreased transfer of T-4 or T-3 to the lipid extracts or tissues; the decrease in transfer was always greater for T-4 than T-3. These studies antedated notions of specific plasma protein binders (TBC or TBPA) of thyroid hormones. We thought we were studying active' lipid or tissue 'uptake' of T-4 or T-3.

"The next step was study of 'uptakes' from

whole plasma. With hyper-, eu-, and hypothyroid plasmas, the rat diaphragm, foreskin, or red blood cell nicely 'diagnosed' the thyroid status of the plasma donor — 'uptakes' were greater from hyper- than from euthyroid plasmas and less from hypo- than from euthyroid plasmas. The standard clinical test involved addition of 1-131 T-3 to a 3 ml. aliquot of whole blood, incubation at 37° for two hours, determination of percent incorporation of T-3 by the washed red cell mass, corrected for hematocrit 'Crisscross' studies (euthyroid cells in hyperthyroid plasmas, etc.) revealed that 'uptakes' were determined by the thyroid status of the plasma donor. This served as the basis for widespread use of resins, coated charcoal, clay, etc., in place of the red cell as the competitive binder of 1-131 T-3 from plasma or serum.

"We offered then the *in vitro* T-3 uptake test which was simple, rapid, reproducible, avoiding administration of radioactivity to the patient, with a differential diagnostic accuracy equal or superior to then available methods, accurate in following therapy of hyper- or hypothyroidism. The test was modified—for pediatrics—to use only 0.5 ml. whole blood. Results were not affected by prior exposure to iodine containing compounds or X-ray dyes which vitiated the then current PBI or 1-131 thyroid uptake tests.

"In continuing series (3,900 tests<sup>1</sup>), we found uptakes were decreased by estrogen and pregnancy (failure of lowered uptake in pregnancy presaged miscarriage) and in families with excess TBC, increased in nephrosis, acidoses, anticoagulant therapy, Dilantin—phenomena which led to studies in many laboratories around the world. For, in addition to the above advantages, citation of our article may be attributed to its introduction at a time of explosive ferment of biological and clinical studies of the thyroid gland.

"In 1977, I was selected by the Mallinck- rodt Company as a 'Founder of Nuclear Medicine' for the development of 'the first T-3 *in vitro* diagnostic test.' "

1. Hamolsky M W, Golodetz A & Freedberg A S. The plasma protein-thyroid hormone complex in man. III. Further studies on the use of the *in vitro* red blood cell uptake of 1-131-I-triiodothyronine as a diagnostic test of thyroid function. *J. Clin. Endocrinol. Metab.* 19:103-16. 1959.