

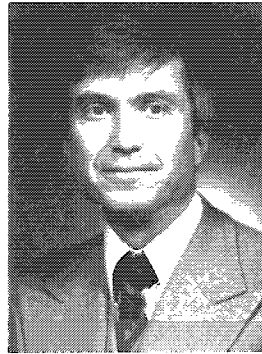
# THYROID TODAY

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## HYPERTHYROIDISM IN CHILDHOOD

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Hyperthyroidism during childhood is almost always due to Graves' disease (diffuse toxic goiter), and much of what is said about the disease in adults applies to children. Other, less frequent, causes of hyperthyroidism in children include neonatal hyperthyroidism or transient Graves' disease, hyperthyroidism produced by functioning adenomas, mild and transient hyperthyroidism that may occur as a part of chronic lymphocytic thyroiditis (Hashimoto's thyroiditis), and, very rarely, hyperfunctioning thyroid carcinoma, acute suppurative thyroiditis, and as a part of polyostotic fibrous dysplasia (McCune-Albright syndrome). Excessive ingestion of thyroid hormone as a cause of hyperthyroidism is occasionally encountered in the pediatric age group.

### Graves' Disease

The basic defect in childhood Graves' disease is the autonomous overproduction of thyroxine ( $T_4$ ) and triiodothyronine ( $T_3$ ) by a diffusely enlarged hyperplastic thyroid gland. It is probably an autoimmune disease but the precise etiology of the thyroid hyperfunction is still unknown. Although Graves' disease is the most common cause of hyperthyroidism in children, only about 5% of all patients with hyperthyroidism (adults and children) are less than 15 years of age. Graves' disease may occur at any age in the pediatric population; its frequency, however, increases with age and reaches a peak during adolescence. Exclusive of the transient Graves' disease in the newborn, it is extremely rare

before the age of five years, and only about one fifth of the pediatric patients reported by Hayles and coworkers<sup>1</sup> had the disease before the age of ten years.

### Clinical Features of Graves' Disease

The onset of Graves' disease may be rapid, but more often it occurs insidiously over weeks or months. Brief remissions may occur, but they are usually followed by recurrences of increasing severity. Spontaneous remissions of years' duration or even for life have been reported, but in most patients the disease is unrelenting in its progress.

Increase in neck size, eye prominence, nervousness, irritability, excessive sweating, restlessness during sleep, emotional lability often accompanied by periods of crying without recognized cause, tremor, increased appetite, weight loss, and heat intolerance are commonly noted presenting complaints. A decline in school performance is a common accompaniment of Graves' disease in the child, and teachers may first direct attention to it. Inability to complete assignments, a shortened concentration span, deterioration in penmanship, and untidiness in work are the complaints made by teachers. Muscle weakness, particularly of the legs, accompanied by palpitation and exhaustion after slight exertion, may be early complaints. Progression of muscle weakness and tremor may produce movement disorders so severe as to be confused with more serious neurologic diseases or intoxication. Purposeful intent of the movements in patients with Graves' disease distinguishes

them from the movement disorder that occurs in patients with chorea. As the disease progresses, bowel movements increase in frequency, weight loss is accelerated, and loss of subcutaneous fat and muscle tissue becomes obvious. Paradoxically, a minority of patients may actually gain weight because of the increased appetite and food consumption. Adolescent girls may note menstrual irregularities, but significant alteration in the menstrual pattern is not common.

Some degree of enlargement of the thyroid gland is almost invariably present in children with Graves' disease, but the degree of toxicity does not correlate with the size of the goiter. The child may first note a swelling in the neck, but more often relatives or friends note enlargement of the neck as the child swallows or extends the head. Less than 5% of children with untreated Graves' disease have symptoms related to the actual size of the thyroid gland, and when present they are usually minor, consisting of a feeling of fullness in the neck.

