

Newborn Screening for Congenital Hypothyroidism: Recommended Guidelines

AAP Section on Endocrinology and Committee on Genetics, and American Thyroid Association Committee on Public Health

Congenital hypothyroidism (CH) represents one of the most common preventable causes of mental retardation. The fetal hypothalamic-pituitary-thyroid axis begins to function by midgestation and is mature in the term infant at delivery. If fetal hypothyroidism develops, untoward effects may be demonstrated in certain organ systems, including the central nervous system and skeleton. However, most infants with CH appear normal at birth. Recent data suggest that the hypothyroid fetus is protected to a certain extent by placental transfer of maternal thyroid hormone; serum thyroxine (T_4) levels in the cord blood of athyroid fetuses approximate one third of maternal levels.¹ In addition, studies in animal models of hypothyroidism demonstrate increased levels of brain iodothyronine deiodinase, the enzyme which converts T_4 to triiodothyronine (T_3). In the hypothyroid fetus, this increased enzyme acting on T_4 of maternal origin is sufficient to produce near normal fetal brain T_3 concentrations.² Thus, it appears that early detection and treatment of congenital hypothyroidism should have the potential to completely reverse the effects of fetal hypothyroidism in all but the most severe cases, for example, athyreotic infants born to mothers with thyroid problems resulting in inadequate placental transfer of maternal thyroid hormone.

Since the development of pilot screening programs for CH in Quebec and Pittsburgh in 1974,³ newborn screening for CH has become routine in essentially all developed countries of the world and is under development in Eastern Europe, South America, Asia, and Africa. In North America it is estimated that more than 5 million newborns are screened, with approximately 1400 infants with congenital hypothyroidism detected annually. The screening programs have benefited patients and their families and produced new information regarding the epidemiology, pathophysiology, diagnosis, and treatment of thyroid disease in infancy and childhood. During this period of implementation and growth of screening programs, many of the issues and questions that originally arose have been resolved, but some remain. These issues include the optimal screening approach,

the follow-up of some infants with low T_4 and normal thyroid-stimulating hormone (TSH) screening results, the role of autoimmunity in the etiology of the disease, and the optimal therapy that leads to maximum potential for normal development for infants in whom the disease is detected.

SCREENING METHOD

Primary T_4 With Backup TSH Measurements

Most North American programs use a two-tiered laboratory approach. An initial filter paper blood spot T_4 measurement is followed by a measurement of TSH in filter paper specimens with low T_4 values. This approach will detect infants with primary hypothyroidism (low or low-normal T_4 with elevated TSH concentrations), with an overall prevalence of 1 in 4000 newborns. There is some evidence to suggest that CH is more prevalent in Hispanic and Native American infants, while it is less prevalent in black infants. In addition, if the T_4 result is reported, this approach can also identify infants with thyroxine-binding globulin (TBG) deficiency or hypothalamic-pituitary hypothyroidism (low or low normal T_4 with normal TSH concentration; prevalence: 1/5000 to 10 000 and 1/50 000 newborns, respectively). Programs that quantify high T_4 values also have the potential to identify infants with hyperthyroxinemia (1/20 000 to 1/40 000 newborns). To ensure identification of infants with CH who have low-normal T_4 values, the T_4 concentration cutoff (for TSH testing) must be increased well into the normal range (to the 10th to 20th percentiles). With a lower percentile cutoff, this approach will miss infants who have a normal T_4 value but elevated TSH concentration. In a comparison of the primary T_4 vs primary TSH screening approach carried out in Quebec by simultaneous T_4 and TSH measurements on the screening specimen, one case out of 93 000 infants screened would have been missed by the primary T_4 approach but would have been detected by the primary TSH approach.⁴

All screening programs employing a primary T_4 with TSH backup approach will follow-up on infants with a low T_4 and elevated TSH screening result. The recall rate (notification of a physician to contact the infant's family to arrange for a blood test) in these screening programs is approximately 0.05%, similar to that in primary TSH screening programs. However, some primary T_4 screening programs also re-

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate. PEDIATRICS (ISSN 0031 4005). Copyright © 1993 by the American Academy of Pediatrics.

port low T_4 results in infants with a filter paper T_4 below an absolute cutoff, eg, 3.0 $\mu\text{g}/\text{dL}$ (39 nmol/L), or with repeatedly low filter T_4 concentrations (in programs with two routine specimens collected at two time periods). The recall rate (and therefore the false-positive rate) will be higher, approaching 0.30% with this practice. For example, in 1990 in California, which did not report low T_4 results, the recall rate was 0.08%, while in Oregon, which reported infants with two low T_4 results below the third percentile, the recall rate was 0.30% (1990 Council of Regional Networks for Genetics Services report⁵). This means that up to 12 normal infants may be recalled for testing for every one case of hypothyroidism. The effect of this higher recall rate, which may lead to psychological harm in normal infants (ie, by creating the "vulnerable child"), must be weighed by personnel of screening programs when they choose their screening methods.

