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and Committee on Genetics, American Thyroid Association, Rosalind S. Brown, and
the Public Health Committee and Lawson Wilkins Pediatric Endocrine Society

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CLINICAL REPORT

Update of Newborn Screening and Therapy for Congenital Hypothyroidism

Guidance for the Clinician in Rendering
Pediatric Care**AMERICAN ACADEMY OF PEDIATRICS**

Susan R. Rose, MD, and the Section on Endocrinology and Committee on Genetics

AMERICAN THYROID ASSOCIATION

Rosalind S. Brown, MD, and the Public Health Committee

LAWSON WILKINS PEDIATRIC ENDOCRINE SOCIETY**ABSTRACT**

Unrecognized congenital hypothyroidism leads to mental retardation. Newborn screening and thyroid therapy started within 2 weeks of age can normalize cognitive development. The primary thyroid-stimulating hormone screening has become standard in many parts of the world. However, newborn thyroid screening is not yet universal in some countries. Initial dosage of 10 to 15 $\mu\text{g}/\text{kg}$ levothyroxine is recommended. The goals of thyroid hormone therapy should be to maintain frequent evaluations of total thyroxine or free thyroxine in the upper half of the reference range during the first 3 years of life and to normalize the serum thyroid-stimulating hormone concentration to ensure optimal thyroid hormone dosage and compliance.

Improvements in screening and therapy have led to improved developmental outcomes in adults with congenital hypothyroidism who are now in their 20s and 30s. Thyroid hormone regimens used today are more aggressive in targeting early correction of thyroid-stimulating hormone than were those used 20 or even 10 years ago. Thus, newborn infants with congenital hypothyroidism today may have an even better intellectual and neurologic prognosis. Efforts are ongoing to establish the optimal therapy that leads to maximum potential for normal development for infants with congenital hypothyroidism.

Remaining controversy centers on infants whose abnormality in neonatal thyroid function is transient or mild and on optimal care of very low birth weight or preterm infants. Of note, thyroid-stimulating hormone is not elevated in central hypothyroidism. An algorithm is proposed for diagnosis and management.

Physicians must not relinquish their clinical judgment and experience in the face of normal newborn thyroid test results. Hypothyroidism can be acquired after the newborn screening. When clinical symptoms and signs suggest hypothyroidism, regardless of newborn screening results, serum free thyroxine and thyroid-stimulating hormone determinations should be performed.

INTRODUCTION

Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation. In most cases, the disorder is permanent and results from an

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Key Words

congenital hypothyroidism, thyroid hormone, thyroid-stimulating hormone, newborn screening

Abbreviations

CH—congenital hypothyroidism
TH—thyroid hormone
 T_4 —thyroxine
 T_3 —triiodothyronine
TSH-R—thyrotropin receptor
TRBAb—thyrotropin receptor-blocking antibody
 FT_4 —free thyroxine
TSH—thyroid-stimulating hormone
TBG—thyroid-binding globulin
LBW—low birth weight
VLBW—very low birth weight
L- T_4 —levothyroxine
TRH—thyrotropin-releasing hormone
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abnormality in thyroid gland development (dysgenesis or agenesis) or a defect in thyroid hormonogenesis. Less commonly, the altered neonatal thyroid function is transient, attributable to the transplacental passage of maternal medication, maternal blocking antibodies, or iodine deficiency or excess. In rare cases, CH may result from a pituitary or hypothalamic abnormality (central or secondary/tertiary hypothyroidism). Recent advances in molecular and cell biology have led to improved understanding of normal thyroid physiology and of genes involved in thyroid gland development and disease. In addition, the mechanism and precise temporal sequence of thyroid hormone (TH) modulation of target gene expression are being elucidated.¹⁻⁸

The initial American Academy of Pediatrics recommendation for newborn screening for CH was published in 1993.⁹ Screening for CH is one of dozens of newborn screening tests conducted. The rapid advances in our knowledge in the decade since the 1993 publication have prompted reevaluation of the problem and the identification of new questions and concerns.

TH concentrations are low in the fetus during the first half of pregnancy. During this time, the fetus is entirely dependent on maternal TH; its supply to the fetus is controlled by the placenta and the thyroid status of the mother. The fetal hypothalamic-pituitary-thyroid axis begins to function by midgestation and is mature in the term infant at delivery. Despite the critical importance of TH on multiple organ systems, especially the brain, most infants with CH appear normal at birth. The hypothyroid fetus appears to be protected at least in part by placental transfer of maternal TH. This was best illustrated by the demonstration that cord blood thyroxine (T₄) concentration at birth in infants unable to synthesize T₄ was nonetheless one third to one half that of normal infants.¹⁰ In addition, there is increased intracerebral conversion of T₄ to triiodothyronine (T₃), resulting in increased local availability of T₃ despite the low serum concentrations.¹¹⁻¹³ Indeed, normal or near-normal cognitive outcome is possible in even the most severely affected infants with CH. This is true as long as postnatal therapy is early and adequate and maternal thyroid function is normal. In contrast, when both maternal and fetal hypothyroidism are present, whether attributable to severe iodine deficiency, potent thyrotropin receptor (TSH-R)-blocking antibodies (TRBAb) (or TSH-blocking immunoglobulins), or maternal-fetal PIT1 deficiency, there is a significant impairment in neurointellectual development despite adequate therapy soon after birth.^{6,14,15} Maternal hypothyroidism alone during early gestation can lead to mild but significant cognitive impairment of the offspring.^{6,15-19} In this report, attention is focused on the problem of CH alone; identification and treatment of maternal hypothyroidism has been the subject of several recent reviews.^{20,21}

Pilot screening programs for CH were developed in

Quebec, Canada, and Pittsburgh, Pennsylvania, in 1974 and have now been established in Western Europe, North America, Japan, Australia, and parts of Eastern Europe, Asia, South America, and Central America.²²⁻²⁴ In North America, more than 5 million newborns are screened and approximately 1400 infants with CH are detected annually. Certainly the main objective of screening, the eradication of mental retardation after CH, has been achieved. In addition to the profound clinical benefit, it has been estimated that the cost of screening for CH is much lower than the cost of diagnosing CH at an older age. This estimate does not include the loss of tax income resulting from impaired intellectual capacity in the untreated but noninstitutionalized person. Newborn screening also has revealed the prevalence of the various causes of CH, including a series of transient disorders found predominantly in preterm infants. The incidence of CH has been found to be 4 to 5 times more common than phenylketonuria, for which screening programs were originally developed. The overall incidence of CH ranges from 1 in 3000 to 1 in 4000 newborn infants.^{15,25} The incidence of CH is higher in Hispanic individuals and lower in black individuals.²⁵ There is a 2:1 incidence in females compared with males, and there is an increased risk in infants with Down syndrome.