The untreated thyroid gland affected by Graves' disease is firm, smooth, and nontender, and its borders are easily outlined. A difference in the size of the lobes is not uncommon, and the isthmus shares in the enlargement. The size of the gland may vary greatly from patient to patient, but the gland is rarely more than three to four times the normal size at the time the disease is recognized. The thyroid gland of the adolescent has an average weight of approximately 15 gm, is quite soft, and therefore often difficult to palpate. The goiter of Graves' disease, however, is usually easily detected.

Although the ophthalmopathy of Graves' disease perhaps is more common among children than adults, it tends to be less severe in its manifestation. Exophthalmos, either unilateral or bilateral, lid retraction, and stare are the most common eye signs noted and account for the excited, stimulated, anxious look of the patient. Mild itching of the eyes and lacrimation may be occasional complaints. The degree of ophthalmopathy may vary considerably during the course of the disease, and in a rare patient this sign may precede the hyperthyroidism of Graves' disease by months or years. Further, the degree of ophthalmologic involvement does not correlate with the degree of thyrotoxicosis, and in some patients ophthalmopathy persists or worsens as the toxicity of the disease is controlled. In a survey of 147 adult patients with childhood-onset Graves' disease, 22 patients expressed concern about the ophthalmopathy of the disease during adult life.<sup>2</sup> None of these patients, however, required surgical intervention to control the ophthalmopathy.

#### Laboratory Investigation of Graves' Disease

In most instances the only test required to confirm the diagnosis of Graves' disease is measurement of total serum thyroxine ( $T_4$ ). Normal values for children are shown in Table 1. In circumstances where the clinical situation suggests hyperthyroidism and the  $T_4$  value is normal, a serum triiodothyronine ( $T_3$ ) level should be obtained to exclude  $T_3$  thyrotoxicosis, a condition not commonly seen in children. Occasionally, however, patients treated with antithyroid drugs, radioactive iodine, or surgery may still appear thy-

**Table 1 Normal Serum  $T_4$  Values from Birth to Adulthood**

Age	Total $T_4$ * ( $\mu\text{gm}\%$ )	
	Mean	Range
Cord blood	11.3	7.3 - 15.3
1 - 3 days	15.5	10.1 - 20.9
1 - 2 weeks	13.2	9.8 - 16.6
2 - 4 weeks	12.4	8.2 - 16.6
1 - 4 months	11.4	7.1 - 15.0
4 - 12 months	9.6	5.5 - 13.5
1 - 6 years	9.1	5.6 - 12.6
6 - 10 years	8.3	4.9 - 11.7
10 - 16 years	7.2	3.8 - 10.6
16 - 20 years	7.5	4.1 - 10.9
Adult	7.9	4.7 - 11.1

\*Total  $T_4$  data represents  $T_4$  results as determined by the Murphy-Pattee protein-binding  $T_4$  method;  $T_4$  radioimmunoassay (RIA) results are 15% higher.

Modified from Fisher DA: *J of Pediatr* 82:1-9, 1973. Adapted by permission of the publisher.

rotoxic on follow-up examination with elevated  $T_3$  levels but normal  $T_4$  values. Accurate methods for estimating total circulating  $T_4$  and  $T_3$  in the blood are generally available, and increased levels of these hormones provide a reliable indication that the disease is present. Because total  $T_4$  is a measure largely of  $T_4$  bound to circulating protein the concentration of  $T_4$  may be influenced by substances that alter binding proteins. Conditions that are known to alter binding of  $T_4$  are shown in Table 2.

Rarely, the diagnosis of hyperthyroidism may require measurement of radioactive iodine uptake. Measurement of  $^{131}\text{I}$  uptake may be helpful in the diagnosis of a patient with Graves' disease. Every effort, however, should be made to reduce the administered dose in order to minimize the radiation load.  $^{99\text{m}}\text{Tc}$  uptake may be useful for thyroid scanning when a nodule is palpated. The use of  $^{99\text{m}}\text{Tc}$  offers several advantages over  $^{131}\text{I}$  for this purpose since the  $^{99\text{m}}\text{Tc}$  uptake can be measured rapidly after the injection and the radiation dose is minimal. Recently, the short-lived isotope  $^{123}\text{I}$  has been introduced both for thyroid scanning and determining thyroid uptake. The physical characteristics of this isotope make it unusually suitable for thyroid imaging and for reducing the radiation load. In difficult diagnostic cases, thyroid autonomy, a characteristic of Graves' disease both with and without hyperthyroidism, can be established either by a conventional  $T_3$  suppression test or by stimulation with thyrotropin-releasing hormone (TRH).

