

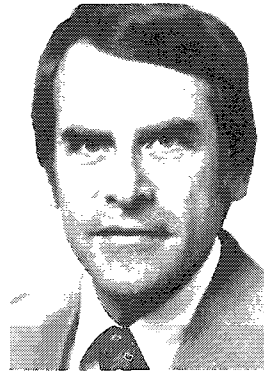
# THYROID TODAY

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## HYPOTHYROIDISM IN CHILDHOOD

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The effects of thyroid hormones are widespread. They influence oxygen consumption and heat production; nerve function; the metabolism of lipids, carbohydrates, proteins, nucleic acids, vitamins, and inorganic ions; and, importantly, they modulate the effects of other hormone actions. These effects are manifest in all age groups. During childhood and adolescence thyroid hormones also exert important effects on growth and maturation, and they are necessary for normal pubertal development. Abnormalities in growth and development are the earliest and most sensitive indicators of thyroid hormone deficiency during the first two decades of life.

The exception to this statement is congenital hypothyroidism. It is now clear that thyroid hormones are not necessary for normal or near normal somatic growth during fetal life and that most infants with hypothyroidism at birth have relatively few and subtle clinical manifestations. Thus a clinical diagnosis usually is delayed. In a recent series of 46 cretins, clinical identification was delayed beyond four months in 71% and beyond six months in 54%.<sup>1</sup> Early clinical diagnosis must, therefore, be based on a high index of suspicion regarding nonspecific symptoms and signs. These signs are summarized in Table I. The large birth weight is due to prolonged gestation, in the 42 to 44 week range. The presence of two or three of the manifestations listed in Table I without other explanation should lead the

physician to order serum thyroxine ( $T_4$ ) and thyroid-stimulating hormone (TSH) concentration measurements.

The subtle manifestations of hypothyroidism in the newborn gradually progress to more classical manifestations. Cretinoid facies are due to accumulation of myxedema in the subcutaneous tissues and tongue. The infant develops increasing difficulty in nursing and handling his salivary secretions. The hoarse cry is due to myxedema of the vocal cords. More prolonged hypothyroidism leads to marked muscular hypotonia and mental torpor. The umbilical hernia and characteristic potbelly are due to hypotonia of the smooth muscles of the gut as well as the striated muscles of the abdominal wall. Bradycardia, diminished pulse pressure, and sometimes pericardial effusion result from myxedematous infiltration of the heart and pericardial tissues. Inadequate perfusion of peripheral tissues progressively occurs; the extremities are cool and may exhibit pallor and circulatory mottling. The most profound manifestation, however, is growth retardation. This growth retardation is due to impaired protein synthesis, reduced peripheral oxygenation, and decreased intake and absorption of nutrients.<sup>2</sup> With the passage of time, growth retardation is progressively more obvious, diaphyseal bone growth is reduced and epiphyseal growth and mineralization may largely cease; demineralization, however, also is reduced, so that skeletal roentgenograms show reduced length

**TABLE I**

Signs of Hypothyroidism Peculiar to Infancy and Childhood

of long bones and delayed epiphyseal maturation in association with normal or increased bone density.<sup>2-4</sup>

With delay in treatment there is a progressive reduction in mental capacity manifested as reduced IQ and cerebellar dysfunction; 72% of infants with the diagnosis of congenital hypothyroidism delayed four to six months have IQ values below 90; 20% have IQ values below 50;<sup>1</sup> 60% of such infants have ataxic symptoms.<sup>5</sup> Mass screening programs for detection of congenital hypothyroidism in the neonatal period have established a frequency of the disorder of 1 in 4,000 to 5,000 births in North America and have proven the effectiveness of screening for early detection.<sup>6,7</sup> As of October 1977, according to information collated by the newborn screening committee of the American Thyroid Association, some 730,000 newborn infants had been screened in the United States and Canada; 166 newborns with permanent congenital hypothyroidism have been detected, an incidence of 1 in 4,400 births. About 85% of the hypothyroid infants have primary thyroid dysgenesis, some 10% have goitrous hypothyroidism associated with a defect in thyroid hormone production, and 3% to 5% have TSH deficiency due to a sporadic or familial hypothalamic-pituitary disorder (Table II).<sup>6,8-11</sup>

