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# NEW INSIGHTS INTO THE PHYSIOLOGY OF THYROID HORMONE DEIODINATION

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The major secretory product of the thyroid gland is 3,5,3′,5′-tetraiodo-L-thyronine (L-thyroxine, $T_4$), which is about ten times more abundant in thyroid secretion than is 3,5,3′-triiodo-L-thyronine ($T_3$). However, evidence indicates that almost all the metabolic potency of thyroid hormone secretion is accounted for by $T_3$. About 80% of $T_3$ in humans is generated extrathyroidally by the removal of the iodine atom in the 5′ position (Figure 1). Thus, 5′-deiodination of $T_4$ may be viewed as a process of *activation.* Kinetic studies indicate that about 35% of the $T_4$ secreted is metabolized to $T_3$. Approximately 40% is deiodinated in the 5 position, resulting in metabolically inactive 3,3′,5′-triiodo-L-thyronine (reverse $T_3$ or $rT_3$); this deiodinative process can be viewed as *inactivation.* The remaining $T_4$ is disposed by biliary excretion and other minor pathways.[1,2] (See R.R. Cavalieri, THYROID TODAY, Volume III, Number 7, November 1980).

The molecular basis of the greater biological potency of $T_3$ is the at least ten times greater affinity of specific nuclear receptors for this hormone, compared with $T_4$.[3] L-triiodothyronine has a predominantly intracellular localization as opposed to $T_4$.[4] L-thyroxine, because of its greater affinity for the plasma binding proteins, remains extracellular to a great extent. At physiologic serum thyroid hormone concentrations, more than 90% of the iodothyronine specifically bound to nuclear receptors is $T_3$.[5] Given the greater affinity of the receptors for $T_3$, and the extracellular location of $T_4$, ten times greater $T_4$ concentrations than are present would be necessary to achieve the same degree of occupancy of the receptors if the activation process, namely conversion of $T_4$ to $T_3$, did not take place.

As shown in Figure 1, further deiodination of the iodothyronine "nucleus" occurs. This gives rise to the three diiodothyronines, to 3- and 3′-monoiodothyronine, and finally to thyronine itself. It is possible to measure these metabolites in human serum; typical results from different laboratories are summarized in Table 1. There are several reasons for the variable serum concentrations of these $T_4$ deiodination products: differences in production rates and metabolic clearance rates, and the binding affinities of the various products for human serum proteins.

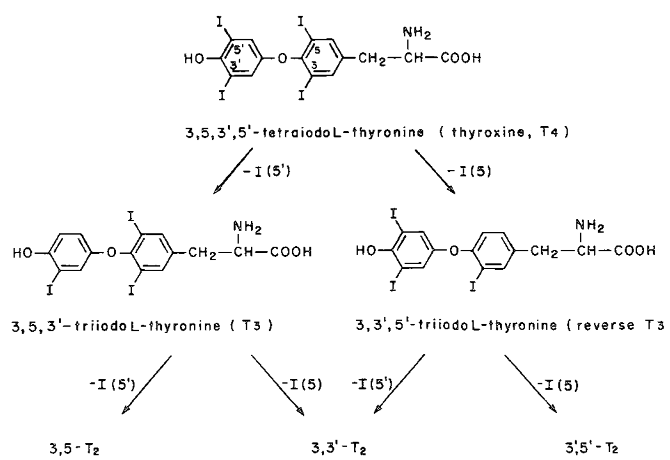


**Figure 1.**
**Structure and pathways of deiodination of various iodothyronines.**

Although $T_3$ and $rT_3$ are produced in approximately equal amounts, and the affinity of $rT_3$ for the major thyroid hormone binding proteins is slightly higher than that of $T_3$, the concentration of $rT_3$ is lower than that of $T_3$. This is the case because $rT_3$ is more rapidly cleared from the serum than is $T_3$, predominantly by 5'-deiodination in the liver and kidney. In these tissues, the 5'-deiodinase for $T_4$ and for $rT_3$ is probably the same enzyme. This is thought to explain the fact that in situations such as severe illness or starvation, where there is an impairment of the $T_4$ to $T_3$ conversion process and a fall in serum $T_3$ level, serum $rT_3$ concentrations also rise.[6] Based on current kinetic studies, it would appear that 3,3'-diiodothyronine is the most important product of the deiodination of $rT_3$ and $T_3$, but its clearance is so rapid as to result in extremely low serum concentrations that are difficult to quantitate accurately by radioimmunologic procedures.[7] Since none of the diiodothyronines has metabolic activity, measurements are of interest primarily to the investigator.