#### Treatment of Graves' Disease

For many years there has been controversy over the most appropriate method of treating hyperthyroidism in the child. Children respond to therapy much as adults do, and all of the conventional modalities of treatment, namely, antithyroid drugs, radioiodine, and thyroidectomy, have strong

**Table 2 Drugs or Conditions that Alter the Plasma Protein Binding**

Increased plasma protein binding	Decreased plasma protein binding
Pregnancy	Androgens
Newborn infants	Anabolic steroids
Estrogens (including oral contraceptives)	Prednisone
Perphenazine	Diphenylhydantoin
Acute intermittent porphyria	Major illness
Infectious hepatitis	Surgical stress
Genetically determined	Nephrotic syndrome
	Active acromegaly
	Genetically determined

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advocates. All forms of treatment have some disadvantages. Since the cause of Graves' disease is not known, treatment is directed toward its control rather than its cure. The parents of the child should be told from the outset that control does not mean cure and that life-long surveillance is necessary.

#### **Antithyroid Drugs**

Medical treatment using antithyroid drugs is the most widely accepted form of treatment for Graves' disease in the child.<sup>3</sup> Advocates of its use stress its effectiveness, ease of administration, safety, relative lack of complications, and economy. On the other hand, emotional upsets within the family created by long-term antithyroid medication therapy, failures due to inadequate compliance, repeated recurrences, and drug reactions have been noted in all large series of patients treated with antithyroid drugs.<sup>4</sup>

The major agents employed in the chemotherapy of thyrotoxicosis are drugs of the thioamide class. The agents most commonly employed are propylthiouracil and methimazole. These drugs are effective in blocking the synthesis of thyroid hormone. Propylthiouracil offers the advantage, perhaps more theoretical than practical, of blocking peripheral conversion of  $T_4$  to  $T_3$ . Adverse, but relatively minor, drug reactions are not uncommon in children treated with thioamide drugs and include urticarial skin rash, drug fever, arthralgia, myalgia, granulocytopenia, loss of taste sensation, enlargement of lymph nodes or salivary glands, and abnormal hair pigmentation. In most instances these reactions are transitory even with continued use of the drug. More serious reactions such as agranulocytosis, granulocytopenia associated with systemic symptoms, hepatitis, arthritis, or a lupus-like syndrome are uncommon. Agranulocytosis occurs in less than 1% of treated patients. This problem, should it occur, generally develops within the first weeks or months of therapy and is heralded by fever, malaise and sore throat. When therapy is begun, the patient should be instructed to discontinue the drug and notify the physician immediately should these symptoms develop.