Primary TSH Measurements

A majority of European and Japanese programs favor screening by means of primary TSH measurements, supplemented by T_4 determinations for those infants with elevated TSH values. With this approach, infants with TBG deficiency, hypothalamic-pituitary hypothyroidism, and hypothyroxinemia with delayed TSH elevation will be missed. In the Quebec study previously mentioned, comparing results of testing by simultaneous primary T_4 with TSH backup with results obtained by a primary TSH approach, two cases of CH that would have been missed out of 93 000 infants screened by the primary TSH approach would have been detected by the primary T_4 approach.⁴ The recall rate with a primary TSH screening approach is approximately 0.05%. At this rate, two infants will be recalled for testing for every case detected.

Newer TSH assay techniques, such as the enzyme-linked immunoassays, chemiluminescent assays, and fluoroimmunoassays, offer the advantages of using nonradioactive labels and greater 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 infants and mothers presents problems with this switch. Twenty-five percent or more of newborns are now discharged in the first 24 hours and 40% in the second 24 hours of life and would therefore have their first screening specimen obtained before 48 hours of age, when the normal TSH level may exceed the 20 mU/L cutoff value. This would result in an unacceptably high recall rate for this group of infants unless the TSH cutoff was adjusted for age. Experience using newer assays in a primary TSH screening approach in a population of infants discharged early is necessary to determine the effects on recall rates and the possibility of any false-negative test results.

Combined Primary T_4 and TSH Measurements

Within the next few years, methods for the simultaneous measurement of both T_4 and TSH will be

available. This may represent the ideal screening approach. Until further advances are made in the state of the art of screening, the choice of the method should be based on the experience of the program, needs of the population, and availability of resources. Until T_4 and TSH determinations can be done practically on all infants, physicians should be aware of potential limitations of each method of screening for CH. Even in the absence of technical and human errors, studies quoted previously suggest that 5% to 10% of newborns with CH will have normal screening hormone concentrations regardless of the type of approach used and can be missed by the screening programs.

THE SPECIMEN

Every infant should be tested before discharge from the nursery. As described above, results from specimens collected in the first 24 to 48 hours of life may lead to false-positive TSH elevations using any screening test approach. However, screening before discharge is preferable to missing the diagnosis of hypothyroidism because of the lack of a clearly defined policy regarding responsibility for blood collection from infants discharged early. Because newborn blood specimens are used for a variety of tests and shared among different laboratories, every effort should be made to collect adequate and sufficient blood in the recommended manner (see *Blood Collection on Filter Paper for Neonatal Screening Programs: Approved Standard*⁶).

It is highly desirable that the blood be collected when the infant is between 2 and 6 days of age, but there will be 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 premature neonate, blood should be obtained within 7 days after birth. Particular care must be taken with infants in neonatal intensive care units; in such cases more urgent medical problems may result in an oversight in specimen collection. 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.

Programs in approximately 10 states, representing 10% of newborns in the United States, perform newborn screening on specimens routinely collected at two time periods, initially in the first 5 days of life, and later at the first return visit, usually between 2 and 6 weeks of age.⁵ These programs report that CH is detected in approximately 10% of the affected infants only as a result of collection of a second specimen. This represents an incidence of CH of approximately 1:30 000 resulting from the second screening.⁵ Infants with CH detected at the later screening time tend to be mildly affected, often with compensated hypothyroidism, or to have delayed TSH elevations.⁷ Whether these cases represent transient or permanent cases is unknown. However, some will have thyroid dysgenesis (ectopia, aplasia, or hypoplasia) on thyroid scanning, while others ap-

pear to have increased uptake and a large gland, suggestive of dyshormonogenesis, similar to disorders detected by the first screening.⁷ Some may represent acquired primary hypothyroidism secondary to iodine overload or other causes. Primary TSH screening programs and programs that do not routinely test a second specimen do not experience or report a higher number of missed cases compared with programs that do test a second specimen. This fact suggests that either these infants have transient disease or the disease is undiagnosed until an age when they appear to have acquired hypothyroidism.