Little is known about regulation of the rate of $T_3$ deiodination, which seems to occur predominantly by inner ring deiodination to produce 3,3'-diiodothyronine. This reaction is not required for the hormone to bind to its nuclear receptor nor for its biological activity. The putative enzyme is especially active in the central nervous system tissue; it also is present in the liver, but not in the kidneys or in the pituitary gland. Activity of $T_3$ 5-deiodinase in rat brain parallels thyroid status; whether these changes could have some role in the regulation of the concentration of $T_3$ in the central nervous system is speculative.[8]

**Table 1. Concentrations of Various Iodothyronines in Normal Human Sera**

| Iodothyronine | Concentration |
|---|---|
| L-thyroxine ($T_4$) | 5–11 μg/dl |
| 3,5,3'-triiodo-L-thyronine ($T_3$) | 80–220 ng/dl |
| 3,3',5'-triiodo-L-thyronine (reverse $T_3$) | 10–30 ng/dl |
| 3,3'-diiodothyronine | 1.5–8 ng/dl |
| 3',5'-diiodothyronine | 2–4 ng/dl |
| 3,5-diiodothyronine | 4–8 ng/dl |

### Localization and Biochemistry of $T_4$ to $T_3$ Conversion

Serum $T_3$ levels are considered to be a good reflection of the intracellular concentration of the hormone; this is supported by experimental as well as clinical observations in many tissues. Patients with slow but steady progression of thyroid gland destruction, either by chronic lymphocytic thyroiditis or after therapeutic doses of radioiodine, are euthyroid clinically as long as the serum concentration of $T_3$ is maintained at mid-normal levels. Many experiments support this concept. In animal studies in which the 5'-deiodination of $T_4$ to $T_3$ is blocked with propylthiouracil (PTU), serum $T_3$ decreases and serum $T_4$ remains normal. Such animals develop evidence of biochemical hypothyroidism, eg, growth hormone decreases and the level of the thyroid hormone sensitive enzyme, hepatic mitochondrial α-glycerophosphate dehydrogenase, is also reduced.[9]

Unfortunately, it is not possible to extrapolate from serum $T_3$ concentrations to intracellular $T_3$ in all tissues. The first hint that this might be the case came from clinical studies in which apparently euthyroid patients with iodine deficiency had normal serum $T_3$ concentrations together with reduced $T_4$ and elevated serum thyroid-stimulating hormone (TSH) levels.[10] It was not clear how the pituitary gland was informed that increased rates of TSH secretion were required for maintenance of normal serum $T_3$ concentration under these circumstances. When this phenomenon was evaluated in animals, appropriate doses of $T_4$ caused a rapid decrease in pituitary TSH release in hypothyroid rats without causing a detectable increase in the serum $T_3$. This effect was subsequently shown to be due to the rapid conversion of $T_4$ to $T_3$ in pituitary tissue.[11,12] The effect of $T_4$ could be blocked by iopanoic acid (Telepaque®) (Figure 2), a competitive inhibitor of $T_4$ to $T_3$ conversion in all tissues,[13,14] but not by PTU, an inhibitor active in the liver and kidney. The presence of intracellular $T_3$ was not reflected by changes in the serum $T_3$ concentration. We estimated that about 50% of the intrapituitary $T_3$ was produced locally from $T_4$ in the pituitary.