In Graves' disease it is my policy to initiate propylthiouracil therapy in a dose of 5 mg/kg/day (three divided doses by mouth). In teenagers approximately 100 mg tid may be given. Clinical improvement is usually noted within five to seven days after initiating therapy. After three to eight weeks of treatment the majority of patients can have their dose tapered by one third to one half. The dose thereafter is adjusted as needed to maintain the patient euthyroid. Some clinicians use a combined therapy of a thioamide and replacement thyroid hormone in the therapy of Graves' disease believing that such treatment may result in an increased remission response and better reduction in goiter.<sup>3</sup> Treatment with propylthiouracil is usually continued for 18 months (or more) at which time it is gradually discontinued. Some investigators terminate therapy earlier utilizing the  $T_3$  suppression test or the one hour oral radioiodine uptake test to determine if the pathological process is controlled. Recently Greer and coworkers<sup>5</sup> have suggested that in adults short-term antithyroid drug therapy from one to eight months in duration and terminating with establishment of euthyroidism may be as effective in producing a lasting remission rate as more conventional regimens in which antithyroid drugs are given for one year or more. In studies with a follow-up period of four years or more, the incidence of remission after withdrawal of antithyroid therapy ranges from 40% to 70%. If an exacerbation of hyperthyroidism occurs following the discontinuation of therapy, it usually occurs in the first 18 months (80% to 90% of the cases). If this occurs, I re-treat my patients with propylthiouracil for a further 12 months. If recurrence happens again following the tapering of the dose of propylthiouracil then the patient is a candidate for radioiodine or surgical therapy. In rare instances patients who present with severe hyperthyroidism may require a short-term course of propranolol hydrochloride (2 mg/kg/day in divided doses orally for one to three weeks) in addition to the thioamide therapy recommended previously.

#### **Radioiodine**

Although radioiodine is considered a standard form of treatment for hyperthyroidism in adults, the use of  $^{131}I$  in the treatment of children with Graves' disease has been controversial. The thyroid gland of the young probably is more prone to neoplastic change after radiation exposure than is the adult thyroid. This problem has not thus far posed a serious complication in young patients treated for Graves' disease with radioiodine, and it is possible that neoplastic transformation may not occur if large enough doses of the isotope are used to ablate all thyroid cells. Concern nevertheless persists. If enough isotope is administered to ensure ablation of all thyroid cells, the large amount of isotope required increases the possibility of late genetic effects from irradiation. Geneticists express concern about possible long-term effects of all types of ionizing radiation administered to young persons. An accurate appraisal of the risk of radiation will not be available for many years, and the decision about its use must be made by the physician and the parents of the child and, in the case of an older child, perhaps with the child's understanding. It has been my practice to use radioiodine only in patients who have

serious complicating illnesses that preclude, or make difficult, treatment with other modalities.

Many physicians have chosen to use  $^{131}\text{I}$  in the treatment of Graves' disease in children, and the results are impressive.<sup>6</sup> The treatment programs have been much the same as those for adults. The dosage of isotope is calculated on the basis of the estimated weight of the goiter, and the accumulated uptake of isotope in the thyroid gland as determined by tracer studies. Some have given the entire calculated dose at one time, whereas others have given the isotope in smaller doses at intervals. As would be expected, many patients require more than a single dose of the isotope for control, even when a relatively large dose has been given initially. Although this form of therapy is quite effective, it should be noted that complete control with  $^{131}\text{I}$  requires weeks or months. This can be an undesirable feature of the treatment, at least in some patients. Minor degrees of swelling and tenderness of the thyroid gland may follow administration of  $^{131}\text{I}$ , but no other immediate complications are to be expected.

### *Surgery*

Subtotal thyroidectomy was the only effective method of treatment during the first half of the century. It remains a satisfactory and accepted method and at the Mayo Clinic has been used as the treatment for most of their pediatric patients. It is rapid and effective in controlling hyperthyroidism, and in their experience it has provided gratifying results with minimum risk. Successful surgical treatment is made possible by the effectiveness of iodides in producing rapid reduction in toxicity and a decrease in the vascularity of the thyroid gland. Iodides, either as Lugol's solution (ten drops three times daily) or potassium iodide (10% solution, five drops three times daily) administered over seven to ten days, will greatly reduce toxicity and the size of the goiter. The thyroid gland escapes the effect of iodides after prolonged administration, and so their usefulness in the control of hyperthyroidism is restricted to preparation for surgery. Propranolol hydrochloride may be given in combination with iodides. Since propranolol hydrochloride may hide the manifestations of hyperthyroidism, reliance must be placed on the serum levels of  $\text{T}_3$  or  $\text{T}_4$  as guides in the control of hyperthyroidism. In an occasional patient with severe toxicity, preoperative treatment with antithyroid drugs for four weeks may be advisable before treatment with iodides is instituted.