Iodine deficiency remains the most common treatable cause of mental retardation worldwide. Associated nutritional deficiencies in selenium and iron may have an effect on neurologic development and on thyroidal response to iodine therapy.²⁶ Many countries have initiated salt iodination.²⁵⁻²⁸ Although North America is usually considered to be an iodine-sufficient area, recent epidemiologic evidence suggests that a number of pregnant women may be iodine deficient.²⁹ There is also some concern that maternal iodine deficiency may be reappearing in developed countries despite salt iodination because diet-conscious young women may avoid iodine-supplemented salt and breads.^{30,31} Iodine supplementation before or during pregnancy will normalize thyroid function in the mother and the newborn.^{31,32}

The hypothalamic-pituitary-thyroid axis is finely tuned to maintain a fairly stable concentration of free thyroxine (FT₄) within any individual.³³ Divergence from this individual optimal "set point" because of underfunction of the thyroid gland results in an increase in thyroid-stimulating hormone/thyrotropin (TSH) concentration. The exception to this is when the hypothalamus or pituitary gland is unable to respond (in central hypothyroidism, rare pituitary resistance to FT₄ feedback, or in an occasional child with Down syndrome).

Thus, TSH is elevated if thyroid gland function is impaired and FT₄ decreases from its individual optimal set point, although TSH concentration is not elevated in central hypothyroidism.

Although much has been learned, some questions

remain. These issues include the optimal screening approach and the follow-up of infants with low T_4 and normal TSH concentrations. Finally, continued efforts are ongoing to establish the optimal therapy that leads to maximum potential for normal development for infants with CH.

SCREENING METHOD

Two screening strategies for the detection of CH have evolved: a primary TSH/backup T_4 method and a primary T_4 /backup TSH method (Fig 1). In addition, an increasing number of programs use a combined primary TSH plus T_4 approach.

Primary TSH With Backup T_4 Measurements

Most programs in Europe, Japan, Canada, Mexico, and the United States screen by using primary TSH measurements, supplemented by T_4 determinations for infants with elevated TSH values. With this approach, delayed TSH elevation in infants with thyroid-binding globulin (TBG) deficiency, central hypothyroidism, and hypothyroxinemia will be missed. Delayed TSH elevation is particularly common in infants with low birth weight (LBW [$<2500\text{g}$]) and very low birth weight (VLBW [$<1500\text{g}$]). In the Quebec study, 2 cases of permanent CH (of 93 000 infants screened) would have been missed by the primary TSH approach and detected by the primary T_4 approach.³⁴ The recall rate (notification of a physician to contact the infant's family to arrange for a blood test) with a primary TSH screening approach is approximately 0.05%. At this rate, 2 infants will be recalled for testing for every case detected.

Current TSH assay techniques (enzyme-linked immunoassays, chemiluminescent assays, and fluoroimmunoassays) use nonradioactive labels and have improved sensitivity with the potential for better separation between normal and abnormal TSH concentrations. Thus, many screening programs are considering switching to a primary TSH approach. However, the trend toward early discharge of mothers and infants (before 48 hours of age) presents a problem with the switch to a primary TSH approach because of the normal increase in TSH postnatally. With early hospital discharge, the first screening specimen commonly is obtained before 48 hours of age. Recent data using a sensitive and specific immunofluorometric assay indicate that normal TSH values before 24 hours of age are not as high as those using previous assays and usually less than the cutoff value of 20 to 25 mU/L.^{35,36} A 50% reduction in abnormal values occurred when age-adjusted TSH cutoffs were used.³⁷ Thus, the current experience using newer assays in a primary TSH screening approach in a population of infants discharged after 24 hours of age shows lower patient recall rates with negligible false-negative test results.

Primary T_4 With Backup TSH Measurements

An initial filter-paper blood-spot T_4 measurement is followed by a measurement of TSH for filter-paper specimens with low T_4 values.^{9,25} The primary T_4 approach will detect primary hypothyroidism in infants with low or low-normal T_4 with elevated TSH concentrations (prevalence ranging from 1 in 3000 to 1 in 4000 newborn infants). In addition to detecting primary hypothyroidism, the primary T_4 /backup TSH approach can also identify infants with TBG deficiency (prevalence ranging from 1 in 5000 to 10 000 newborn infants) and central hypothyroidism (low or low-normal T_4 with normal TSH concentration; prevalence: 1 in 50 000 newborn infants). Programs that quantify high T_4 values also have the potential to identify infants with hyperthyroxinemia (1 in 20 000 to 1 in 40 000 newborn infants). This approach, however, will miss the condition in an infant with an initially normal T_4 concentration and delayed increase in TSH. To ensure identification of infants with CH who have low-normal T_4 values, most screening programs use a T_4 concentration cutoff of $<10\text{th}$ percentile for the days' assay. Comparison of the primary T_4 versus primary TSH screening approach was conducted in Quebec (1983).³⁴ One case (of 93 000 infants screened) would have been missed by the primary T_4 approach and detected by the primary TSH approach.³⁴

Programs using a primary T_4 with secondary TSH approach will follow-up on infants with a low T_4 and elevated TSH screening result. The recall rate for primary hypothyroidism in these screening programs is approximately 0.05%, similar to that in primary TSH screening programs.³⁸ However, some primary T_4 screening programs also report low T_4 results below an absolute cutoff (eg, 3.0 $\mu\text{g}/\text{dL}$ [39 nmol/L]) in infants even if the TSH was normal. The recall rate (and therefore the false-positive rate) will be higher (approaching 0.30%) with this practice. For example, in a 1990 study in California, which did not report low T_4 results, the recall rate was 0.08%. In contrast, a study performed in Oregon, which reported infants with 2 low T_4 results $<3\text{rd}$ percentile, the recall rate was 0.30%.³⁹ This means that up to 12 normal infants may be recalled for testing for every 1 case of hypothyroidism.