Accurate screening results depend on good-quality blood spots. The recall of an infant for testing because of an unsatisfactory filter paper specimen causes needless delay in diagnosis and treatment of a newborn with hypothyroidism. 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 one side only. Filter paper spots should not be handled, placed on wet surfaces, or contaminated by coffee, milk, or other substances. All of the foregoing have the potential to invalidate the results regardless of the method used. Although the 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 the erroneous reporting of the results.

Mothers who have undergone treatment for thyroid disorders, who have a history of autoimmune thyroid abnormalities, or who have a history of a previous child with goitrous or nongoitrous CH should be identified during pregnancy to expedite the testing of the offspring. In this setting, cord serum can be collected and rapidly tested for thyroid abnormalities.

TEST RESULTS

Transmission of Results and Follow-up Testing

The responsibility for transmission of screening test results back to the physician or hospital identified on the screening filter paper card should rest with the authority or agency that performed the test. It is recommended that the screening test results be entered into the patient's record. Based on applicable state law, when an abnormal screening result is found, the responsible physician should be notified immediately so that he or she can arrange for follow-up testing. If the 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.

Normal T₄ Values

The normal range of T₄ values and the T₄ percentile cutoff level for TSH testing usually are established by individual screening programs. Most pro-

grams have chosen to use a 10th percentile cutoff for TSH assay, and most programs do not report low T₄, normal TSH results. As described previously, screening programs in which routine second specimens are obtained (when the infant is 2 to 6 weeks of age) have indicated that approximately 10% of hypothyroid infants will have screening T₄ values in the normal range, either with an elevated TSH concentration or with an initially low TSH value and delayed TSH increment; these infants will be missed on the initial screening test.⁷ It remains controversial whether low T₄, normal TSH results should be reported. It is clear, however, that infants with CH can be missed in newborn screening programs. Subsequent testing should be done on serum during infancy whenever there is a clinical suspicion of hypothyroidism or familial dyshormonogenesis.

Low T₄ and Elevated TSH Values

Any infant with a low T₄ level and TSH concentration greater than 40 mU/L is considered to have primary hypothyroidism until proved otherwise.* Such infants should be examined immediately and have confirmatory serum tests done to verify the diagnosis. Treatment with replacement *l*-thyroxine should be initiated before the results of the confirmatory tests are available. (Clinical management of infants with hypothyroidism is described in the following section.) In cases in which the screening TSH concentration is only slightly elevated, above 20 mU/L but less than 40 mU/L, another filter paper specimen should be obtained for a subsequent screening test.

A small number of infants with abnormal screening values will have transient hypothyroidism as demonstrated by normal T₄ and TSH concentrations on the confirmatory (follow-up to screening) laboratory tests. Transient hypothyroidism frequently results from intrauterine exposure to antithyroid drugs (including iodine), maternal antithyroid antibodies, or endemic iodine deficiency. Cases also have been reported with prenatal or postnatal exposure to excess iodides (povidone iodine, iodinated contrast materials). The practice of using liberal quantities of iodine-containing solutions as disinfectants in newborn nurseries should be balanced against the potential for producing transient hypothyroidism. Transient hypothyroidism appears to be rare in North America (estimated at 1:50 000); most cases appear to be the result of transplacental passage of thyrotropin receptor-blocking antibodies. Transient hypothyroidism occurs more commonly in Europe (1/200 to 1/8000), most likely associated with postnatal iodine exposure in infants born in Europe's areas of low iodine environment. Idiopathic transient hypothyroidism in cases associated with postnatal iodine exposure is 30 times more common among premature neonates. Other features that suggest a transient condition are relatively modest elevation of TSH levels

*All TSH [and T₄] levels here are reported for serum. Some laboratories report screening results per unit of blood, a value that is approximately half the level in serum. We recommend that all laboratories report results per unit of serum.

(20 to 60 mU/L), male sex, and a eutopic gland on radioisotope scanning.