The disadvantages of subtotal thyroidectomy surgery include the anesthetic risk, possible severance of or injury to the recurrent laryngeal nerves, inadvertent removal of the parathyroid glands, keloid formation, possible recurrence of the hyperthyroidism following surgery, and the development of hypothyroidism after surgery. In most large centers the incidence of major complications such as vocal cord paralysis and hypoparathyroidism is less than 5%. Total thyroidectomy has recently been advocated.<sup>7</sup> Advocates of this procedure report excellent results and the possibility of recurrent hyperthyroidism is removed. Nevertheless it would seem probable that risk of injury to the recurrent laryngeal nerves or loss of the parathyroid glands would be increased with this procedure.

### **$\text{T}_3$ Thyrotoxicosis**

Hyperthyroidism associated with normal  $\text{T}_4$  levels but elevated  $\text{T}_3$  levels is a rare occurrence in childhood but is said to account for up to 5% of the cases of hyperthyroidism in adults. In children it has been described in patients with Graves' disease, Hashimoto's thyroiditis, and functioning adenoma.<sup>8,9,10</sup> Adenomas are surgically removed; in the other situations the management is the same as for Graves' disease and Hashimoto's thyroiditis as described elsewhere in this article.

### **Hyperthyroidism Associated with Chronic Lymphocytic Thyroiditis (Hashimoto's Thyroiditis)**

The association between Graves' disease and Hashimoto's thyroiditis has been known for some time. The clinical, laboratory, and histologic overlap of these two entities may make their separation difficult. Thirty percent of the pediatric patients with Graves' disease who underwent subtotal thyroidectomy at the Mayo Clinic had histologic changes suggesting Hashimoto's thyroiditis. Many investigators feel that Hashimoto's thyroiditis and Graves' disease have a common etiology but represent different points in the spectrum of the pathological process. The average age at onset of Hashimoto's thyroiditis in children is between six and sixteen years, with a peak incidence at ten to eleven years of age. However, it may be found in infants. Ninety percent or more of the cases are in girls, and the disease tends to cluster in families.

Hashimoto's thyroiditis is the most common cause of goiter found in children and adolescents. Eighty-five percent of cases have euthyroid goiters; such cases are found routinely on examination or following the patient's complaint of "a swelling in the neck." Ten percent of cases have symptoms and signs of hypothyroidism at the time of diagnosis, and approximately 5% of patients have features of hyperthyroidism. Ophthalmopathy has been reported in patients with Hashimoto's thyroiditis who are hyperthyroid, and also in those who have presented in the euthyroid state. The goiter of Hashimoto's thyroiditis is variable in size but usually two to five times larger than normal. It is more lobulated, and harder and more irregular in consistency and shape, than the gland of Graves' disease. A correct diagnosis can be made in most cases with the aid of several laboratory studies and without a biopsy of the thyroid gland.<sup>11</sup> It is important to make an exact diagnosis, as many investigators believe that most patients with thyroiditis are, or will become, hypothyroid and require lifelong replacement thyroid hormone therapy.

Severe hyperthyroidism in patients with Hashimoto's disease is uncommon and usually self-limited. When present, it may require therapy with antithyroid medication. In patients requiring treatment it is my policy to initiate propylthiouracil therapy (5 mg/kg/day in three divided doses with reduction by one third to one half in three to eight weeks). The clinical status and serum thyroid-stimulating hormone (TSH) level of the patient are subsequently followed. When the patient begins to show an elevated TSH level indicating a failing thyroid gland and impending hypothyroidism, replacement sodium levothyroxine therapy is initiated and the propylthiouracil is gradually discontinued.

This usually occurs six to twelve months following the initiation of propylthiouracil therapy.

