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# Reverse T<sub>3</sub> or perverse T<sub>3</sub>? Still puzzling after 40 years

**F**OUR DECADES AFTER reverse T<sub>3</sub> (3,3'-triiodothyronine) was discovered, its physiologic and clinical relevance remains unclear and is still being studied. But scientific uncertainty has not stopped writers in the consumer press and on the Internet from making unsubstantiated claims about this hormone. Many patients believe their hypothyroid symptoms are due to high levels of reverse T<sub>3</sub> and want to be tested for it, and some even bring in test results from independent laboratories.

## ■ HOW THYROID HORMONES WERE DISCOVERED

The 20th century saw important advances in knowledge of the biochemistry of thyroid hormones (**Figure 1**),<sup>1-18</sup> such as the isolation of thyroxine (T<sub>4</sub>) by Kendall<sup>1</sup> in 1915 and its synthesis by Harington and Barger<sup>3</sup> in 1927. Another milestone was the isolation and synthesis of triiodothyronine (T<sub>3</sub>) by Gross and Pitt-Rivers<sup>5</sup> in 1953. In 1955, Pitt-Rivers et al<sup>6</sup> suggested that T<sub>3</sub> is formed in vivo from conversion of T<sub>4</sub>, but this theory remained unproven in humans at that time.

In 1970, Braverman et al<sup>9</sup> showed that T<sub>4</sub> is converted to T<sub>3</sub> in athyreotic humans, and Sterling et al<sup>10</sup> demonstrated the same in healthy humans. During that decade, techniques for measuring T<sub>4</sub> were refined,<sup>11</sup> and a specific radioimmunoassay for reverse T<sub>3</sub> allowed a glimpse of its physiologic role.<sup>12</sup> In 1975, Chopra et al<sup>13</sup> noted reciprocal changes in the levels of T<sub>3</sub> and reverse T<sub>3</sub> in systemic illnesses—ie, when people are sick, their T<sub>3</sub> levels go down and their reverse T<sub>3</sub> levels go up.

In 1977, Burman et al<sup>17</sup> developed a radio-

## Thyroid hormones: A timeline

**1907**—Marine reports that iodine is necessary for thyroid function.

**1915**—Kendall<sup>1</sup> isolates thyroxine.

**1926**—Harington<sup>2</sup> determines the chemical structure of thyroxine.

**1927**—Harington and Barger<sup>3</sup> synthesize thyroxine.

**1931**—Loeb and Bassett extract and purify thyroid-stimulating hormone from bovine pituitaries.

**1949**—Hoskins describes negative feedback of thyroid hormones on the pituitary gland.

**1952**—Gross and Pitt-Rivers<sup>4</sup> demonstrate T<sub>3</sub> in human plasma.

**1953**—Gross and Pitt-Rivers<sup>5</sup> isolate and synthesize T<sub>3</sub>.

**1955**—Pitt-Rivers et al<sup>6</sup> suggest T<sub>4</sub> is converted to T<sub>3</sub> in vivo.

**1957**—Development of the first techniques to measure T<sub>3</sub>.<sup>7</sup>

**1959**—Galton and Pitt-Rivers<sup>8</sup> identify the acetic acid analogues of T<sub>4</sub> and T<sub>3</sub> (tetrac and triac) in mammalian tissues.

**1970**—Schally and Guilleman identify thyrotropin-releasing hormone in humans, receiving the Nobel Prize for this work in 1977.

**1970**—Braverman et al<sup>9</sup> and Sterling et al<sup>10</sup> discover conversion of T<sub>4</sub> to T<sub>3</sub> in humans.

**1974**—Chopra<sup>11,12</sup> develops radioimmunoassays for T<sub>4</sub> and reverse T<sub>3</sub>.

**1975**—Chopra et al<sup>13</sup> describe reciprocal changes in serum concentrations of reverse T<sub>3</sub> and T<sub>3</sub> in systemic illnesses.

**1976**—Burman et al<sup>14</sup> identify reverse T<sub>3</sub>, 3,3'-T<sub>2</sub>, T<sub>3</sub>, and T<sub>4</sub> in human amniotic fluid and in cord and maternal serum.

**1976–1978**—First reports of the euthyroid sick syndrome or low T<sub>3</sub> syndrome.<sup>15,16</sup>

**1977**—Burman et al<sup>17,18</sup> confirm reverse T<sub>3</sub> is present in the serum of normal individuals and develop a radioimmunoassay for 3,3'-T<sub>2</sub>.