A few infants with transient congenital hypothyroidism due to a maternal drug ingestion also have been detected. The incidence of congenital hypothyroidism associated with maternal Hashimoto's thyroiditis<sup>12</sup> probably is small; no clear association has been established to date in the ongoing North American screening programs. Finally, several euthyroid infants with normal serum  $T_4$  and elevated serum TSH concentrations have been detected in those screening programs doing primary TSH screening or TSH screening on infants with the lowest 10% of blood  $T_4$  values. The abnormalities in these infants are not yet clear; some probably represent thyroid dysgenesis with enough residual tissue to supply adequate thyroid hormone at least during early infancy. Others probably represent milder defects in thyroid hormone synthesis, TSH unresponsiveness or hyporesponsiveness, or thyroxine resistance syndromes (Table I).<sup>13,14</sup> The proportion of these infants who will develop hypothyroidism is not known. The total number of these infants also is unknown at present; they may represent as many as 20% to 25% of infants with congenital abnormalities in thyroid function, so that the total incidence of congenital abnormalities of thyroid function may approximate 1 in 3,000 to 3,500 births.

The diagnosis of primary congenital hypothyroidism is based on low serum levels of  $T_4$  for age and elevated serum TSH concentrations (Tables III and IV).<sup>15-18</sup> Decreased thyroid reserve or peripheral resistance to the effect(s) of thyroid hormone may be manifested by normal  $T_4$  levels with increased serum TSH concentrations. A failing thyroid gland also is indicated by a pattern of low serum  $T_4$  with elevated serum triiodothyronine ( $T_3$ ) and TSH concentrations.<sup>15</sup> Hypothalamic or pituitary hypothyroidism is manifested by a low serum  $T_4$  level with low or normal serum TSH concentration. Such patients also

**A. Newborn**

1. Birth weight > 4,000 gm
2. Posterior fontanelle > 0.5 cm
3. Rectal temperature < 95° F
4. Respiratory distress in term infant
5. Edema
6. Delay in passage of meconium > 48 hours
7. Jaundice > 3 days in term infant

**B. Childhood**

1. Growth retardation
2. Delayed dental development
3. Delayed bone maturation
4. Delayed puberty
5. Precocious pubertal changes
6. Muscular hypertrophy

**C. Adolescence**

1. Growth retardation
2. Delayed bone maturation
3. Delayed puberty
4. Menstrual disorders in females

**TABLE II**

Causes of Hypothyroidism in Childhood

**A. Congenital hypothyroidism (cretinism)**

1. Errors in thyroid gland embryogenesis (thyroid dysgenesis)
  - a. Thyroid aplasia
  - b. Thyroid dysplasia
    - 1) Ectopic remnant in pathway of descent
    - 2) Rudimentary thyroid in normal location
2. Congenital errors of thyroid function (goitrous cretinism, familial cretinism)
  - a. TSH unresponsiveness
  - b. Failure of thyroid gland to concentrate iodide
  - c. Organofaction defects
  - d. Iodotyrosine deiodinase defects
  - e. Defects in thyroglobulin metabolism
  - f. Reduced tissue response to thyroid hormones
3. Hypothalamic-pituitary hypothyroidism
4. Maternal ingestion of goitrogenic drugs
5. Congenital hypothyroidism associated with maternal Hashimoto's thyroiditis
6. Endemic cretinism

**B. Acquired hypothyroidism**

1. Chronic (Hashimoto's) thyroiditis
2. Thyroid dysgenesis
3. Congenital errors of thyroid function
4. Hypothalamic-pituitary hypothyroidism
5. Drug-induced goiter
6. Endemic goiter

have low serum T<sub>3</sub> levels and have normal or decreased responses, respectively, to exogenous thyrotropin-releasing hormone (TRH) rather than the augmented response characteristic of primary hypothyroidism (Table IV).<sup>15</sup>

Acquired hypothyroidism during the first two decades of life derives from many causes (Table I). Under the age of 5 to 6 years hypothyroidism may develop because of decompensation of a previously existing congenital abnormality; a patient with thyroid dysgenesis and a significant volume of residual thyroid tissue in the normal or an ectopic position may become hypothyroid as thyroid hormone needs increase with growth.<sup>19,20</sup> It seems that most dysplastic glands have a limited capacity to hypertrophy in parallel with body growth. In addition lingual thyroid glands at the base of the tongue have been removed surgically or have spontaneously necrosed, resulting in hypothyroidism. Patients with inborn defects in thyroid metabolism may be compensated or partially compensated early and decompensate as thyroid hormone requirements increase with growth.<sup>16</sup> Drug-induced goiter is uncommon in childhood but may occur in patients taking iodides, cobalt-containing drugs, lithium salts, para-aminosalicylic acid, aminoglutethimide, phenylbutazone, or antithyroid drugs (propylthiouracil, methimazole, perchlorate, thiocyanate).<sup>16</sup> Naturally occurring goitrogens have been reported in ground water, soy beans, and plant members of the genus *Brassica* (such as cabbage). Hypothalamic or pituitary hypothyroidism (TRH or TSH deficiency or both) may develop secondary to central nervous system tumors. Usually other pituitary hormone deficiencies and hypothalamic or central nervous system dysfunction are present. Isolated idiopathic TSH deficiency has been reported but is uncommon.<sup>9</sup>