#### **Hyperthyroidism in Infants**

Infants born of mothers who have, or have recently had, Graves' disease may have transient Graves' disease, a problem which has recently been extensively reviewed by Fisher.<sup>12</sup> The disease is present at, or very soon after, birth, and recovery is to be expected by three months of age. The problem affects males and females with equal frequency and recurrence in later life has not been described. The clinical and laboratory manifestations of the disease resemble those of childhood Graves' disease with the exception that tachycardia may be more severe and lead to heart failure. The enlarged thyroid may produce feeding and respiratory problems in such infants and diarrhea may be marked. The cause of the transient Graves' disease of infancy is not known but the placental transmission of maternal immunoglobulins (long-acting thyroid stimulator [LATS] or thyroid-stimulating immunoglobulin [TSI]) to the infant has been demonstrated in some patients. Treatment is directed at reducing thyroid hormone synthesis and at minimizing the cardiovascular complications of the disease. Propylthiouracil in a dosage of 5 mg/kg/day in three divided doses orally (eg, by gavage) is usually administered. Lugol's solution may also be given in a dosage of one or two drops (six to twelve mg of iodine) orally every eight hours. Digitalization and treatment with propranolol hydrochloride in a dosage of 2 mg/kg/day in divided doses orally should be employed in infants with severe tachycardia and impending cardiac failure.

A more severe and persistent type of Graves' disease which has its onset in infancy has been recognized.<sup>13</sup> This form of the disease is characterized by its severity, its persistence for months or years, its resistance to treatment, and by premature fusion of cranial sutures, microcephaly, mental retardation and short stature.

#### **Thyroid Neoplasms Associated with Hyperthyroidism**

Hyperthyroidism due to a functioning adenoma or to an adenomatous goiter is extremely rare during pediatric years. Well-documented association of carcinoma and

hyperthyroidism have been reported only rarely in children. If there is a firm, palpable nodule in the thyroid gland with associated palpable nodes in the tracheoesophageal or jugular node chains or both then carcinoma should be suspected.

#### **Polyostotic Fibrous Dysplasia (McCune-Albright)**

The syndrome of polyostotic fibrous dysplasia (McCune-Albright syndrome), first described in 1937, is characterized by disseminated, brown, nonelevated pigmented areas on the skin and endocrine hyperfunction. The endocrinopathies described include sexual precocity, hyperthyroidism, hyperparathyroidism, acromegaly, and Cushing's syndrome. The disease<sup>14</sup> occurs more commonly among girls than boys, and precocity occurs in one third of the affected girls but is rare among boys. Hyperthyroidism is the second most common of the complicating endocrinopathies and is often associated with single or multiple adenomas arising in the thyroid gland.

#### **REFERENCES**

1. Hayles AB, Chaves-Carballo E: *Clin Pediatr (Phil)* 6:681-685, 1967.
2. Hayles AB, Kennedy RLJ, Beahrs OJ, et al: *J Clin Endocrinol Metab* 19:138-151, 1959.
3. Barnes HV, Blizzard RM: *J Pediatr* 91:313-320, 1977.
4. Hayles AB, Chaves-Carballo E: *Mayo Clin Proc* 40:889-894, 1965.
5. Greer MA, Kammer H, Bouma DJ: *N Engl J Med* 297: 173-176, 1977.
6. Safa AM, Schumacher OP, Rodriguez-Antunez A: *N Engl J Med* 292: 167-171, 1975.
7. Altman RP: *J Pediatr Surg* 8:295-300, 1973.
8. Mitsuma T, Owens R, Shenkman L, et al: *J Pediatr* 81:982-984, 1972.
9. Harland PC, McArthur RG, Fawcett DM: *Acta Paediatr Scand* 66:525-528, 1977.
10. Popma BH, Cloutier MD, Hayles, AB: *Mayo Clin Proc* 48:273-275, 1973.
11. Fisher DA: *J Pediatr* 82:187, 1973.
12. Fisher DA: *Am J Dis Child* 130:133-134, 1976.
13. Hollingsworth DR, Mabry CC: *Am J Dis Child* 130:148-155, 1976.
14. DiGeorge AM: *J Pediatr* 87:1018-1020, 1975.