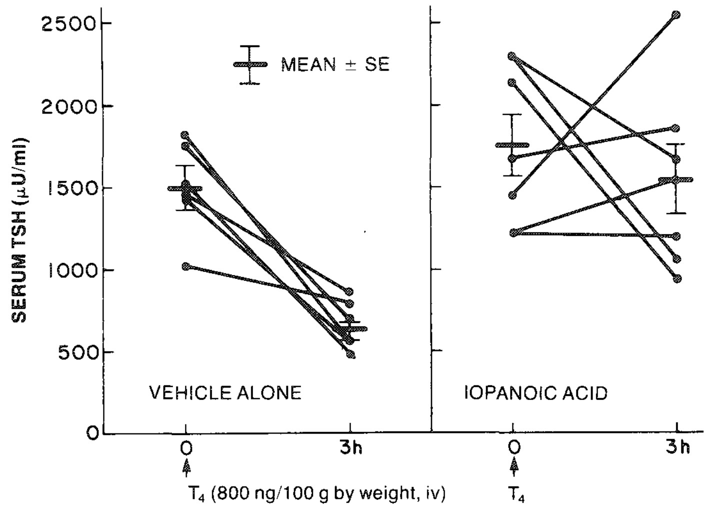


**Figure 2.**
**Effect of blocking $T_4$ to $T_3$ conversion on the acute suppression of serum TSH induced by $T_4$ in hypothyroid rats.**

Thus, the simple concept that serum $T_3$ concentration reflects intracellular $T_3$ concentration is only partly true. For some tissues, both serum $T_3$ and $T_4$ will need to be considered. In the liver and kidney, serum $T_3$ is the most important source of nuclear $T_3$ with only small quantities of intracellular $T_3$ derived exclusively from intracellular $T_4$. However, in the anterior pituitary, the cerebral cortex, and the cerebellum, significant contributions are derived from intracellular $T_4$ to $T_3$ conversion (Table 2).[15]

**Table 2. Sources of $T_3$ Bound to Nuclear Receptor in Various Rat Tissues**

| | Serum $T_3$, % | $T_3$ produced locally from $T_4$, % |
|---|---|---|
| Kidney | 95 | 5 |
| Liver | 80 | 20 |
| Anterior Pituitary | 50 | 50 |
| Cerebral Cortex | 25 | 75 |
| Cerebellum | 50 | 50 |

Since the mid-seventies our knowledge of the biochemistry of $T_4$ to $T_3$ conversion has increased enormously. By and large, the liver and the kidney have been found to be the most active tissues on a weight basis and probably the source of most of the $T_3$ generated extrathyroidally in the euthyroid state. The enzyme is recovered in membrane-enriched fractions of kidney and in microsomal fractions of liver homogenates. It requires reduced thiols for activity and is inhibited uncompetitively by PTU;

this mechanism probably involves the tight binding of the drug to an essential sulfhydryl in the enzyme.[16,17] Methimazole (Tapazole®) does not inhibit this enzyme. We have designated this enzyme activity as Type I or *PTU-sensitive $T_4$ 5'-deiodinase* to distinguish it from the Type II $T_4$ 5'-deiodinase activity found in both the anterior pituitary and central nervous system. Type II $T_4$ 5'-deiodinase has a Michaelis constant ($K_m$) for $T_4$ that is much lower than that of the Type I enzyme; its kinetics suggest a sequential, rather than an alternating mechanism, and it is not inhibited by PTU (Table 3). This resistance to inhibition by PTU accounts for the failure of this drug to block the acute $T_4$-induced suppression of TSH release mentioned earlier.[12,18,19]

**Table 3. Biochemical and Physiological Characteristics of Two Enzymatic Activities That Convert $T_4$ to $T_3$ (5'-Iodothyronine Deiodinase)**

| | Type I | Type II |
|---|---|---|
| Effect of PTU | inhibition | none |
| Km for $T_4$ | "high" | "low" |
| Tissue localization | liver, kidney | pituitary, CNS |
| Response to hypothyroidism | decrease | increase |
| Response to hyperthyroidism | increase | decrease |
| Possible physiological role | provide $T_3$ to serum | provide $T_3$ to cells |

