

THE DIFFERENCE IN THYROID HORMONE METABOLISM BETWEEN MAMMALIAN FETUSES AND ADULTS AND ITS IMPLICATIONS

Sing-Yung Wu, M.D., Ph.D.

Radiology and Research Services, VA Medical Center, Long Beach, California 90822, U.S.A.

Received date: 22 May 2020

Revised date: 12 June 2020

Accepted date: 02 July 2020

*Corresponding author: Sing-Yung Wu, M.D., Ph.D.

Radiology and Research Services, VA Medical Center, Long Beach, California 90822, U.S.A.

SUMMARY

The neonatal screening program for congenital hypothyroidism (CH) implemented nearly half a century ago has helped a lot of neonates with CH. However, judging from the early involvement of thyroid hormone (TH) in brain development, the reliance on the neonatal strategy to reverse 'ALL' of the cerebral and other developmental anomalies may be in question, and there is room for improvement. The study from our group in the past three decades has demonstrated that sulfo-conjugation is the primary pathway for TH metabolism in developing fetuses in utero that is distinctly different from adults. Our studies have also shown that 3,3'-diiodothyronine sulfate (3, 3'-T2S) is a major fetal metabolite in inactivating TH in the developing mammals that do not need the active catabolic hormones. Further, 3, 3'-T2S has been shown to cross the placenta and return to the maternal circulation. The appearance of W-compound, a material detected by 3, 3'-T2S-specific antibody in human maternal and fetal circulation has been shown to correlate significantly to fetal thyroid function. It is time to consider a different approach by taking advantage of the difference in TH metabolism between fetuses and adults. Further study on the sulfation pathway may provide an alternative strategy to the current neonatal screening and the "catch-up" therapy after birth.

KEYWORDS: Congenital hypothyroidism, Fetal Thyroid Hormone Metabolism, Fetal Thyroid Function Marker, W Compound.

INTRODUCTION

The Neonatal screening program for congenital hypothyroidism (CH) has allowed early treatment of this disorder and improving long term outcomes.^[1-3] However, despite the systematic screening and treatment of CH, mild brain damages do occur.^[4,5] Since thyroid hormone (TH) is involved early in the first trimester in fetal brain development, including the proliferation, migration, and differentiation of neuronal cells,^[6,8] the defects cannot be totally reversible postnatally is expected. These irreversible changes can impact on child IQ, cognitive, and motor measures.^[1,4,9-12] Children affected may present reduced socio-educational achievement.^[13,14] higher risk of autistic trait.^[10] and higher ADHD (attention-deficit/hyperactivity disorder) symptoms.^[15] More recently, it has been found higher preconception maternal iodine intakes are associated with higher child IQ.^[16] indicating intervention before or during pregnancy may help the future outcome of children. Unfortunately, the CH incidence in the United States showed a trend of increasing from ~ 1:4100 in 1987 to ~ 1:2400 in 2002.^[17] Besides, despite the USA

being considered to be iodine sufficient for the general population, the US dietary iodine intakes have decreased drastically since the 1970s, with deficiency reemerging in vulnerable groups such as women of reproductive age.^[18] All these findings indicate that there is room for improvement in the current strategy with neonatal screening. Further study of fetal thyroid hormone metabolism and function may provide an alternate approach in managing CH, which is warranted to avert unwanted consequences.

The Unique Feature of Fetal Thyroid Hormone Metabolism

This lab, in collaboration with Dr. D. A. Fisher at UCLA-Harbor General Medical Center, has found in mammalian fetuses that sulfo-conjugation is the major pathway for TH metabolism (Fig. 1, 19, 20).

Before the onset of active synthesis and release of TH, iodothyronines detected in the fetus are maternal in origin.^[11,22] This period is approximately the first 17 gestational days (d) in rats, 50d in sheep, and 90d in humans (Fig. 1, the upper horizontal light dotted line).

The proposed scheme for ovine fetal iodothyronine metabolism in late gestation (near term) depicts the production rates for sulfoconjugated thyroid hormone

analogs (shown as numbers in parentheses along with the thick arrows in Fig. 1).