Combined Primary TSH Plus T_4 Measurements

Methods for the simultaneous measurement of T_4 and TSH are available (DELFLIA data). This represents the ideal screening approach, especially once it is possible for FT₄ to be measured accurately and cost-effectively in the eluates from filter-paper blood spots. Until T_4 and TSH determinations can be performed practically for all infants, physicians should be aware of the potential limitations of each method of screening for CH.

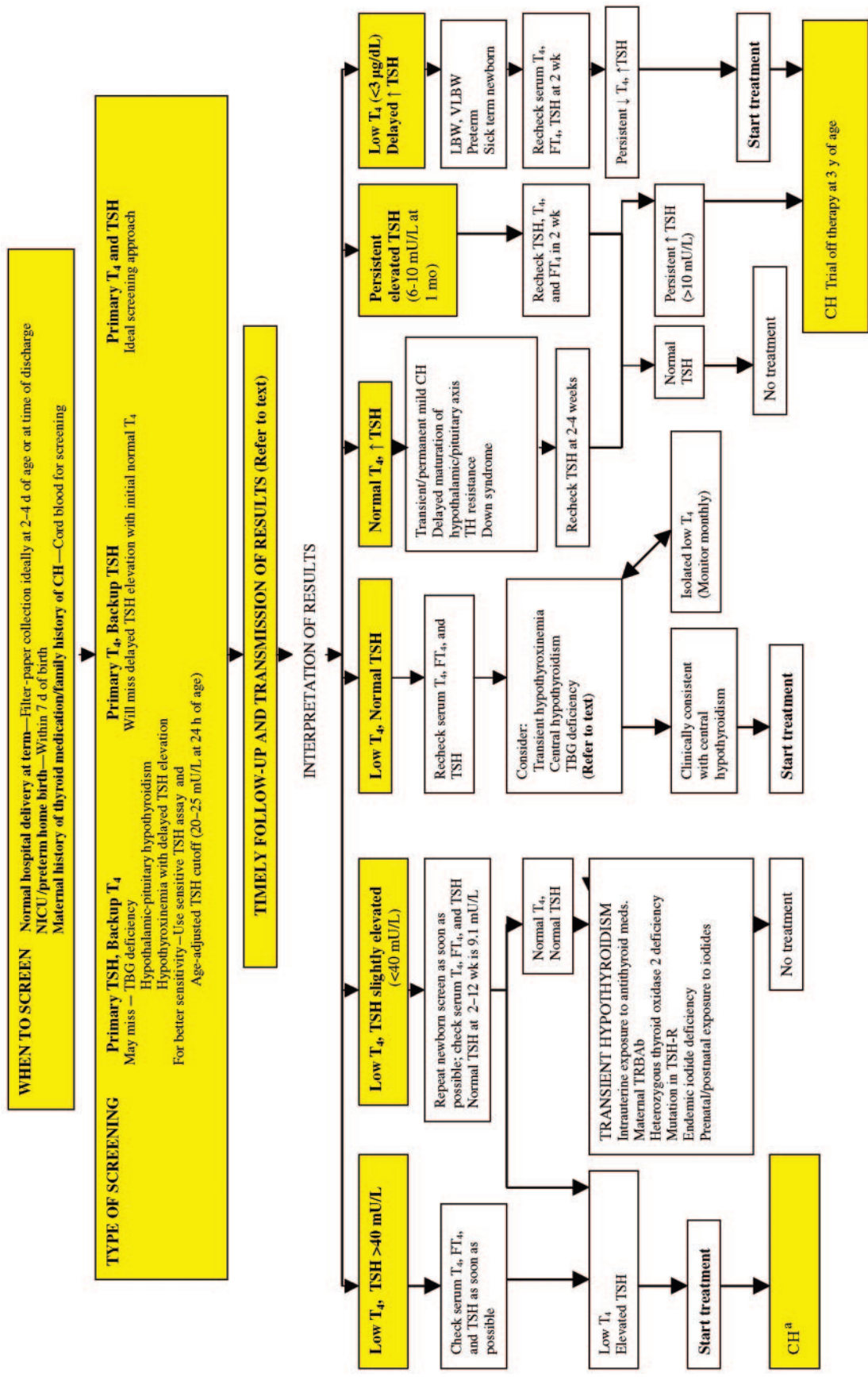


FIGURE 1 Newborn screening for CH. ^a Management of CH is summarized in Table 1.

THE SPECIMEN

Every infant should be tested before discharge from the nursery, optimally by 48 hours to 4 days of age. As noted above, specimens collected in the first 24 to 48 hours of life may lead to false-positive TSH elevations when using any screening test approach. However, screening before hospital discharge or before transfusion is preferable to missing the diagnosis of hypothyroidism. False-negative results may occur by screening a very sick newborn or after transfusion. Because newborn blood specimens are used for a variety of screening tests and shared among different laboratories, every effort should be made to collect adequate and sufficient blood in the recommended manner.³⁹

It is highly desirable that the blood be collected when the infant is between 2 and 4 days of age, but there are situations in which this is virtually impossible. In infants discharged from the nursery before 48 hours of age, blood should be obtained before discharge. In instances such as home births or in the case of a critically ill or preterm neonate, blood should be obtained by 7 days of age, recognizing that samples obtained after 4 days of age are late for screening of congenital adrenal hyperplasia or metabolic disease. Particular care must be taken with infants in NICUs. In such cases, more urgent medical problems may result in missed newborn screening. When an infant is transferred to another hospital, the first hospital must indicate whether the specimen has been collected. The second hospital should obtain a specimen if there is no proof that blood was collected before the transfer.