### Physiological Implications

In addition to the difference in the biochemical requirements for $T_4$ to $T_3$ conversion, there are characteristic responses of the two enzymes to alterations in thyroid status. These are summarized in Table 3. Type II $T_4$ 5'-deiodinase activity is increased in cerebral cortex, cerebellum, and pituitary extracted from hypothyroid rats.[8] Given the importance of local $T_3$ generation, and hence the dependence of the cortex $T_3$ concentration on the plasma $T_4$, such a mechanism would prevent a decrease in tissue $T_3$ subsequent to a decrease in plasma $T_4$ when the thyroid gland is failing.

Brain differentiation and maturation are known to require thyroid hormone. There are numerous studies that show the biochemical, physiological, and morphological consequences of hypothyroidism during brain development. When graded congenital hypothyroidism was induced in rats, only those with more marked hypothyroidism showed biochemical evidence of thyroid hormone deficiency in the brain. These rats could tolerate as much as a 90% reduction in serum $T_4$ without showing evidence of hypothyroidism in the cerebral cortex, except for the fact they had a 10- to 15-fold increase in Type II $T_4$ 5'-deiodinase activity. To test whether this augmented enzyme activity could maintain the intracerebral $T_3$ concentration within normal limits, a minute dose of $T_4$ was given. The serum $T_4$ and $T_3$ levels were barely changed but the intracortical concentration of $T_3$ was normalized. This increment in $T_3$ was reflected by a significant increase in one of the enzymes used as markers of the thyroid status of the cortex; both the increment in cortical $T_3$ and in this enzyme were abolished by iopanoic acid.[20] These studies strongly indicate that the increased Type II $T_4$ 5'-deiodinase activity observed in hypothyroidism is of physiological significance for those tissues, like the cerebral cortex, that obtain most of their $T_3$ from local $T_4$ to $T_3$ conversion and not from the serum. One may question what teleological purpose is served by having $T_4$ to $T_3$ conversion increase in anterior pituitary, since this might tend to blunt the physiologically appropriate increase in TSH secretion that should occur when serum $T_4$ decreases. While the final answer is not known, it is possible that the major increase in pituitary $T_4$ 5'-deiodinase in hypothyroidism occurs in the somatotroph, not the thyrotroph, and thyroid hormone is required for normal rates of growth hormone synthesis. This possibility is being explored in our laboratory.

As mentioned, the role of the Type I $T_4$ 5'-deiodinase in liver and kidney is to provide $T_3$ to the serum and, therefore, to most peripheral tissues. These include heart and skeletal muscle, which do not appear to be capable of generating significant quantities of $T_3$, at least on the basis of *in vitro* studies. The concentration of $T_3$ in liver and kidney also depends mainly on the serum $T_3$ level.

Type I $T_4$ 5'-deiodinase activity changes in a number of physiological and pathophysiological conditions. Thus, the well-known reduction of serum $T_3$ seen in the "euthyroid sick" syndrome is due to decreased $T_4$ to $T_3$ conversion. The concomitant reduction observed in the capacity of kidney and liver to catalyze $T_4$ to $T_3$ conversion in experimental models has led to the conclusion that the decreased enzyme activity in these two tissues is the basic mechanism. All things being equal, one would anticipate that those tissues more dependent on plasma $T_3$ concentration are the most affected. The reduced availability of $T_3$ in these tissues along with some resistance to thyroid hormone action, specifically to its calorigenic effect, may be viewed as of physiological advantage in such conditions. However, in spite of extensive speculation, the significance is not yet clear (see G. Schussler, THYROID TODAY, Volume III, Number 3, June 1980). Similarly, the physiological significance of the increased enzyme activity observed in kidney and liver in experimental hyperthyroidism and the reduction observed in hypothyroidism also are not well understood.