FETAL THYROID METABOLISM

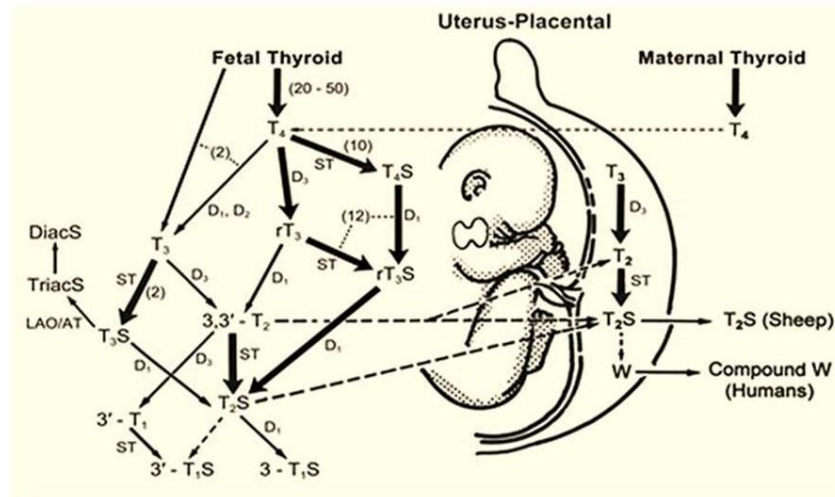


Fig. 1. Postulated metabolic pathways for ovine fetal thyroid hormones (35). Heavy solid lines indicate pathways that are more active in fetuses than in adults; thin solid lines, pathways that are less active in fetuses. The upper horizontal light dotted line depicts T₄ of maternal origin moving to the fetal compartment in the first trimester, before the fetal thyroid begins functioning. Other broken lines represent unconfirmed pathways. Numbers in parentheses indicate published production rates (µg/kg/d) (21). (D₁, D₂, and D₃: type I, type II, and type III iodothyronine deiodinases; ST: iodothyronine sulfotransferases (SULT); LAO/AT: L-amino acid oxidase/aminotransferase; DiacS: sulfated 3,3'-diiodothyroacetic acid.)

The high production rate (µg/kg/d) of T₄ sulfate (T₄S) reflects the activity of the sulfation pathway (Fig. 1 and)^[21] The rT₃S production rate likely represents both sulfation of rT₃ and inner-ring deiodination of T₄S. This scheme is shown in Fig. 1 and also predicts 3,3'-T₂S is a major thyroid hormone metabolite in the fetus. Intravenous infusion of radioiodine labeled T₃ and T₄ into near term fetuses, labeled T₂S was identified as the

major fetal iodothyronine metabolite in maternal urine.^[23] Besides, in thyroidectomized sheep model, we found that 3,3'- T₂S excretion in maternal urine reflects fetal thyroid function.^[24] These data indicate clearly that maternal-fetal transfer of TH and its metabolites is a two-way street, although ovine placenta is less permeable as compared to rat or human (Table 1).

Table 1: Comparison of sheep, rat and humans in the study of fetal-to -maternal transfer of iodothyronines in pregnancy.

	Sheep	Human	Rat
Length of Gestation :	150 d	280 d	21 d
Species	precocial	precocial	altricial
Thyroid Function at birth:	mature	mature	immature
	(similar to humans)		(2nd trimester to human)
CNS Development at birth	mature	intermediate	immature
Placenta: type:	epitheliochorial	haemomonochorial	haemotrichorial
origin:	maternal and fetal	fetal only	fetal only
layers:	6	3	4
Placental permeability to TH (vs. human)	less permeable	----	more permeable
Animal model to study placenta in late gestation	yes	----	no

We have shown that high concentrations of sulfated iodothyronine analogs in human and ovine fetal serum.

These include T₄S, T₃S, rT₃S, and 3,3'-T₂S (T₂S).^[20] The high gradient between fetal and maternal serum concentrations of iodothyronine sulfates raises the possibility that there may be significant fetal to maternal transfer of iodothyronine sulfoconjugates. In humans, we found high levels of radioimmunoassayable T₂S in maternal serum.^[25] and urine.^[26] Levels increased with the progression of pregnancy and peaked before parturition. At delivery, a 20-fold increase in serum