Some state screening programs, testing 10% of newborns in the United States, perform newborn screening on specimens routinely collected at 2 time periods. These programs report that CH is detected in approximately 10% of the affected infants only as a result of collection of a second specimen. The additional incidence of CH based on a second screening at 2 weeks of age is approximately 1 in 30 000.^{38,40} Infants with CH detected at the later screening time tend to be of LBW or VLBW, with mild or delayed TSH elevations.⁴¹ Whether these cases represent transient or permanent cases is unknown. Some have thyroid dysgenesis (ectopia, aplasia, or hypoplasia) on thyroid scanning. Others appear to have increased uptake and a large thyroid gland, suggestive of dyshormonogenesis.⁸ Either these infants have transient disease or their disease is undiagnosed until a later age, when they appear to have acquired hypothyroidism.

Accurate screening results depend on good-quality blood spots. The filter paper designed for newborn screening bears printed circles. Capillary blood samples are placed in these circular areas to fill and saturate them. Spotting blood over a previous blood spot, or double spotting, causes invalid results, and these blood spots should not be used. The recall of an infant for testing because of an unsatisfactory filter-paper speci-

men causes needless delay in diagnosis and treatment of a newborn with CH. Specimens that are technically unsatisfactory or contain insufficient amounts of blood should not be assayed. Blood samples should be collected on approved filter-paper forms, dried at room temperature, and not subjected to excessive heat. The blood should completely saturate the filter paper and be applied to 1 side only. Filter-paper spots should not be handled, placed on wet surfaces, or contaminated by coffee, milk, or other substances. Any of these have the potential to invalidate the results regardless of the method used. Testing of an unsatisfactory specimen (because of insufficient blood) can result in a false-negative TSH value. False-negative values can also result from human error in the processing of satisfactory specimens or in erroneous reporting of the results.

TEST RESULTS

Transmission of Results and Follow-up Testing

Newborn screening test results must be communicated rapidly back to the physician or hospital identified on the screening filter-paper card. The responsibility for transmission of these results rests with the authority or agency that performed the test. In general, when an abnormal screening result is found, the responsible physician is notified immediately so that he or she can arrange for follow-up testing. Screening test results should be entered into the patient's record. If the informed physician is no longer caring for or cannot locate the infant, he or she should notify the newborn screening laboratory immediately. In such situations, the local health department is often helpful in locating these infants to ensure that they are not lost to follow-up.

Low T_4 and Elevated TSH Values

Any infant with a low T_4 concentration and TSH concentration greater than 40 mU/L* is considered to have primary hypothyroidism. Such infants should be examined immediately and have confirmatory serum testing performed to verify the diagnosis. Treatment with replacement levothyroxine (L- T_4) should be initiated as soon as confirmatory tests have been drawn and before the results of the confirmatory tests are available. (Clinical management of infants with hypothyroidism is described in the following section.) For cases in which the screening TSH concentration is only slightly elevated but less than 40 mU/L, another filter-paper specimen should be obtained for a second newborn screening. Ten percent of infants with confirmed CH have TSH values between 20 and 40 mU/L. It is important that age-appropriate normative values be used. The reference

* All filter-paper TSH [and T_4] levels here are reported as serum equivalents. Some laboratories report screening results per unit of blood, a value that is approximately half the concentration in serum. We recommend that all laboratories report results per unit of serum, because TSH and T_4 are preferentially distributed into the serum.

range for TSH for the most common time of TSH reevaluation (between 2 and 6 weeks of age) is 1.7 to 9.1 mU/L.⁴²

Normal T₄ and Elevated TSH Values

Hyperthyrotropinemia is characterized by elevated serum TSH concentrations during the neonatal period despite normal T₄ and FT₄ concentrations. The etiology is probably heterogeneous and can be either a transient or permanent thyroid abnormality^{43–46} or delayed maturation of the hypothalamic-pituitary axis. Inactivation mutations in the TSH-R cause compensated, mild (subclinical) primary hypothyroidism in the neonatal period. The incidence of both transient and persistent hyperthyrotropinemia and CH appears to be higher in infants with Down syndrome. In some cases, transient neonatal hyperthyrotropinemia persists until 10 years of age or later.

There is controversy regarding the need for TH therapy in this setting. There have been no long-term studies to evaluate cognitive development in this group of patients. TSH concentration is the most sensitive indicator that the hypothalamic-pituitary axis is sensing less T₄ than the body “perceives” as optimal. Most physicians would consider a persistent basal TSH concentration higher than 10 mU/L (after the first 2 weeks of age) to be abnormal.⁴² Therefore, if the TSH elevation persists, the infant should be treated. If such infants are not treated, measurement of FT₄ and TSH should be repeated in 2 and 4 weeks, and treatment should be initiated promptly if the FT₄ and TSH concentrations have not normalized.

The management of infants with TSH elevations between 6 and 10 mU/L that persist after the first month of life is even more controversial. TSH concentrations are slightly higher in the first few months of life. A TSH range of 1.7 to 9.1 mU/L has been reported for children 2 to 20 weeks of age (Quest Diagnostics reference values, Lyndhurst, NJ). Thus, using the adult reference range for TSH will result in treatment of many euthyroid children. Consequently, if a decision is made to treat such children, a trial off therapy at 3 years of age should be performed.

Low T₄ and Normal TSH Values

Infants with normal TSH but low T₄ values (defined as 2 SDs below the mean for the reference range for age, usually below 10 μg/dL in the newborn infant) may have thyroid insufficiency. The low T₄ with normal TSH profile is seen in 3% to 5% of neonates. This pattern may result from hypothalamic immaturity (particularly in preterm infants, 12% of all newborn infants). Low T₄ but normal TSH results are also observed during illness, with protein-binding disturbances such as TBG deficiency (1 in 5000), in central hypothyroidism (1 in 25 000 to 1 in 50 000 newborn infants; see next 3 paragraphs),⁴⁷ or with primary hypothyroidism and delayed

TSH elevation (1 in 100 000 newborn infants). Newborn infants who are preterm or ill are found with disproportionate frequency among those with this set of laboratory values.⁴⁸ In neonates/infants, inhibition of TSH (causing low T₄ concentrations) can result from constant infusions of dopamine or high-dose glucocorticoids.