**Figure 1.**

immunoassay for reverse  $T_3$  that confirmed its presence in the serum of normal humans. Further, they showed that serum reverse  $T_3$  levels were low in hypothyroid patients and in athyreotic patients receiving low daily doses of levothyroxine. Conversely, reverse  $T_3$  levels were high in hyperthyroid patients and in athyreotic patients receiving high doses of levothyroxine (**Figure 2**).<sup>17</sup>

The end of the 70s was marked by a surge of interest in  $T_4$  metabolites, including the development of a radioimmunoassay for 3,3'-diiodothyronine (3-3' $T_2$ ).<sup>18</sup>

The observed reciprocal changes in serum levels of  $T_3$  and reverse  $T_3$  suggested that  $T_4$  degradation is regulated into activating ( $T_3$ ) or inactivating (reverse  $T_3$ ) pathways, and that these changes are a presumed homeostatic process of energy conservation.<sup>19</sup>

## ■ HOW THYROID HORMONES ARE METABOLIZED

In the thyroid gland, for thyroid hormones to be synthesized, iodide must be oxidized and incorporated into the precursors 3-moniodotyrosine (MIT) and 3,5-diiodotyrosine (DIT). This process is mediated by the enzyme thyroid peroxidase in the presence of hydrogen peroxide.<sup>20</sup>

### The thyroid can make $T_4$ and some $T_3$

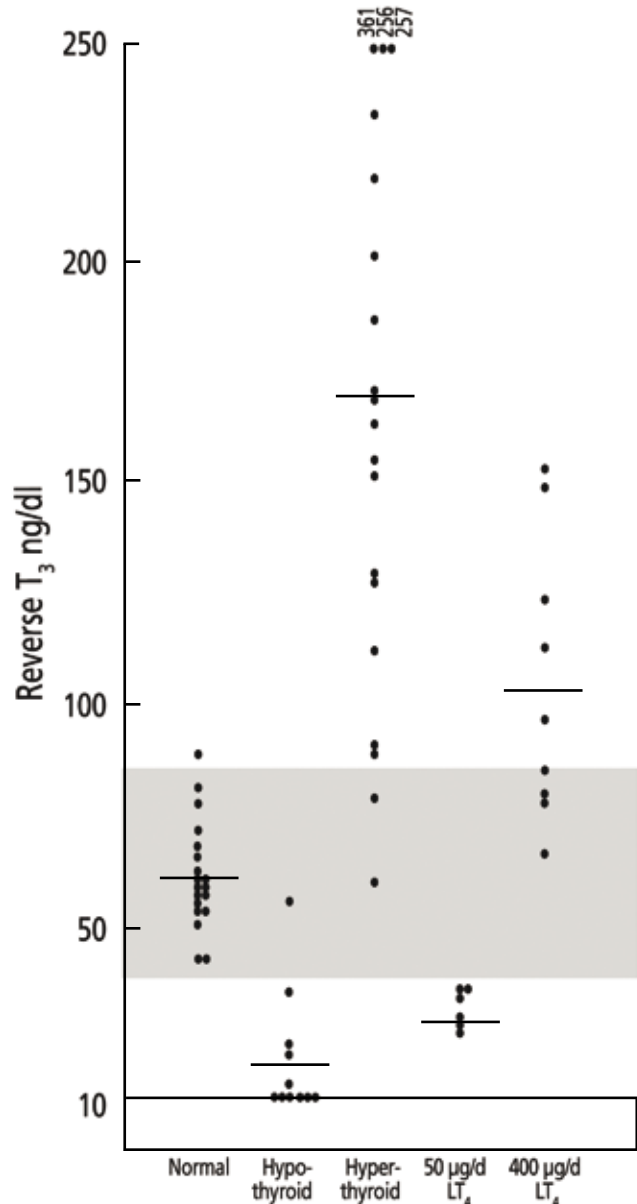
$T_4$  is the main iodothyronine produced by the thyroid gland, at a rate of 80 to 100  $\mu\text{g}$  per day.<sup>21</sup> It is synthesized from the fusion of 2 DIT molecules.

The thyroid can also make  $T_3$  by fusing 1 DIT and 1 MIT molecule, but this process accounts for no more than 20% of the circulating  $T_3$  in humans. The rest of  $T_3$ , and 95% to 98% of all reverse  $T_3$ , is derived from peripheral conversion of  $T_4$  through deiodination.

### $T_4$ is converted to $T_3$ or reverse $T_3$

The metabolic transformation of thyroid hormones in peripheral tissues determines their biologic potency and regulates their biologic effects.