"T₂S" (Fig. 2) was found compared to non-pregnant women and "T₂S" levels returned to non-pregnant values in 7 to 10 days (Fig. 3). On closer examination, the radioimmunoassayable "T₂S" did not cochromatograph with synthetic T₂S by HPLC (25). The authentic T₂S was hydrolyzed by hot-acid digestion.^[25] Using this procedure, the recovery of T₂S-crossreactive material (W-Compound) was near 82% in fetal and maternal serum.^[27,28]

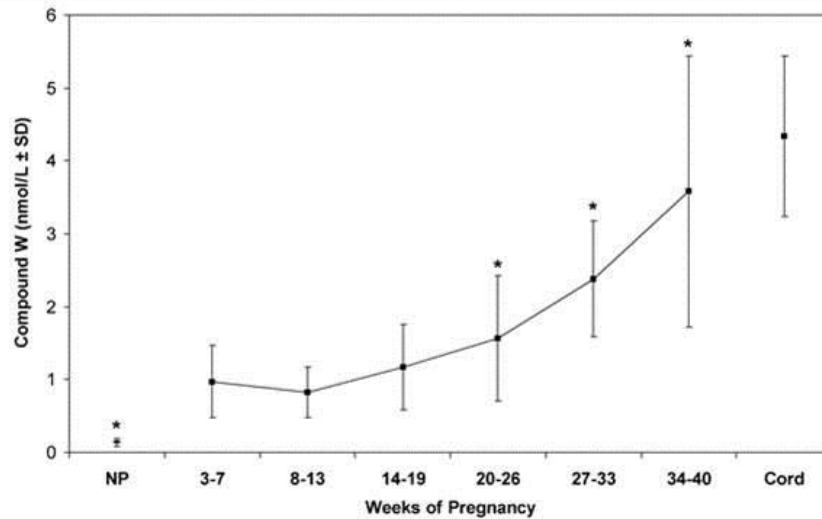


Fig. 2: Changes of Compound W at different gestation periods. Normal values of T₂S-crossreactive material (W-compound) in serum from pregnant women, nonpregnant women (NP), and newborns. Vertical bars are mean ± 1 SD. * p < 0.05 cf. 3-7 weeks pregnancy.

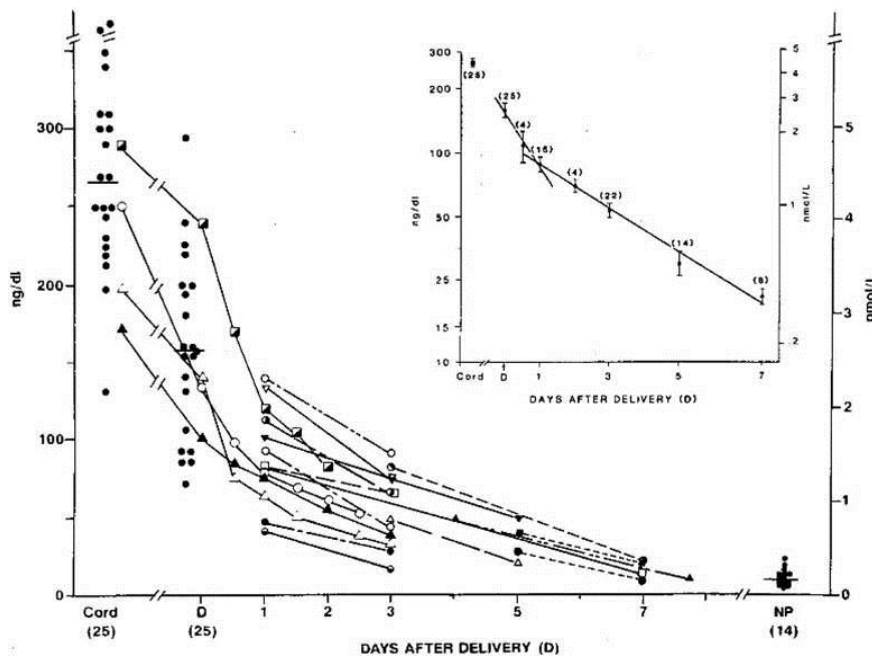


Fig. 3: Change of serum concentrations of W-Compound in cord and maternal serum. W-Compound, expressed as ng/dl of T₂S, in newborns and maternal serum samples at the time of delivery(D). The connected lines represent serial measurements in the same patients (n = 18). T₂S concentrations also were measured in 14 nonpregnant women (NP) for comparison. The decrease in serum W-compound concentrations after parturition is depicted in the semilog plot in the inset. The closed circles and vertical bars represent the mean ± SEM, and (n) represents the total number of samples studied at each time period in a total of 35 patients.
W-Compound, A Potential And Non-Invasive Marker For Fetal Thyroid Function