Transient hypothyroxinemia is seen to some extent in many preterm infants.^{36,48} Immaturity of the hypothalamic-pituitary axis may be physiologically normal for the infant's gestational age. Preterm serum T₄ and FT₄ concentrations are lower than those of term infants, but the TSH concentrations are comparable to term infants.^{49,50} Serum TBG concentrations are only slightly low in preterm infants and do not account for the degree of hypothyroxinemia. Consequently, the FT₄ is rarely as low as the total T₄. Serum inhibitors of T₄ binding, present in many patients with nonthyroidal illness, may be an additional contributor to the decreased T₄ values.

In contrast to transient hypothyroxinemia, the presence of midline facial abnormalities, hypoglycemia, microphallus, or visual abnormalities should suggest the possibility of a hypothalamic-pituitary abnormality. Septo-optic dysplasia, often associated with pituitary hormone deficiencies, can manifest as central hypothyroidism.^{51,52} Genetic mutation in HESX-1 has been described in septo-optic dysplasia. Clinical symptoms of hypopituitarism, such as neonatal hypoglycemia (from growth hormone and adrenocorticotrophic hormone deficiencies), polyuria (from antidiuretic hormone deficiency), or small phallus in boys (from gonadotropin deficiencies), along with the presence of blindness, congenital nystagmus, or midline defects of the brain, should alert the physician to suspect the diagnosis of septo-optic dysplasia. Alternatively, multiple pituitary hormone deficiencies suggest a genetic defect in the cascade leading to fetal pituitary formation, such as PROP1, LHX3, and POU1F1.^{4,53} DNA screening for these molecular abnormalities could be beneficial in the future for the rapid and accurate detection of these affected infants during the first weeks of life, but is not yet available clinically.

Isolated TSH-releasing hormone (TRH) deficiency may cause low-normal T₄ and low or normal TSH concentrations. Secondary (or central) hypothyroidism may be suspected in infants with low T₄ and FT₄ and low TSH concentrations.^{32,43} Mutations have been identified in the β subunit of TSH, TRH gene, and TRH receptor gene.^{54,55} Finally, congenital TSH and growth hormone deficiencies may occur as a result of a difficult birth or anoxia.⁵⁶

In programs that report low T₄ with normal TSH results, there is no clear consensus regarding optimal follow-up. Such programs have elected to take no further action, to follow-up with serial filter-paper screening tests until the T₄ value becomes normal, or to request a second blood sample for measurement of FT₄ and TSH

concentrations. Most infants with low T_4 and normal TSH have normal FT_4 values, and subsequent thyroid function test results are normal. Programs that choose to pursue further laboratory testing must weigh the benefit of detecting TBG deficiency or the rare case of hypopituitary-hypothyroidism or delayed TSH increase against the cost and the psychological effect on the family. The responsibility of deciding which course of action to follow rests with the physician providing the care of the infant. Treatment of these infants (with the exception of those with central hypothyroidism or delayed TSH increase) with L- T_4 has not yet been shown to be beneficial.^{48,57-59}

Low T_4 and Delayed TSH Increase

Many infants with low T_4 concentrations and normal TSH values on initial screening (1 in 100 000 newborn infants) who are subsequently found to have an elevated TSH concentration are LBW, VLBW, or critically ill preterm and term neonates. Serum TSH values in these infants increase during the first few weeks of life to concentrations characteristic of primary hypothyroidism. It is unclear whether infants with this delayed TSH elevation have an abnormality of pituitary-thyroid feedback regulation, transient hypothyroidism (eg, iodine induced), or a mild form of permanent CH. Long-term follow-up of these infants has not been reported. It is important, therefore, that serum FT_4 and TSH be tested in infants with overtly low T_4 concentrations or in any infant with suggestive signs of hypothyroidism. Infants with low T_4 and a delay in elevation of TSH values and those with normal T_4 concentrations and elevated TSH values might be missed on initial screening. Neither a primary T_4 /backup TSH nor a primary TSH/backup T_4 screening strategy will detect the rare infant with a normal T_4 at birth but delayed TSH increase. Even in the absence of technical and human errors, 5% to 10% of LBW and VLBW newborn infants with CH may have normal screening hormone concentrations regardless of the approach used.

Some screening programs routinely obtain a second specimen at 2 to 6 weeks of age and/or obtain a serum sample from any infant with 2 successive T_4 values below an absolute cutoff (<3rd percentile). Whatever strategy is used, subsequent testing should be performed on serum during infancy whenever there is a perceived risk of hypothyroidism, as in familial dysmorphogenesis or in infants with clinical suspicion of hypothyroidism. In addition, a second specimen should be drawn at 2 weeks of age in monozygotic twins, because fetal blood mixing may mask the screening test results.⁶⁰

However, a second screen has not become routine because of (1) increased cost, (2) relatively low yield of cases, (3) diversion and dilution of key personnel, (4) inability to implement new programs, and (5) absence of such cases missed in primary TSH screening programs.

Finally, the cognitive and developmental prognosis of this cohort is uncertain because the etiology in most cases is unknown and there are no definitive follow-up data.

As an alternative strategy, other programs have attempted to identify high-risk patient groups so that routine rescreening can be targeted to these infants. There is a disproportionate incidence of delayed TSH increase in VLBW infants (incidence of CH: 1 in 250), LBW infants (incidence of CH: 1 in 1589), and neonates in intensive care settings or with cardiovascular abnormalities.⁶¹ Therefore, some screening programs routinely screen again at 2 weeks and 6 weeks of age all VLBW and all LBW infants in the NICU, especially in newborns known to have cardiac disease. It is likely that most of these infants do not have permanent CH. If hyperthyrotropinemia persists at 6 weeks of age, TH replacement should be started, consistent with therapy of other forms of transient CH, and the infant should be retested after 3 years of age (after stopping therapy for 4–6 weeks) (see “Assessment of Permanence of Hypothyroidism”).

Transient TSH Elevation

A small number of infants with abnormal screening values will have transient hypothyroidism as demonstrated by normal serum T_4 and TSH concentrations on the confirmatory (follow-up to screening) laboratory tests. Transient hypothyroidism is relatively rare in North America (estimated at 1 in 50 000) in contrast to iodine-deficient areas of the world; it is much more common in preterm infants but may occur in apparently healthy term infants. Transient hypothyroidism may result from intrauterine exposure to maternal antithyroid drugs, maternal TRBAb, heterozygous thyroid oxidase 2 deficiency, germ-line mutations in the TSH-R, endemic iodine deficiency, or prenatal or postnatal exposure to excess iodides (povidone iodine, iodinated contrast materials).^{31,32,43,62,63} Transient iodine-induced CH is not usually evident at birth and, therefore, may not be detected if newborn screening is performed in the first few days postnatally.