### Clinical Implications

The changes in the rates of iodothyronine deiodination that occur in response to a number of stimuli, along with other concomitant changes in thyroid physiology, complicate the interpretation of blood tests. Thus, in the "euthyroid sick" patient there may be changes in the production rate and in the distribution of $T_4$ along with the decreased rate of $T_4$ to $T_3$ conversion alluded to above.[21] The low levels of serum $T_4$ and $T_3$ certainly suggest hypothyroidism. In this context, serum TSH and antithyroid antibodies may be of help. The accumulation of $rT_3$, a reflection of the impaired 5'-deiodinase activity (Type I $T_4$ 5'-deiodinase) has been claimed to be helpful in distinguishing between a low $T_3$ due to illness and that due to hypothyroidism. However, when the substrate, $T_4$, is also low, such an increment in serum $rT_3$ may not occur.

The fact that intracellular $T_3$ concentrations in some tissues, such as in the pituitary and brain, are not reflected by serum $T_3$ levels leads to another problem in interpretation of results of thyroid function testing.[15] Since TSH secretion appears to be regulated by both $T_4$ and $T_3$, it would be expected that there would be situations in which a normal serum $T_3$ level could be accompanied by an increase in TSH, despite the fact that the patients may appear to be clinically euthyroid. As shown in Table 4, one such situation occurs in iodine deficiency where a reduction in thyroidal iodine leads to an increase in the ratio of $T_3$ to $T_4$ in thyroid secretion. This is associated with a decrease in serum $T_4$ and an increase in serum TSH. The TSH increase presumably is a consequence of the reduction in $T_4$ alone, since the serum $T_3$ level remains constant. The maintenance of serum $T_3$ at normal levels is facilitated by the TSH increase in several ways. The iodide trapping mechanism is activated, leading to increased thyroidal clearance of iodide from the plasma. Organification is stimulated, and the turnover of thyroidal iodoproteins is accelerated with decreases in the quantity of stored thyroglobulin. Based on recent studies of intrathyroidal $T_4$ to $T_3$ deiodination, a PTU-sensitive process, it seems likely that there is also a TSH-induced acceleration of $T_4$ to $T_3$ conversion within the thyroid gland itself.[22] All of these events acting together result in a significant increase in the ratio of $T_3$ to $T_4$ in thyroid secretion with maintenance of serum $T_3$ at relatively normal levels, even in patients with a severe deficiency of iodine.

A similar phenomenon has been observed in early hypothyroidism due to autoimmune thyroiditis; often the first change noted is a decrease in plasma $T_4$ and an elevation in serum TSH level in patients who are clinically euthyroid, but who may have thyroid enlargement. This phenomenon also may be seen in patients with Graves' disease who are treated with radioiodine and subsequently develop a gradual onset of hypothyroidism. Lastly, these results characteristically are found in patients with Graves' disease who are treated with either methimazole or PTU. By virtue of their capacity to inhibit organification, these drugs cause intrathyroidal iodine deficiency and presumably the same set of adaptive physiological responses as previously described. Such patients will have subnormal serum $T_4$ concentrations, normal concentrations of $T_3$, and may develop increases in serum TSH. This can be important since the increase in thyroid size that occurs as a consequence of increased TSH secretion might also indicate the possibility of an increased circulating thyroid immunostimulator, hence the need for more, rather than less, antithyroid drug. Thus, both serum $T_4$ and $T_3$ should be monitored in such patients; should thyroid enlargement occur, the serum TSH should be measured.[15]