Prior studies suggest strongly that W-Compound is a metabolite of fetal thyroid hormone capable of transplacental fetal to maternal transfer.^[20,25-27] Both maternal and fetal W-Compound levels increase progressively during gestation with significant direct correlation (in both mothers and fetuses). Additionally, in 436 paired cord and maternal sera obtained at delivery, a highly significant positive correlation was observed between fetal W-Compound and fetal FT4.^[28] A significant positive correlation was also observed between serum levels of fetal W-Compound and fetal FT4 and between maternal and fetal W-Compound.^[29] In contrast, no correlation was observed between maternal serum W-Compound and maternal serum FT4 in euthyroid or hyperthyroid women. Furthermore, maternal W-Compound levels seem to reflect the effects of drugs on fetal thyroid function.^[29] In women on propylthiouracil (PTU), maternal W-Compound levels were in the low normal range and did not show the usual increase with the progression of gestation.^[29] The lack of progression in maternal W-Compound levels was confirmed in a recent study of 22 pregnant women treated with anti-thyroid medication.^[30] A significant increase in maternal W-Compound was observed when the PTU dose was decreased or discontinued. Consistent with being an analog of iodothyronine, we recently found a high level of iodine content in highly purified W Compound preparation. The sample was analyzed by a Triple Quadrupole ICP-MS (Inductively Coupled Plasma Mass Spectrum).^[31]

Summary

The present evidence suggests that T3 removed from fetal circulation appears in maternal compartments as T2S in sheep and W-Compound in humans. Further study of the sulfo-conjugation pathway in the fetus and fetal to the maternal transfer of thyroid hormone analogs may provide an alternate approach in managing CH, which may improve unwanted consequences from using neonatal screening alone.

Future Studies of Fetal-Thyroid Hormone Metabolism

To promote further thyroid hormone metabolism in the fetus, the Thyroid Research Lab at VA Long Beach will provide investigators (who present CV, research protocol, and publications) with the following tools. These include specific antibodies and methods of measuring the enlisted thyroid hormone analogs, as shown below.

TH Analogs

1. Specific antibody and radioimmunoassay of 3,3',5'-Triiodothyronine Sulfate (rT3S) (VACO-awarded invention ownership: GPB# 20-576, June 23, 1993).^[32]
2. Specific antibody and radioimmunoassay of 3,3'-Diiiodothyronine Sulfate (T2S) (VACO-awarded invention ownership: GPB# 20-575, June 17, 1993).^[24-27]

3. Fetal Thyroid Function Indicator by Radioimmunoassay of W Compound in Maternal Sera During Pregnancy (VACO-awarded invention ownership: GPB# 20-671, June 1, 1995).^[24-27]
4. "Fetal Thyroid Function Indicator in Serum and Urine", September 23, 1997 Patent No. 5,670,380, U.S. Department of Commerce, Patent and Trademark Office.^[24-27]
5. Specific antibody and radioimmunoassay of Thyroxine Sulfate (T4S).^[33,34]
6. Specific antibody and radioimmunoassay of 3'-Monoiodothyronine sulfate (3'-T1S).^[35]
7. Specific antibody and radioimmunoassay of Triac Sulfate (TriacS).^[35]
8. Specific antibody and radioimmunoassay of 3,3'-Diiiodothyronine (T2).^[36]
9. Specific antibody and radioimmunoassay of 3,3',5'-Triiodothyronine (rT3)

Declaration: No conflict of interest.