Transplacental passage of potent maternal TRBAb (incidence: 1 in 180 000) is a much less common cause of transient CH but should be suspected if there is a maternal history of autoimmune thyroid disease or if there is a history of previous affected offspring. In this setting, cord serum can be collected and rapidly tested for thyroid abnormalities. The half-life of immunoglobulin G in the neonate is approximately 3 to 4 weeks,⁶⁴ and TRBAb usually disappear from serum of affected infants by 3 to 6 months of age, depending on the antibody potency.

Because the transient nature of the hypothyroidism will not be recognized clinically or through laboratory tests in some infants, initial treatment will be similar to that in any infant with permanent CH. In these cases, it

is important to determine at some later time whether the hypothyroidism is permanent and whether the infant in fact requires lifelong treatment (see "Assessment of Permanence of Hypothyroidism"). However, in the newborn infant with transient hypothyroidism whose mother is receiving an antithyroid drug, the T_4 and TSH values tend to return to normal within 1 to 3 weeks after birth without treatment.

CLINICAL MANAGEMENT OF NEWBORN INFANTS WITH LOW T_4 AND ELEVATED TSH VALUES

Infants with low T_4 and elevated TSH concentrations have CH until proven otherwise. Management should include the following (Table 1):

1. The infant should be seen by his or her physician without delay. Consultation with a pediatric endocrinologist is recommended to facilitate diagnostic evaluation and optimal management.
2. A complete history, including prenatal thyroid status (maternal drugs and medications) and family history should be obtained, and physical examination should be performed.
3. Serum should be obtained for confirmatory measurements of TSH and FT_4 . An elevated thyroglobulin concentration may suggest dysthyronogenesis. Care must be taken to compare the serum results to normal TH concentration for age. When there is history of a maternal autoimmune thyroid disorder or a previously affected infant, measurement of TRBAs in the infant and/or mother may identify a transient form of neonatal hypothyroidism.
4. Education of parents by trained personnel using booklets or visual aids is highly desirable. Education should focus on (a) the etiology of CH, (b) the lack of

correlation of parental lifestyle during pregnancy with causes of the disease, (c) the benefit of early diagnosis in preventing mental retardation, (d) the appropriate manner in which TH is administered and the substances (eg, soy, iron, calcium, and fiber) that can interfere with TH absorption, (e) the importance of adherence to the treatment plan, and (f) the importance of periodic follow-up care.

5. Optional diagnostic studies include thyroid ultrasonography or iodine 123 (^{123}I) or sodium technetium 99m pertechnetate (^{99m}Tc) thyroid uptake and/or scan to identify functional thyroid tissue. Although ^{123}I tends to give a more accurate uptake and scan picture, it may not be readily available in all hospitals. ^{99m}Tc is generally more readily available and a much less expensive radioisotope. The half-life of ^{123}I is 13.3 hours, compared with 8 days for iodine 131 (^{131}I). ^{123}I exposes the infant to much lower doses of ionizing radiation compared with ^{131}I (probably one 100th of the ^{131}I dose [H.-M. Park, MD, Professor Emeritus, Radiology, Indiana University, personal communication, September 16, 2004]).

There remains some controversy regarding the risk-benefit ratio of early thyroid scanning of infants with suspected hypothyroidism. For physicians who opt for imaging, the benefits can be summarized as follows:

1. If an ectopic gland is demonstrated, a permanent form of thyroid disease and CH has been established.
2. The absence of thyroid gland uptake is most often associated with thyroid aplasia or hypoplasia. When radioiodine uptake is absent but ultrasonographic examination reveals a normal gland, a TSH-R defect, iodine-transport defect, or maternal transfer of TRBAs may be present.
3. Normal scan findings (or a goiter) indicate a functioning thyroid gland with regard to iodine uptake and alert the physician to a probable hereditary defect in T_4 synthesis. Measurement of serum thyroglobulin will help to separate thyroglobulin synthetic defects from other causes of hypothyroidism.⁶⁵ Exposure to an exogenous goitrogen other than iodine, such as antithyroid drugs, will produce a similar picture. Finally, some infants exposed to maternal TRBAs may have a normal scan if their hypothyroidism is partially compensated. The identification of a genetically mediated thyroid synthetic enzyme defect is especially important for families planning on having additional children. In such cases, the scan enables the physician to arrange for genetic counseling.
4. Some infants with normal scan findings at birth who do not fall into one of the above categories may have a transient form of hypothyroidism. These infants should undergo a careful follow-up evaluation after 3

TABLE 1 Management of CH

Initial workup
Detailed history and physical examination
Referral to pediatric endocrinologist
Recheck serum TSH and FT_4
Thyroid ultrasonography and/or thyroid scan (see text for recommendations)
Medications
L- T_4 : 10–15 $\mu g/kg$ by mouth once daily
Monitoring
Recheck T_4 , TSH
2–4 wk after initial treatment is begun
Every 1–2 mo in the first 6 mo
Every 3–4 mo between 6 mo and 3 y of age
Every 6–12 mo from 3 y of age to end of growth
Goal of therapy
Normalize TSH and maintain T_4 and FT_4 in upper half of reference range
Assess permanence of CH
If initial thyroid scan shows ectopic/absent gland, CH is permanent
If initial TSH is <50 mU/L and there is no increase in TSH after newborn period, then trial off therapy at 3 y of age
If TSH increases off therapy, consider permanent CH

years of age, when it is safe to discontinue treatment temporarily under the conditions described in "Assessment of Permanence of Hypothyroidism."

Treatment need not be delayed to perform the scan. A thyroid scan can be performed within the first few days of treatment, because the elevated TSH found in patients with permanent CH rarely normalizes within this time period. A serum TSH measurement should be obtained at the time of the scan. If L-T₄ therapy has caused the TSH concentration to be <30 mU/L, ultrasonography can still be performed. A scan can be performed after the child is 3 years of age, when TH treatment can be interrupted without danger to the developing central nervous system.