There is another group of patients in whom an elevation in serum total and free $T_4$ levels is associated with euthyroidism. Such a syndrome has been observed following oral cholecystography with either iopanoic acid or ipodate (Telepaque® or Oragrafin®).[13] Following administration of these agents, serum $T_3$ decreases, serum $T_4$ increases, and serum TSH may increase slightly. This is the physiological response to inhibition of the Type I and Type II $T_4$ 5′-deiodinase enzymes. The pituitary gland is "fooled" into reacting as if the thyroid secretion has diminished and it releases TSH to compensate. Such a syndrome also has been described in patients receiving the antiarrhythmic agent, amiodarone. Amiodarone also may act as a competitive inhibitor of $T_4$ to $T_3$ conversion, since a portion of this molecule bears a striking similarity to the outer ring of $T_4$.[23] In certain patients who are severely ill, there may be a sufficient decrease in $T_4$ to $T_3$ conversion, and sufficient autonomy of thyroid secretion, such that serum $T_4$ also may increase while $T_3$ is reduced to very low levels. While the physician should be suspicious of underlying autonomous thyroid function in such patients, eg, euthyroid Graves' disease or nontoxic nodular goiter, they may not be hyperthyroid at the time serum $T_4$ level is elevated. Theoretically, they may have such a dramatic decrease in $T_4$ to $T_3$ conversion that a compensatory increase in TSH secretion is activated. Lastly, patients receiving large doses of propranolol (>120 mg/day) for angina or hypertension may develop a syndrome similar to that seen after the oral administration of cholecystographic agents.[24] In such patients, serum $T_4$ levels may be modestly elevated and serum $T_3$ levels may be normal. This effect of propranolol is not associated with the β-adrenergic antagonist effect since it has been demonstrated with the D as well as with the L isomer of the drug, and it does not occur with the second generation β-adrenergic inhibitors such as atenolol.[25,26]

Every clinician recognizes the difficulty of attempting to make the diagnosis of hyperthyroidism in the patient receiving large doses of propranolol. To eliminate the diagnosis of true hyperthyroidism in patients receiving this drug, as well as in those who have received gallbladder dyes or are severely ill, a thyrotropin-releasing hormone (TRH) stimulation test should be performed. An increase in TSH following administration of TRH will, in almost every patient, eliminate the diagnosis of hyperthyroidism. The absence of an increase in TSH after TRH is consistent with true hyperthyroidism, although a blunted TSH response may occur normally in patients with severe illness or in elderly people. In this group of patients, such a response is not diagnostic of hyperthyroidism. Thus, in all of the situations listed in Table 4, euthyroid patients may have alterations in the usually dependable screening test of thyroid dysfunction, and in serum $T_4$ or free $T_4$ concentrations, and yet not demonstrate clinical abnormality.

**Table 4. Situations of Apparent Discrepancy Between Serum $T_4$ (Total or Free) and Clinical Thyroid Status**

| |
|---|
| A reduced serum $T_4$ in a euthyroid patient |
| Iodine deficiency |
| Early hypothyroidism due to autoimmune thyroiditis |
| During antithyroid drug therapy for Graves' disease |
| An increased serum $T_4$ in a euthyroid patient |
| After oral cholecystography or during amiodarone therapy |
| In some patients with severe illness |
| Rarely in patients receiving propranolol |
| In familial dysalbuminemic hyperthyroxinemia or other rare abnormalities of circulating binding proteins |

It should also be recalled that there may be a familial syndrome in euthyroid patients in which serum $T_4$ or free $T_4$ index is increased and the serum $T_3$ level is normal. Most such patients have been found to have an abnormal serum albumin that binds $T_4$ with increased avidity. The increase in the affinity of this protein for $T_3$ is not nearly so great as it is for $T_4$, so if the method for estimating the free fraction of $T_4$ employs $T_3$, ie, a $T_3$ resin or charcoal uptake, an elevated free thyroxine index is reported. In tests employing $T_4$ to estimate the free fraction of $T_4$, a reduction in free fraction is recognized. One or two such patients with similar abnormalities due to changes in $T_4$-binding prealbumin (TBPA) also have been identified. These abnormalities have no relationship to problems of $T_4$ to $T_3$ conversion, but from a diagnostic point of view, they present a similar chemical profile.[27]

Lastly, a few families have been described who have hyperthyroidism with elevated levels of serum $T_4$, $T_3$, and TSH. Some have TSH-producing tumors that can be recognized by finding an increase in the $\alpha$ subunit of TSH in the serum (see I. Kourides, THYROID TODAY, Volume III, Number 2, April/May