REFERENCES

1. Leger, J., Congenital hypothyroidism: a clinical update of long-term outcome in young adults. Eur J Endocrinol, 2015; 172: R67-77.
2. LaFranci S, 2018, Clinical treatments and detection of congenital hypothyroidism, UpToDate, Nov 08, 2018.
3. Sanchez AR, MJC Guindulain, MA Merillas, SR Segura, JCM Nararro, MDR Arnao, Diagnosis and follow-up of patients with congenital hypothyroidism detected by neonatal screening, An Pediatr (Barc), 2019; 90(4): 250.e1-250.e8.
4. Haddow, J.E., Palomaki, G.E., Allan, W.C., Williams, J.R., Knight, G.J., Gagnon, J., O'Heir, C.E., Mitchell, M.L., Hermos, R.J., Waisbren, S.E., Faix, J.D., Klein, R.Z. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med, 1999; 341: 549-555.
5. Clairman H., J. Skocic, J.E. Lischinsky, J. Rovet, Do children with congenital hypothyroidism exhibit abnormal cortical morphology? Pediatr Res., 2015; 78: 286-297.
6. Bernal J., Thyroid hormone in brain development and function, Feingold KR, Anawalt B, Boyce A, et al. editors, Endotext [Internet], South Dartmouth: MDText.com, Last update September 2, 2015.
7. Forthead AJ, AL Fowden, Thyroid hormones in fetal growth and parturition maturation, J Endocrinol, 2014; 221: R87-R103.
8. Morreale de Escobar, G., Obregon, M.J., Escobar del Rey, F. Role of thyroid hormone during early brain development. Eur J Endocrinol, 2004; 151: U25-U37.
9. Derakhshan A, TIM Korevaar, PN Taylor, D Levie, M Guxens, VWV Jaddoe, SM Nelson, H Tiemeier, RP Peeters, The association of maternal thyroid autoimmunity during pregnancy with child IQ, J Clin Endocrinol Metab, 2018; 103: 3729-3736.