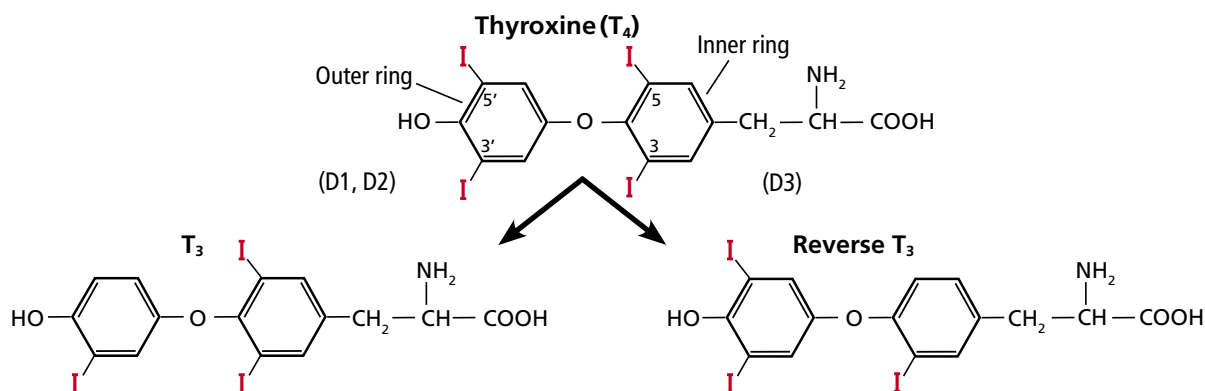
The number 4 in  $T_4$  means it has 4 iodine atoms. It can lose 1 of them, yielding either  $T_3$  or reverse  $T_3$ , depending on which iodine atom it loses (**Figure 3**). Loss of iodine from the five-prime (5') position on its outer ring yields  $T_3$ , the most potent thyroid hormone, produced at a



**Figure 2.** Individual values of serum reverse  $T_3$  levels in normal, hypothyroid, and hyperthyroid people and in athyreotic patients who had been given 50  $\mu\text{g}$  of levothyroxine ( $\text{LT}_4$ ) and 400  $\mu\text{g}$  of  $\text{LT}_4$  daily.

Reproduced from Burman KD, Dimond RC, Wright FD, Earll JM, Bruton J, Wartofsky L. A radioimmunoassay for 3,3',5'-L-triiodothyronine (reverse  $T_3$ ): assessment of thyroid gland content and serum measurements in conditions of normal and altered thyroidal economy and following administration of thyrotropin releasing hormone (TRH) and thyrotropin (TSH). *J Clin Endocrinol Metab* 1977; 44(4):660-672, by permission of Oxford University Press.

rate of 30 to 40  $\mu\text{g}$  per day.<sup>21</sup> On the other hand, when  $T_4$  loses an iodine atom from the five (5) position on its inner ring it yields reverse  $T_3$ , produced at a rate slightly less than that of  $T_3$ , 28 to 40  $\mu\text{g}$  per day.<sup>21</sup> Reverse  $T_3$  is inactive.



**Figure 3.** Thyroxine (T<sub>4</sub>) can shed 1 iodine atom to become the active thyroid hormone 3,5,3'-triiodo-L-thyronine (T<sub>3</sub>) in a reaction catalyzed by D1 and D2, or its inactive isomer 3,3',5'-triiodo-L-thyronine (reverse T<sub>3</sub>) in a reaction catalyzed by D3. In further reactions (not shown) both molecules successively lose more iodine atoms, eventually becoming T<sub>0</sub>.

Both T<sub>3</sub> and reverse T<sub>3</sub> can shed more iodine atoms, forming in turn various isomers of T<sub>2</sub>, T<sub>1</sub>, and ultimately T<sub>0</sub>. Other pathways for thyroid hormone metabolism include glucuronidation, sulfation, oxidative deamination, and ether bond cleavage.<sup>20–22</sup>

#### D1 and D2 catalyze T<sub>3</sub>, D3 catalyzes reverse T<sub>3</sub>

Three types of enzymes that mediate deiodination have been identified and designated D1, D2, and D3. In humans they are expressed in variable amounts throughout the body:

- D1 mainly in the liver, kidneys, thyroid, and pituitary, but notably absent in the central nervous system
- D2 in the central nervous system, pituitary, brown adipose tissue, thyroid, placenta, skeletal muscle, and heart
- D3 in the central nervous system, skin, hemangiomas, fetal liver, placenta, and fetal tissues.<sup>23</sup>

D1 and D2 are responsible for converting T<sub>4</sub> to T<sub>3</sub>, and D3 is responsible for converting T<sub>4</sub> to reverse T<sub>3</sub>.