1980). Another group has pituitary resistance to the effects of thyroid hormone such that supranormal concentrations of $T_4$ and/or $T_3$ are required to suppress pituitary TSH secretion (see S. Refetoff, THYROID TODAY, Volume III, Number 6, October 1980). Since other peripheral tissues do not share this resistance, hypermetabolism in the presence of TSH secretion is the consequence.[28] A few such patients have been reported in whom the administration of $T_3$, but not $T_4$, suppresses TSH and leads to euthyroidism. It has been hypothesized that such patients may have a defect in $T_4$ to $T_3$ conversion, presumably in the pituitary thyrotroph.[29]

From a physiological point of view, the necessity for $T_4$ to $T_3$ conversion for activation is an adaptive advantage to man in that it provides another level of regulation of the concentration of the hormone, $T_3$, in the tissues. Thus, because of the need of such a process for TSH suppression, maximal levels of stimulation of a failing thyroid gland can be achieved with normal levels of serum $T_3$, the main source of $T_3$ for tissues such as heart, liver, and kidney. In serious illness, a reduction in the rate of $T_4$ to $T_3$ conversion also may represent an adaptive advantage. In conditions of reduced serum levels of $T_4$, the brain is protected by a remarkable increase in its capacity to catalyze $T_4$ to $T_3$ conversion. Furthermore, the existence of two different enzymatic pathways of $T_3$ generation can be viewed as a mechanism regulating the thyroid status of some tissues independently from others, which makes teleological sense. From a practical point of view, these mechanisms may complicate the interpretation of thyroid function tests in patients with various nonthyroidal diseases and in those receiving certain drugs.