**TABLE III**  
Normal Serum Thyroid Hormone, T<sub>3</sub> Uptake, and TSH Concentrations in Childhood

	T <sub>4</sub> (μg/dl)	T <sub>3</sub> (ng/dl)	TSH (μU/ml)	T <sub>3</sub> Uptake (%/normal serum)
Cord blood	10.9 (6.6-18.1)	50 (15-85)	9.0 (<2-40)	
2-5 days	15.1 (8.5-22)	185 (115-285)	< 20	
3-12 months	11.0 (7.6-16.0)	176 (110-275)	< 10	1.0 (0.88-1.12)
1-5 years	10.5 (7.3-15.0)	168 (105-269)	< 10	1.0 (0.88-1.12)
6-10 years	9.3 (6.4-13.3)	150 (94-241)	< 10	1.0 (0.88-1.12)
11-16 years	8.1 (5.6-11.7)	133 (8.3-213)	< 10	1.0 (0.88-1.12)

**TABLE IV**  
Laboratory Test Results in Various Types of Thyroid Function Abnormalities in Children\*

	Serum T <sub>4</sub>	Serum T <sub>3</sub> Resin Uptake	Serum TSH	Serum T <sub>3</sub>	Serum TBG	Serum TSH Response to TRH
Primary Hypothyroidism	D	D	I	N-D	N	I
Hypothalamic (TRH) Hypothyroidism	D	D	N	D	N	N
Pituitary (TSH) Hypothyroidism	D	D	N	D	N	D
Decreased Thyroid Reserve	D	D	I	I	N	I
TBG Deficiency	D	D	N	D	D	N

\*D=decreased; N=normal; I=increased

The most common cause of acquired hypothyroidism in children after 6 years of age is Hashimoto's thyroiditis, also referred to as lymphocytic thyroiditis or autoimmune thyroiditis. This entity now is the single most frequent thyroid disorder seen during childhood and adolescence.<sup>21,22</sup> Hashimoto's thyroiditis was diagnosed in 1.3% of a series of 5,000 school children 11 to 18 years of age surveyed in a recent study.<sup>21</sup> There is a progressively increasing incidence of the disorder with age to a peak incidence during the fourth to fifth decades; the female to male incidence ratio is 6-10 to 1.<sup>22</sup> There usually is a strong family history of thyroid disease, including asymptomatic goiter, hypothyroidism, and hyperthyroidism.<sup>23</sup> These families have a high incidence of significant circulating concentrations of antithyroid antibodies and appear to be at risk to develop Hashimoto's thyroiditis as well as Graves' disease (thyrotoxicosis).<sup>23</sup>

Hashimoto's thyroiditis characteristically manifests a prolonged chronic course; in the early stages the patients are asymptomatic except for mild to moderate thyroid enlargement (goiter).<sup>24-26</sup> Some 50% to 70% of patients are identified initially as having an asymptomatic goiter. On careful questioning of the patient, pressure symptoms in the neck sometimes can be elicited. Five percent to 10% of patients will have symptoms or signs suggesting hyperthyroidism,<sup>24</sup> including irritability, nervousness, increased sweating, and hyperactivity. Ten percent to 20% may have symptoms or signs of hypothyroidism.<sup>24</sup> As in adults, these may include cardiovascular and metabolic manifestations such as bradycardia, decreased pulse pressure, hypoactivity, cold intolerance, recurrent constipation, and poor appetite without weight loss. However, the earliest manifestations of thyroid deficiency are growth retardation and delayed development (dental age, bone age, pubertal signs) (Table I).

In prepubertal children precocious puberty and muscular hypertrophy are occasionally observed to be associated with the hypothyroid state.<sup>27-33</sup> The mechanism of the muscle hypertrophy is not clear. Firm and prominent muscles are common in hypothyroidism and may be more apparent in children because of their immature proportions. Muscle strength is usually normal or reduced, but can be increased. Mild elevations of creatine phosphokinase (CPK), lactic dehydrogenase (LDH), SGOT and SGPT may occur.<sup>27</sup> Serum gonadotropins have been found to be elevated in untreated hypothyroid girls with sexual precocity and markedly elevated serum TSH levels.<sup>33</sup> In some of these girls breast development and galactorrhea have occurred in association with elevated serum prolactin levels.<sup>16, 29, 32</sup> Precocious testicular enlargement has been reported in hypothyroid juvenile males. Increased serum gonadotropin levels are present in these patients, sometimes in association with enlargement of the sella turcica.<sup>30</sup> Again precocious gonadotropin secretion seems more likely to occur in patients with higher levels of serum TSH. When the onset of the hypothyroid state occurs post-pubertally in females, secondary menstrual irregularities