The usual dose of ¹²³I, the preferred isotope, is 0.925 MBq (25 μCi). This represents a small amount of radiation exposure, equivalent to the amount of exposure with 2 to 3 chest radiographs. However, the radiation exposure is potentially 100 times greater if ¹³¹I or large doses of isotope are administered. For this reason, the procedure should be performed by experienced personnel with optimal equipment, using the minimally recommended tracer dose.

To avoid unnecessary radiation, some investigators prefer ultrasonography as the initial imaging procedure to identify the presence and location of thyroid tissue.⁶⁶⁻⁶⁸ However, gray-scale ultrasonography is much less sensitive than scintigraphy in detecting the presence of ectopic thyroid tissue, the most common cause of CH. Recent studies have indicated markedly improved sensitivity of color Doppler ultrasonography in diagnosing ectopic thyroid tissue.⁶⁹ If these studies are confirmed, color Doppler ultrasonography may become the optimal imaging procedure for the initial investigation of suspected CH.

TREATMENT

All infants with hypothyroidism, with or without goiter, should be rendered euthyroid as promptly as possible by replacement therapy with TH.^{21,70-72} An optimal cognitive outcome depends on both the adequacy and timing of postnatal therapy, particularly in severe cases of CH (T₄ < 5 μg/dL). However, what constitutes optimal TH therapy is not yet certain. The goal of therapy is to normalize T₄ within 2 weeks and TSH within 1 month. An initial dosage of 10 to 15 μg/kg of L-T₄ (depending on the severity of the initial hypothyroidism) has been recommended. When a higher initial dose of L-T₄ (50 μg [ie, 12-17 μg/kg]) is used, the serum T₄ normalizes in 3 days and the TSH returns to the target range by 2 weeks of therapy.⁷² In the long run, evaluation of cognitive outcome is important after use of this increased dose. Currently the evidence base does not indicate cognitive benefit from thyroid therapy of hypothyroxinemia of prematurity in the absence of TSH elevation.^{48-50,57-59}

Administration of L-T₄ is the treatment of choice. Although T₃ is the more biologically active TH, most brain T₃ is derived from local monodeiodination of T₄, so T₃ should not be used. The pill should be crushed and suspended in a few milliliters of formula, breast milk, or water. Care should be taken to avoid concomitant administration of soy, fiber, or iron. Breastfeeding can continue. Only T₄ tablets should be used; currently there are no liquid formulations licensed by the US Food and Drug Administration. T₄ suspensions that may be prepared by individual pharmacists may lead to unreliable dosage. T₄ is expected to increase to more than 10 μg/dL, FT₄ is expected to increase to more than 2 ng/dL by 2 weeks after initiating therapy, and TSH should normalize by 1 month.⁷³ FT₄ measurement at 1 week of therapy can confirm whether the serum concentration is increasing appropriately. The L-T₄ dose should be adjusted according to the infant's clinical response and serum FT₄ and TSH concentrations.

During therapy, the serum total T₄ or FT₄ should and might be in the upper half of the reference range (target values depend on the assay method used [T₄: 10-16 μg/dL (130-206 nmol/L); FT₄: 1.4-2.3 ng/dL (18-30 pmol/L)]) during the first 3 years of life with a low-normal serum TSH. The latter may sometimes be delayed because of relative pituitary resistance. In such cases, characterized by a normal or increased serum T₄ and an inappropriately high TSH concentration, the T₄ value is used to titrate the dose. Nonadherence to the treatment is the most common cause of persistent TSH elevation and should be excluded. Those infants with low serum T₄ concentrations (below 10 μg/dL [129 nmol/L]) and a TSH concentration greater than 15 mU/L during the first year of life have lower IQ values than patients whose T₄ concentrations were held constant at higher concentrations.³⁵ Thereafter, thyroid function test values should be kept at age-appropriate concentrations, which in children differ from those for adults.⁷⁴ On TH-replacement therapy, TSH levels should be maintained between 0.5 and 2.0 mU/L during the first 3 years of life.⁷⁵ Clinical evaluation of the infant by the practitioner should be conducted at frequent intervals during the first 3 years of age (see "Follow-up"). Because poor compliance and noncompliance have major sequelae, initial and ongoing counseling of parents is of great importance.

Current international organizations such as the American Clinical Laboratory Association recommend that the FT₄, rather than the total T₄, be measured to assess the concentration of the biologically relevant, unbound or free form of circulating T₄.⁷⁵ The cost of total T₄ plus TBG or T₃ resin uptake, versus the FT₄ by most methods (excluding the more costly direct dialyzable or ultrafiltration methods), should be comparable. However, although the total T₄ is a robust measure, it should be recognized that most direct FT₄ assays are influenced,

to some extent, by protein binding. Consequently, the FT₄ values obtained vary between assays.

During TH therapy, 4 or more episodes of insufficiently suppressed TSH (>5 mU/L) after the age of 6 months were the most important variables associated with school delay.⁷⁵ Usually, these episodes are caused by poor parental compliance or impaired T₄ bioavailability. The latter may be caused by inhibition of T₄ intestinal uptake by specific foods (soy, fiber) and medications (iron, calcium), malabsorption, or increased degradation (anticonvulsants; large hemangiomas with high deiodinase activity). The Food and Drug Administration has deemed several generic L-T₄ products to be equivalent to some currently branded preparations. Any change in source of the L-T₄, especially if not a standard brand, requires retitration of the dose.

FOLLOW-UP

Clinical examination, including assessment of growth and development, should be performed every few months during the first 3 years of life. Infants with CH appear to be at increased risk of other congenital anomalies (approximately 10% of infants with CH, compared with 3% in the general population). Cardiovascular anomalies, including pulmonary stenosis, atrial septal defect, and ventricular septal defect, are the most common.