## References:


1. Gavin L, Castle J, McMahon F, et al: Extrathyroidal conversion of thyroxine to 3,3',5'-triiodothyronine (reverse-$T_3$) and to 3,5,3'-triiodothyronine ($T_3$) in humans. *J Clin Endocrinol Metab* 1977;44:733-742.
2. Surks MI, Schadlow AR, Stock JM, et al: Determination of iodothyronine absorption and conversion of L-thyroxine ($T_4$) to L-triiodothyronine ($T_3$) using turnover rate techniques. *J Clin Invest* 1973;52:805-811.
3. Oppenheimer JH, Schwartz HL, Surks MI, et al: Nuclear receptors and the initiation of thyroid hormone action. *Recent Progr Horm Res* 1976;32:529-558.
4. Hennemann G, Smeulers J, van der Does I, et al: Measurement of intracellular $T_3$ and $T_3$ disposal in normal subjects. *Acta Endocrinol (Copenh)* 1976;82:92-97.
5. Surks MI, Oppenheimer JH: Concentration of L-thyroxine and L-triiodothyronine specifically bound to nuclear receptors in rat liver and kidney: Quantitative evidence favoring a major role of $T_3$ in thyroid hormone action. *J Clin Invest* 1977;60:555-562.
6. Schimmel M, Utiger RD: Thyroidal and peripheral production of thyroid hormones: Review of recent findings and their clinical implications. *Ann Intern Med* 1977;87:760-768.
7. Gavin LA, Hammond ME, Castle JN, et al: 3,3'-Diiodothyronine production: A major pathway of peripheral iodothyronine metabolism in man. *J Clin Invest* 1978;61:1276-1285.
8. Kaplan MM, Yaskoski KA: Phenolic and tyrosyl ring deiodination of iodothyronines in rat brain homogenates. *J Clin Invest* 1980;66:551-562.
9. Larsen PR, Frumess RD: Comparison of the biological effects of thyroxine and triiodothyronine in the rat. *Endocrinology* 1977;100:980-988.
10. Delange F, Hershman JM, Ermans AM: Relationship between the serum thyrotropin level, the prevalence of goiter and the pattern of iodine metabolism in Idwji Island. *J Clin Endocrinol Metab* 1971;33:261-270.
11. Silva JE, Larsen PR: Pituitary nuclear 3,5,3'-triiodothyronine and thyrotropin secretion: An explanation for the effect of thyroxine. *Science* 1977;198:617-619.
12. Silva JE, Larsen PR: Contributions of plasma triiodothyronine and local thyroxine monodeiodination to triiodothyronine and nuclear triiodothyronine receptor saturation in pituitary, liver and kidney of hypothyroid rats: Further evidence relating saturation of pituitary nuclear triiodothyronine receptors and the acute inhibition of thyroid-stimulating hormone release. *J Clin Invest* 1978;61:1247-1259.
13. Burgi H, Wimpfheimer C, Burger A, et al: Changes of circulating thyroxine, triiodothyronine, and reverse triiodothyronine after radiographic contrast agents. *J Clin Endocrinol Metab* 1976;43:1203.
14. Larsen PR, Dick TE, Markovitz MM, et al: Inhibition of intrapituitary thyroxine to 3,5,3'-triiodothyronine conversion prevents the acute suppression of thyrotropin release by thyroxine in hypothyroid rats. *J Clin Invest* 1979;64:117-128.
15. Larsen PR, Silva JE, Kaplan MM: Relationships between circulating and intracellular thyroid hormones: Physiological and clinical implications. *Endocr Rev* 1981;2:87-102.
16. Visser TJ: Mechanism of action of iodothyronine 5'-deiodinase. *Biochim Biophys Acta* 1979;569:302-308.
17. Leonard JL, Rosenberg IN: Characterization of essential enzyme sulfhydryl groups on thyroxine 5'-deiodinase from rat kidney. *Endocrinology* 1980;106:444-451.
18. Silva JE, Leonard JL, Crantz FR: Evidence for two tissue specific pathways for in vivo thyroxine 5'-deiodination in the rat. *J Clin Invest* 1982;69:1176-1184.
19. Visser TJ, Leonard JL, Kaplan MM, et al: Kinetic evidence suggesting two mechanisms for iodothyronine 5'-deiodination in rat cerebral cortex. *Proc Natl Acad Sci USA* 1982;79:5080-5084.
20. Silva JE, Larsen PR: Comparison of iodothyronine 5'-deiodinase and other thyroid-hormone-dependent enzyme activities in the cerebral cortex of hypothyroid neonatal rat. *J Clin Invest* 1982;70:1110-1123.
21. Kaptein EM, Robinson WJ, Grieb DA, et al: Peripheral serum thyroxine, triiodothyronine and reverse triiodothyronine kinetics in the low thyroxine state of acute nonthyroidal illnesses. *J Clin Invest* 1982;69:526-535.
22. Erickson VJ, Cavalieri RR, Rosenberg LL: Thyroxine-5'-deiodinase of rat thyroid, but not that of liver, is dependent on thyrotrophin. *Endocrinology* 1982;111:434.
23. Burger A, Nicod DP, Lemarchand-Beraud T, et al: Effect of amiodarone on serum triiodothyronine, reverse triiodothyronine, thyroxine, and thyrotropin: A drug influencing peripheral metabolism of thyroid hormones. *J Clin Invest* 1976;58:255-259.
24. Kristensen BO, Weeke J: Propranolol-induced increments in total and free serum thyroxine in patients with essential hypertension. *Clin Pharmacol Ther* 1977;22:864-867.
25. Heyma P, Larkins RG, Campbell DG: Inhibition by propranolol of 3,5,3'-triiodothyronine formation from thyroxine in isolated rat renal tubules: An effect independent of ß-adrenergic blockade. *Endocrinology* 1980;106:1437-1441.
26. Rassu S, Masala A, Alagna S, et al: Acute effect of atenolol on serum thyroid hormones in hyperthyroid patients. *J Endocrinol Invest* 1982;5:39-41.
27. Hyperthyroxinemia: Does it mean hyperthyroidism?, editorial. *Lancet* 1982;1:1286.
28. Weintraub BD, Gershengorn MC, Kourides IA, et al: Inappropriate secretion of thyroid-stimulating hormone. *Ann Intern Med* 1981;95:339.
29. Rosler A, Litvin Y, Hage C, et al: Familial hyperthyroidism due to inappropriate thyrotropin secretion successfully treated with triiodothyronine. *J Clin Endocrinol Metab* 1982;54:76-82.