Because transient hypothyroidism will not be recognized in some infants, initial treatment will be similar to that in any infant with permanent CH. For this reason, it is important to determine at some later time whether or not the hypothyroidism is permanent and whether the infant in fact requires lifelong treatment (see section on "Assessment of Permanence of Hypothyroidism"). The one recognized exception to this is the newborn with transient hypothyroidism whose mother is receiving an antithyroid drug. In virtually all such cases, the T_4 and TSH values return to normal within 1 to 3 weeks after birth without treatment.

Low T_4 and Normal TSH Values

Infants with low T_4 (approximately 2 SD below the mean for the normal range, usually below 10 $\mu\text{g}/\text{dL}$) but normal TSH values seldom have thyroid insufficiency. The low T_4 , normal TSH profile, seen in 3% to 5% of neonates, is often the result of a benign state of hypothalamic immaturity (particularly in premature infants who represent 5% of all newborns). Low T_4 but normal TSH results are also associated with protein-binding disturbances such as TBG deficiency (1/5000) and hypothalamic-pituitary hypothyroidism (1/25 000 to 1/50 000 newborns),⁸ or with primary hypothyroidism in an infant with delayed TSH elevation (1/100 000 newborns). Newborns who are premature or ill are found with disproportionate frequency among those with this set of laboratory values. In programs that report low T_4 , normal TSH results, there is no clear consensus with respect to follow-up. Such programs have elected (1) to take no further action, (2) to follow up with serial filter paper screening tests until the T_4 level becomes normal, or (3) to request a second blood sample for measurement of T_4 and TSH concentrations, along with some assessment of TBG levels, such as a T_3 resin uptake, free T_4 , or TBG itself.

As the vast majority of infants in the low T_4 , normal TSH category have normal findings, 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 rise against the psychological impact on the family and the financial impact on the screening program. In the final analysis the responsibility for deciding which course of action to follow rests with the judgment of the attending physician. Treatment of these infants (with the exception of those with hypopituitary-hypothyroidism or delayed TSH rise) with *l*-thyroxine is seldom justified and may do more harm than good.⁹

Low T_4 and Delayed TSH Increase

There is now ample evidence that infants with CH can be born with low T_4 concentrations and normal-range TSH values (1/100 000 newborns). Serum TSH values in these infants increase during the first few weeks of life to levels characteristic of primary hypothyroidism. It is unclear whether infants with this delayed TSH elevation have an abnormality of pituitary-thyroid feedback regulation, or whether some may have an early acquired form of hypothyroidism.

It is important, therefore, that screening be repeated in infants with overtly low T_4 concentrations, eg, those less than 3 $\mu\text{g}/\text{dL}$ (39 nmol/L) or in any infant with suggestive signs of hypothyroidism.

As indicated earlier, the possibility that infants with low T_4 and a delay in elevation of TSH values, in addition to those with normal T_4 concentrations and elevated TSH values, might be missed on initial screening has prompted some programs to institute a routine second screening test at 2 to 6 weeks of age.⁷ Despite significant detection rates (approximately 1/30 000) with routine collection of a second specimen at 2 to 6 weeks, most programs have not established a routine second screening because of (1) the increased cost of such screening, (2) a relatively low yield of cases, (3) diversion and dilution of key personnel, (4) inability to implement new programs, and (5) uncertain prognosis of this cohort.

CLINICAL MANAGEMENT OF NEWBORNS WITH LOW T_4 AND ELEVATED TSH VALUES

Infants with low T_4 and elevated TSH concentrations have CH until proved otherwise. Management should include the following:

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 (drugs and medications) should be obtained, and physical examination performed.

3. Serum for confirmatory measurements of TSH and T_4 concentrations should be obtained. Care must be taken to compare the serum results to normal thyroid hormone concentration for age.¹⁰ In cases in which an abnormality of TBG is suspected, some assessment of protein binding, eg, a T_3 resin uptake, or a free T_4 determination should be carried out. When there is a history of maternal autoimmune thyroid disorders, measurement of antithyroid antibodies—preferably some measure of thyrotropin receptor-blocking antibodies such as thyrotropin-binding inhibitor immunoglobulin in the infant and/or mother—may help identify a transient form of neonatal hypothyroidism.¹¹

4. Optional diagnostic studies would include a ¹²³I-radioiodine or sodium pertechnetate TC99m uptake and/or scan to identify functional thyroid tissue. While ¹²³I tends to give a more accurate uptake and scan picture, it may not be readily available in all hospitals; TC99m is generally more readily available and a much less expensive radioisotope.