Plasma concentrations of free T<sub>4</sub> and free T<sub>3</sub> are relatively constant; however, tissue concentrations of free T<sub>3</sub> vary in different tissues according to the amount of hormone transported and the activity of local deiodinases.<sup>23</sup> Most thyroid hormone actions are initiated after T<sub>3</sub> binds to its nuclear receptor. In this setting, deiodinases play a critical role in maintaining tissue and cellular thyroid hormone

levels, so that thyroid hormone signaling can change irrespective of serum hormonal concentrations.<sup>22–24</sup> For example, in the central nervous system, production of T<sub>3</sub> by local D2 is significantly relevant for T<sub>3</sub> homeostasis.<sup>22,23</sup>

Deiodinases also modulate the tissue-specific concentrations of T<sub>3</sub> in response to iodine deficiency and to changes in thyroid state.<sup>23</sup> During iodine deficiency and hypothyroidism, tissues that express D2, especially brain tissues, increase the activity of this enzyme in order to increase local conversion of T<sub>4</sub> to T<sub>3</sub>. In hyperthyroidism, D1 overexpression contributes to the relative excess of T<sub>3</sub> production, while D3 up-regulation in the brain protects the central nervous system from excessive amounts of thyroid hormone.<sup>23</sup>

#### ■ REVERSE T<sub>3</sub> AND SYSTEMIC ILLNESS

D3 is the main physiologic inactivator of thyroid hormones. This enzyme plays a central role in protecting tissues from an excess of thyroid hormone.<sup>23,24</sup> This mechanism is crucial for fetal development and explains the high expression of D3 in the human placenta and fetal tissues.

In adult tissues, the importance of D3 in the regulation of thyroid hormone homeostasis becomes apparent under certain pathophysiologic conditions, such as nonthyroidal illness and malnutrition.

Whenever a reduction in metabolism is homeostatically desirable, such as in critically ill patients or during starvation, conversion to

**When people are very sick, their T<sub>3</sub> levels go down and reverse T<sub>3</sub> levels go up**

TABLE 1

**Changes in thyroid hormone levels during illness**

Severity of illness	TSH	Total T <sub>3</sub>	Free T <sub>4</sub>	Reverse T <sub>3</sub>	Probable cause
<b>Mild</b>	No change	Mildly decreased	No change	Mildly increased	Mildly decreased D2, D1
<b>Moderate</b>	No change or mildly decreased	Decreased	No change or mild increase or decrease	Increased	Decreased D2, D1, possibly mildly increased D3
<b>Severe</b>	Decreased	Markedly decreased	Mildly decreased	Mildly increased	Decreased D2, D1, possibly mildly increased D3
<b>Recovery</b>	Mildly increased	Mildly decreased	Mildly decreased	Mildly increased	Unknown

D1 through D3 = iodothyronine deiodinases; T<sub>3</sub>, triiodothyronine; T<sub>4</sub> = thyroxine; TSH = thyroid-stimulating hormone (thyrotropin).

Adapted from Salvatore D, Davies TF, Schlumberger M, Hay ID, Larsen PR. Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds. *Williams Textbook of Endocrinology*. 13th ed. Philadelphia, PA; Elsevier; 2016:334–368, copyright 2016, with permission from Elsevier.

T<sub>3</sub> is reduced and, alternatively, conversion to reverse T<sub>3</sub> is increased. This pathway represents a metabolic adaptation that may protect the tissues from the catabolic effects of thyroid hormone that could otherwise worsen the patient's basic clinical condition.

**Euthyroid sick syndrome or hypothyroid?**

In a variety of systemic illnesses, some patients with low T<sub>3</sub>, low or normal T<sub>4</sub>, and normal thyroid-stimulating hormone (TSH) levels could in fact be “sick euthyroid” rather than hypothyroid. The first reports of the euthyroid sick syndrome or low T<sub>3</sub> syndrome date back to about 1976, and even though assays for reverse T<sub>3</sub> were not widely available, some authors linked the syndrome to high levels of reverse T<sub>3</sub>.<sup>15,16</sup> The syndrome is also known as nonthyroidal illness syndrome.