**TABLE V**  
**Recommended Replacement Dosage of Sodium Levothyroxine in Childhood Hypothyroidism**

	Dose of Sodium Levothyroxine $\mu\text{g}/\text{kg}/\text{day}$
0-1 year	9
1-5 years	6
6-10 years	4
11-20 years	3

From Sato et al.<sup>37</sup> Rezvani and DiGeorge,<sup>35</sup> Abbassi and Aldige.<sup>34</sup>

commonly occur. These include both menorrhagia and hypomenorrhea. A careful examination for signs of hypothyroidism is warranted in any adolescent female with menstrual irregularities or abnormality in the timing of puberty (Table I).

The suspicion of acquired hypothyroidism can be confirmed by measurement of serum concentrations of  $T_4$  and TSH. A low  $T_4$  concentration for age not due to a decreased serum thyroid hormone binding globulin (TBG) level in association with an increased serum TSH concentration indicates primary hypothyroidism (Table IV).<sup>15</sup> To correct for TBG abnormalities, measurements of  $T_4$  and  $T_3$  resin uptake (reported fractionally relative to a control serum pool, e.g., the  $T_3$  index) usually are conducted.<sup>15</sup> The product of the  $T_4$  and the  $T_3$  index is the corrected  $T_4$  or free  $T_4$  index. Serum  $T_3$  concentrations are low or normal in hypothyroid children and usually are not as useful as serum  $T_4$  and TSH measurements in diagnosis. Partial hypothyroidism or decreased thyroid reserve may occur in patients with decreased residual functioning thyroid tissue or inefficient hormone synthesis associated with glandular hyperplasia. Fifty percent to 75% of children presenting with asymptomatic goiter due to Hashimoto's thyroiditis may have a significant decrease in thyroid reserve.<sup>26</sup> In these patients serum TSH levels are increased, serum corrected  $T_4$  levels are normal or low normal, and serum  $T_3$  concentrations are usually normal. With such a pattern of serum thyroid function tests, a careful clinical evaluation should be conducted for signs of compromised growth and development. With hypothalamic or pituitary hypothyroidism (TSH deficiency) the serum corrected  $T_4$  value is low but the serum TSH concentration is not elevated (Table IV). Evaluation of other pituitary hormone secretion and TRH testing should be conducted in these patients.<sup>10</sup>

Hypothyroidism in infancy and childhood is best treated by using sodium levothyroxine. The drug is given orally in a single daily dose. It is not necessary to begin treatment with a reduced dosage. The optimal maintenance dose is the dose which will normalize serum thyroxine (corrected thyroxine) to the midrange (1 SD) for age and which normalizes growth. Recent studies of replacement therapy for hypothyroidism<sup>34, 35</sup> suggest that the optimal dose of

thyroxine is somewhat less than that recommended in the past.<sup>4</sup> Currently recommended doses are shown in Table V and vary with age. Excessive dosage results in accelerated bone maturation<sup>4</sup> and premature cranial synostosis, at times accompanied by increased intracranial pressure and delayed neurological development.<sup>36</sup>

Patients with congenital hypothyroidism appear to have an alteration in the pituitary threshold for TSH secretion such that with normal levels of serum T<sub>4</sub> their serum TSH concentrations and the serum TSH response to TRH are increased.<sup>37</sup> To normalize the TSH response to TRH, larger doses of T<sub>4</sub> are required with relatively high serum T<sub>4</sub> concentrations. This phenomenon appears to represent the clinical counterpart of the neonatal rat studies of Bakke et al. which documented permanent effects of neonatal thyroid hormone deficiency or excess on the feedback sensitivity of the hypothalamic-pituitary axis.<sup>38</sup> These studies<sup>37</sup> suggest that it is important to normalize serum T<sub>4</sub> levels rather than serum TSH concentrations or TSH responses to TRH in infants and children under treatment for congenital hypothyroidism. Abnormal feedback sensitivity seems not to occur in children with acquired hypothyroidism, presumably because the deficiency was not present during the critical period of hypothalamic maturation (20 weeks gestation to postnatal month).<sup>39</sup> Moreover, mental retardation does not occur if the hypothyroid state has its onset after 2 to 3 years of age.

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