10. Levie D, TIM Korevaar, SC Bath, A Dalmau-Bueno, M Murcia, M. Espada, M Dineva, JM Ibarluzea, H Tiemeier, M Rebagliato, MP Rayman, RP Peeters, M Guxens, Thyroid function in early pregnancy, child IQ, and Autistic traits: a meta-analysis of individual participant data, *J Clin Endocrinol Metab*, 2018; 103: 2967-2979.
11. Vulsmat T, M.H. Gons, J.J.De vijlder, Maternal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid dysgenesis. *N Engl J Med*, 1989; 321: 13-16.
12. Pearce EN, Mild-to-moderate iodine deficiency in early pregnancy is associated with lower verbal IQ in children, *Clin thyroidol*, 2019; 31: 195-197.
13. Mitchell, M.L., Klein, R.Z. The sequelae of untreated maternal hypothyroidism. *Eur J Endocrinol*, 2004; 151(3): U45-U48.
14. Leger, J., Ecosse, E., Roussey, M., Lanoe, J.L., Larroque, B., and the French Hypothyroidism Study Group. Subtle health impairment and socioeducational attainment in young adult patients with congenital hypothyroidism diagnosed by neonatal screening: a longitudinal population-based cohort study. *J Clin Endocrinol Metab*, 2011; 96: 1771-1782.
15. Abel MH, E Ystrom, IH Caspersen, HM Meltzer, H Aase, LE Torheim, RB Askeland, T Reichborn-Kjennerud, AL Brantsaeter, Maternal iodine intake and offspring attention-deficit/hyperactivity disorder: results from a large prospective cohort study, *Nutrients*, 2017; 9(11): PMID 29137191.
16. Pearce EN, Higher preconception maternal iodine intakes are associated with higher child IQ, *Clin thyroidol*, 2018; 30: 302-304.
17. Harris K.B., K.A. Pass, Increase in congenital hypothyroidism in New York State and in the United States, *Mol Genet Metab*, 2007; 91: 268-277.
18. Panth P., G.Guerin, N.M. DiMarco, A review of iodine status of women of reproductive age in the USA, *Biol Trace Elem Res*, 2019; 188(1): 208-220.
19. Burrow, G.N., Fisher, D.A., Larsen, P.R. Maternal and fetal thyroid function. *N Engl J Med*, 1994; 331: 1072-1078.
20. Wu, S. Y., W. L. Green, W. S. Huang, M. T. Hays, I. J. Chopra, Alternate pathways of thyroid hormone metabolism, *Thyroid*, 2005; 15: 945-960.
21. Polk, D.H., A. Reviczky, S.Y. Wu, W.S. Huang, D.A. Fisher, Metabolism of sulfoconjugated thyroid hormone in developing sheep, *Am J Physiol (Endocrin Metab)* 29, 1994; 266: E892 – 895.
22. Patel, J, K. Landers, H. Li, R.H. Mortimer, K. Richard, Delivery of maternal thyroid hormones to the fetus, *Trends Endocrinol Metab*, 2011; 22(5): 164-170.
23. Wu, S.Y., Polk, D.H., Huang, W.S., Green, W.L., Thai, B., Fisher, D.A. Fetal-to-maternal transfer of thyroid hormone metabolites in late gestation in sheep. *Pediatr Res.*, 2006; 59: 102-106.
24. Wu, S.Y., W. S. Huang, D. A. Fisher, W.H. Florsheim, K. Kashiwai, D.H. Polk, 3, 3'-diiodothyronine sulfate excretion in maternal urine reflects fetal thyroid function in sheep *Pediatr Res.*, 2001; 50: 358-364.
25. Wu, S.Y., Polk, D.H., Chen, W.L., Fisher, D.A., Huang, W.S., Yee, B. A 3, 3' – diiodothyronine-sulfate cross-reactive compound in serum from pregnant women. *J Clin Endocrinol Metab.*, 1994; 78: 1505-1509.
26. Wu, S.Y., D.A. Fisher, W.S. Huang, P. Beck-Peccoz, S.W. Kuo, C.H.Emerson, W.L. Chen. Urinary Compound W in pregnant women is a potential marker for fetal thyroid function. *Am J Obst-Gynecol*, 1998; 178: 886-91.
27. Wu, S.Y. W. S. Huang, Ho E. , Wu, E. S. C., Fisher, D. A., A 3,3'-diiodothyronine sulfate cross-reactive substance, compound W, in serum from pregnant women – a potential marker for fetal thyroid function, *Pediatr Res*, 2007; 61: 307-312.
28. Wu SY, WL Green, A 3, 3'-diiodothyronine sulfate cross-reactive material (W Compound) a potential marker for fetal hypothyroidism, In *Tech Book: Hypothyroidism – Influence and Treatments*, 2012.
29. Cortelazzi, D. P. S. Morpurgo, P. Azmperini, D. A. Fisher, P. Beck-Peccoz, S. Y. Wu, Fetal Hypothyroidism: New diagnostic and therapeutic approaches, *Europ J Endocrinol*, 1999; 141: 570-578.
30. Vanmiddlesworth, L, N. R. Vanmiddlesworth, R. S. Egerman, A. J. Bush, R. D. Ramsey, L.P. Delmar, E. C. Ho, S. Y. Wu, Thyroid function and 3,3'-diiodothyronine sulfate cross-reactive substance (compound w) in maternal hyperthyroidism with antithyroid treatment, *Endocrine Pract.*, 2011; 17: 170-176.
31. Wu, S.Y., C. Ma, B. X. Xi, T. Synold, A Fresh Look at W- Compound: A Potential Marker for Fetal Thyroid Function, *Pediatric Dimensions*, March, 2018; 29.
32. Wu, S.Y., W.S. Huang, D. Polk, W.L. Chen, A. Reviczky, I.J. Chopra, D.A. Fisher, The development of a radioimmunoassay for 3,3',5'-triiodothyronine sulfate (rT3S) in human serum and amniotic fluid, *J Clin Endocrinol Metab*, 1993; 76: 1625-1630.
33. Wu, S.Y., T.S. Huang, D. Polk, H. Warner, W.L. Green, D.A. Fisher, Identification of thyroxine-sulfate (T4S) in human serum and amniotic fluid by a novel T4S radioimmunoassay, *Thyroid*, 1992; 2: 101-105.
34. Wu, S.Y., D. Polk, S. Wong, A. Reviczky, R. Vu, D.A. Fisher, Thyroxine Sulfate (T4S) is a major thyroid hormone metabolite and a potential intermediate in the monodeiodination pathways in fetal sheep, *Endocrinology*, 1992; 131: 1751-1756.
35. Wu, S. Y. D. H. Polk, E. Ho, D. A. Fisher, 3'-Monoiodothyronine sulfate and triac sulfate are thyroid hormone metabolites in developing sheep, *Pediatr Res*, 2008; 63: 149-153.
36. Wu, S.Y., I.J. Chopra, Y. Nakamura, D.H. Solomon, L.R. Bennett, A radioimmunoassay for measurement

of 3,3'-L-diiodothyronine (T2), J Clin Endocrinol Metab., 1976; 43: 682-685.