Advances in techniques for measuring T<sub>3</sub>, reverse T<sub>3</sub>, and other iodothyronines filled a gap in the understanding of the alterations that occur in thyroid hormone economy during severe nonthyroidal diseases. In 1982, Wartofsky and Burman<sup>25</sup> reviewed the alterations in thyroid function in patients with systemic illness and discussed other factors that may alter thyroid economy, such as age, stress, and diverse drugs.

More recently, the low-T<sub>3</sub> syndrome was revisited with a generalized concept regarding the role of D3 in the syndrome.<sup>26</sup> D3, normally

undetectable in mature tissues, is reactivated in diverse cell types in response to injury and is responsible for a fall in serum T<sub>3</sub> levels. Hypoxia induces D3 activity and mRNA in vitro and in vivo.<sup>27</sup> Recent studies have focused on the role of cytokines in the low T<sub>3</sub> syndrome. For instance, interleukin 6 reduces D1 and D2 activity and increases D3 activity in vitro.<sup>28</sup>

In the outpatient setting, diverse conditions may affect thyroid hormone homeostasis, compatible with mild or atypical forms of low-T<sub>3</sub> syndrome, including caloric deprivation, heart failure, and human immunodeficiency virus infection.<sup>29</sup>

**POSSIBLE CLINICAL UTILITY OF MEASURING REVERSE T<sub>3</sub>****In inpatients**

Unfortunately, measuring serum reverse T<sub>3</sub> levels has not, in general, proven clinically useful for the diagnosis of hypothyroidism in systemically ill patients. Burmeister<sup>30</sup> demonstrated, in a retrospective study, that when illness complicates the interpretation of thyroid function tests, serum reverse T<sub>3</sub> measurements do not reliably distinguish the hypothyroid sick patient from the euthyroid sick patient. The best way to make the diagnosis, Burmeister suggested, is by clinical assessment, combined use of free T<sub>4</sub> and TSH measurements, and patient follow-up.

**Few clinical situations require measurement of reverse T<sub>3</sub> levels**

Indeed, few clinical situations require measurement of reverse T<sub>3</sub> levels. We believe it can potentially be used to help the differential diagnosis between hypothyroidism and euthyroid sick syndrome. Reverse T<sub>3</sub> should always be analyzed in combination with TSH, T<sub>3</sub>, and free T<sub>4</sub> with consideration of the patient's clinical context. Table 1 helps to interpret the results. However, even in these circumstances, serum reverse T<sub>3</sub> levels are not always reliable, as demonstrated by Burmeister.<sup>30</sup> Another situation, even rarer, is in children or adults with massive hemangiomas. These tumors express high levels of D3 that can cause hypothyroidism.<sup>31</sup>

In the outpatient setting, the utility of reverse T<sub>3</sub> measurements is controversial. In intensive care units, the differential diagnosis between hypothyroidism and nonthyroidal illness syndrome can sometimes be difficult. Reverse T<sub>3</sub> levels can be low, normal, or high regardless of the thyroidal state of the patient.<sup>30</sup> Moreover, endogenous changes in the hypothalamic-pituitary-thyroid axis may be further complicated by medications commonly used in intensive care units, such as dopamine and glucocorticoids. Changes in thyroid function should be evaluated in the context of the patient's clinical condition (Table 1).<sup>20</sup> But regardless of the T<sub>3</sub> level, treatment with T<sub>3</sub> or T<sub>4</sub> should not be started without taking into consideration the patient's general clinical

context; controlled trials have not shown such therapy to be beneficial.<sup>20</sup>

### In outpatients

In noncritical conditions that may be associated with mild forms of low T<sub>3</sub> syndrome, patients generally present with low T<sub>3</sub> concentrations concurrently with low or normal TSH. Not infrequently, however, patients present with a serum reverse T<sub>3</sub> measurement and impute their symptoms of hypothyroidism to "abnormal" reverse T<sub>3</sub> levels, in spite of normal TSH levels.

There is no rationale for measuring reverse T<sub>3</sub> to initiate or to adjust levothyroxine therapy—the single test relevant for these purposes is the TSH measurement. The risks of basing treatment decisions on reverse T<sub>3</sub> levels include the use of excessive doses of levothyroxine that may lead to a state of subclinical or even clinical hyperthyroidism.

### TAKE-HOME MESSAGE

The existence of an inactivating pathway of thyroid hormones represents a homeostatic mechanism, and in selected circumstances measuring serum reverse T<sub>3</sub> may be useful, such as in euthyroid sick patients. The discovery of the molecular mechanisms that lead to the reactivation of D3 in illness is an important field of research.

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