There is some controversy regarding the risk-benefit ratio of early thyroid scanning of infants with suspected hypothyroidism. For those physicians who opt for imaging, the benefits can be summarized as follows: (a) If an ectopic gland is demonstrated, a permanent form of thyroid disease and hypothyroidism has been established. (b) The absence of thyroid gland uptake is most often associated with thyroid aplasia or hypoplasia. In this setting, an ultrasound

examination of the thyroid gland can be carried out. If this confirms the absence of any thyroid tissue, thyroid aplasia and permanent hypothyroidism have been established.¹² In the situation in which uptake is absent but ultrasound examination reveals a normal gland, either a TSH receptor or iodine transport defect, or maternal transfer of thyrotropin receptor-blocking antibodies may be present. Measurement of thyrotropin-binding inhibitor immunoglobulin in infants and/or mothers will identify the latter disorder. (c) Normal scan findings (or a goiter) indicate a functioning thyroid gland (at least with regard to iodine uptake) and alert the physician to the possibility of a hereditary defect in thyroxine synthesis. Measurement of serum thyroglobulin will help to separate out the thyroglobulin synthetic defects from the peroxidase or deiodinase defects.¹³ Exposure to an exogenous goitrogen other than iodine, such as anti-thyroid drugs, will produce a similar picture. Finally, some infants exposed to maternal thyrotropin receptor-blocking antibodies may have a normal scan if their hypothyroidism is partially compensated. The identification of a genetically mediated thyroid synthetic enzyme defect is especially important to those families planning additional children. In such cases the scan enables the physician to arrange for genetic counseling. (d) 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 years of age, when it is safe to discontinue treatment temporarily under the conditions described in the section on "Assessment of Permanence of Hypothyroidism."

If a scan with ¹²³I is not performed within the first week after starting treatment, exogenous thyroxine medication will inhibit TSH and interfere with the uptake of any radionuclide scanning agent. However, treatment should never be delayed to obtain a satisfactory scan. If need be, the scan can be postponed until after the child is 3 years of age when treatment can be briefly interrupted without danger to the developing central nervous system.

Despite the arguments in favor of thyroid scanning or imaging, there remains the possibility of a slight, but undefinable, risk of radiation exposure, particularly if ¹³¹I and 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. The preferable isotope for optimal scanning is ¹²³I; when this radioisotope is not available, TC99m is a reasonable, less expensive alternative.

5. In addition to the other recommendations, ancillary studies such as bone maturation by standard means or by bone surface measurements may be of prognostic value.

6. Education of parents by trained personnel using booklets or visual aids is highly desirable. Education should focus on the following: (a) the etiology of congenital hypothyroidism; (b) the lack of correlation of parental life-style during pregnancy with causes of the disease; (c) the impact of early diagnosis in preventing mental retardation; (d) the appropriate man-

ner in which thyroxine is administered; and (e) the importance of periodic follow-up care.

TREATMENT

Administration of *l*-thyroxine is the treatment of choice. While T₃ is the more biologically active thyroid hormone, the majority of brain T₃ is derived from local monodeiodination of T₄. The average dose of *l*-thyroxine at the start of treatment is 10 to 15 µg/kg of weight.¹⁴ Infants with very low (<5 µg/dL) or undetectable serum T₄ concentrations should begin to receive 50 µg daily. Only thyroxine tablets should be used; currently there are no Food and Drug Administration-approved liquid formulations. Thyroxine suspensions that may be prepared by individual pharmacists may lead to unreliable dosage. Thyroxine tablets can be crushed daily, mixed with a few milliliters of water, breast milk, or formula, and fed to the infant. The *l*-thyroxine dose will need to be adjusted according to the infant's clinical response and determinations of serum T₄ and TSH concentrations. The serum T₄ concentration (corrected for variation in TBG levels) should be maintained at all times in the upper half of the normal range during the first 3 years of life.¹⁵ There is clear evidence that those infants with low serum T₄ levels (below 10 µg/dL [129 nmol/L]) during the first year of life, particularly if those levels are accompanied by a TSH concentration greater than 15 mU/L, have lower IQ values than patients whose T₄ levels were held constant at higher concentrations.^{16,17} In most cases, the dose of *l*-thyroxine will need to be increased gradually as the patient grows through infancy and childhood.