Infants need to undergo frequent laboratory and clinical evaluations of thyroid function, growth, and development to ensure optimal T₄ dosage and adherence to their therapy regimen. Serum T₄ and TSH measurements should be performed:

1. at 2 and 4 weeks after the initiation of L-T₄ treatment;
2. every 1 to 2 months during the first 6 months of life;
3. every 3 to 4 months between 6 months and 3 years;
4. every 6 to 12 months until growth is completed; and
5. at more frequent intervals when compliance is questioned, abnormal values are obtained, or dose or source of medication has been changed; FT₄ and TSH measurements should be repeated 4 weeks after any change in L-T₄ dosage.

The aim of therapy is to ensure normal growth and development by maintaining the serum total T₄ or FT₄ concentration in the upper half of the reference range in the first year of life, with a serum TSH in the reference range (optimally 0.5–2.0 mU/L).

Some infants will have serum TSH concentrations in the range of 10 to 20 mU/L despite T₄ concentrations in the upper half of the reference range. Rarely, the elevated TSH relative to the FT₄ value is hypothesized to result from in utero hypothyroidism, producing a resetting of the pituitary-thyroid feedback threshold. A failure of the serum FT₄ concentration to increase into the

upper half of the reference range by 2 weeks and/or failure of the TSH concentration to decrease to less than 20 mU/L within 4 weeks after initiation of L-T₄ administration should alert the physician that the child may not be receiving adequate L-T₄ regularly. At this point, careful inquiry should be made regarding compliance, dose of medication, and method of administration. When attempting to achieve the optimal concentration of circulating FT₄, physicians should always bear in mind the adverse effects of excessive medication and thus be prepared to monitor blood concentrations of FT₄ at close intervals. Prolonged hyperthyroidism has been associated with premature craniosynostosis.

DEVELOPMENTAL OUTCOME

Growth rate and adult height are normal in children with CH in whom TH therapy is consistently maintained.^{68,76,77} The best outcome occurred with TH therapy started by 2 weeks of age at 9.5 μg/kg or more per day, compared with lower doses or later start of therapy.⁷¹ There are only minor differences in intelligence, school achievement, and neuropsychological tests in adults with CH that was treated early with TH compared with control groups of classmates and siblings.^{78–82} Residual defects can include impaired visuospatial processing and selective memory and sensorimotor defects. Whether these minor differences are preventable by further optimizing postnatal therapy remains controversial.

In contrast to the excellent outcome in infants with CH that is treated early, the prognosis for normal mental and neurologic performance is less certain for infants with CH that is not detected early by newborn screening. Although physical recovery is good and stature is normal,⁷⁷ when replacement therapy is begun later but within the first 2 months of life, infants with severe hypothyroidism at birth and intrauterine hypothyroidism (retarded skeletal maturation at birth) may still have a low-to-normal IQ.¹⁸ Similarly, although more than 80% of infants given replacement therapy before 3 months of age have an IQ greater than 85, 77% of these infants show some signs of minimal brain damage, including impairment of arithmetic ability, speech, or fine motor coordination in later life. Even in early-treated patients with CH, auditory brainstem evoked potentials were abnormal in 25% of 27 children studied. The reason for this is not known but might suggest that prenatal maternal T₄ production does not provide complete protection for the developing central nervous system.⁸⁴ In another study, processing of visuospatial relationships remained affected in adolescents with CH.⁸⁵ The effect of underlying severity of CH combines with the effects of TH dose and of age at onset of TH therapy.³⁵ Otherwise, neurologic and intellectual outcome do not correlate well with the degree of T₄ deficiency found in neonatal screening.

Transplacental transfer of maternal T₄ in the first

trimester may protect the brain during early development.¹⁵ For the same reason, maternal hypothyroidism during fetal development can have persistent neurodevelopmental effects on the child.^{15,16,19} Serum T₄ concentrations at term in athyreotic infants are 25% to 50% of those in normal neonates. These concentrations, although low, may contribute to fetal brain development. It is thought that the low-to-normal intelligence of patients with CH treated early in life results most commonly from inadequate treatment or poor compliance.

It must be noted that TH treatment regimens used today are more aggressive in targeting early correction of TSH than were the regimens used 20 or even 10 years ago. Thus, newborn infants with CH today may have an even better intellectual and neurologic prognosis than adults with CH who were evaluated in the reports discussed above.

ASSESSMENT OF PERMANENCE OF HYPOTHYROIDISM

CH is permanent if the thyroid scan reveals an ectopic gland or absent thyroid tissue (confirmed by ultrasonographic examination) or if the serum TSH is seen to increase above 10 mU/L after the first year of life, presumably because of insufficient T₄ replacement.

If no permanent cause of CH was found by scan or there was no TSH increase after the newborn period, then L-T₄ administration should be discontinued for 30 days at some point after the child is 3 years of age.⁸⁶ After 30 days, serum should be obtained for measurement of FT₄ and TSH values. It is critical that this follow-up laboratory assessment be obtained in a timely manner and that there be no loss of follow-up. If the FT₄ is low and the TSH value is elevated, permanent hypothyroidism is confirmed and TH therapy should be reinstated. If the FT₄ and TSH concentrations remain in the reference range, euthyroidism is assumed and a diagnosis of transient hypothyroidism recorded. It is important that the child not be lost to follow-up. The physician should monitor the child carefully and repeat the thyroid function tests at the slightest suspicion of recurrence of hypothyroid symptoms. If the results are inconclusive, careful follow-up and subsequent testing will be necessary.

More severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days. An alternative option is to reduce the TH-replacement dosage by half. If after 30 days the TSH is elevated above 20 mU/L, the permanence of hypothyroidism is confirmed and full replacement therapy should be resumed. If the serum TSH value has not increased, then TH treatment should be discontinued for another 30 days with repeated serum FT₄ and TSH determination as described above.

ADMONITION

Finally, physicians cannot and must not relinquish their clinical judgment and experience in the face of normal

newborn thyroid test results. Failure of normal development can result from hypothyroidism in infants who had normal T₄ and TSH newborn screening results. Hypothyroidism can manifest or be acquired after the newborn screening. Rarely, the newborn screening test results can be in error, or human error can result in failure to notify the infant's physician of abnormal test results.⁸⁷ When clinical symptoms and signs suggest hypothyroidism, regardless of newborn screening results, serum FT₄ and TSH determinations should be performed.

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