FOLLOW-UP

Routine clinical examination, including assessment of growth and development, should be performed at regular intervals, approximately every few months during the first 3 years of life. Infants with congenital hypothyroidism appear to be at increased risk for other congenital anomalies, which occur in approximately 10% of these infants as compared to 3% in the general population. Cardiovascular anomalies are the most common association; these include pulmonary stenosis, atrial septal defect, and ventricular septal defect.

Infants will need to undergo more frequent laboratory evaluations of thyroid function (as compared to clinical evaluation) to ensure optimal thyroxine dosage. Serum T₄ and TSH measurements should be carried out:

1. At 2 and 4 weeks after the initiation of *l*-thyroxine treatment
2. Every 1 to 2 months during the first year of life
3. Every 2 to 3 months between 1 and 3 years of age
4. Every 3 to 12 months thereafter until growth is completed
5. At more frequent intervals when compliance is questioned or abnormal values are obtained

The T₄ and TSH measurements and physical examination, if indicated, should be performed 2 weeks after any change in *l*-thyroxine dosage.

Those screening procedures that are not designed to measure high levels of T₄ or low levels of TSH on

filter paper blood specimens should not be used to monitor serum T₄ or TSH concentrations.

The aim of therapy is to ensure normal growth and development and to maintain the serum total T₄ or free T₄ concentration in the upper half of the normal range (10 to 16 µg/dL [130 to 206 nmol/L] for total T₄; free T₄ depends on the method, but approximates 1.4 to 2.3 ng/dL [18 to 30 pmol/L]) in the first year of life, with a serum TSH suppressed into the normal range (usually below 10 mU/L). Some infants will have serum TSH concentrations in the 10 to 20 mU/L range, despite T₄ levels in the upper half of the normal range. The elevated TSH relative to the T₄ concentration appears to be the result of in utero hypothyroidism producing a resetting of the pituitary-thyroid feedback threshold. A failure of the serum T₄ concentration to increase into the upper half of the normal range by 2 weeks and/or the TSH concentration to decrease to less than 20 mU/L within 4 weeks after initiation of *l*-thyroxine administration should serve to alert the physician that the child may not be receiving adequate *l*-thyroxine regularly. At this point, careful inquiry should be made regarding compliance, dose of medication, and method of administration. When attempting to achieve the optimal level of circulating T₄, physicians should always bear in mind the danger of excessive medication and thus be prepared to monitor blood levels of T₄ at close intervals. Overtreatment for long periods of time has been associated with premature craniosynostosis and may adversely affect the tempo of brain maturation.

ASSESSMENT OF PERMANENCE OF HYPOTHYROIDISM

Permanent hypothyroidism can be assumed if the thyroid uptake and/or scan reveals an ectopic gland or absent thyroid tissue (confirmed by an ultrasound examination) or if the serum TSH is seen to increase above 20 mU/L after the first year of life, presumably because of insufficient T₄ replacement.

When permanence of thyroid disease is not established, *l*-thyroxine administration should be discontinued for 30 days, at some point after the child is 3 years of age. At that time, serum should be obtained for measurement of T₄ and TSH levels. If the T₄ is low and the TSH level is elevated, permanent hypothyroidism is confirmed and therapy is reinstated. If the T₄ and TSH concentrations remain in the normal range, euthyroidism is assumed and a diagnosis of transient hypothyroidism recorded. In this instance, however, the physician should monitor the child carefully and repeat the thyroid function test at the slightest suspicion of relapse. If the results are inconclusive, careful follow-up and subsequent testing will be necessary.

Since some more severely affected children may become clinically hypothyroid when treatment is discontinued for 30 days, one option where suspicion of permanence is high is to reduce replacement dosage by half. If after 30 days the level of serum TSH is elevated above 20 mU/L, the permanence of hypothyroidism is confirmed and full replacement therapy is resumed. However, if the serum TSH level has

not risen, then treatment is discontinued for another 30 days with repeated serum T₄ and TSH determination as described previously.

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 have had normal T₄ and TSH screening results. Hypothyroidism can become manifest or acquired after the screening tests have been carried out, or, rarely, the test results can be in error, or human error can result in failure to notify the infant's physician of abnormal test results.¹⁸ When clinical symptoms and signs suggest hypothyroidism, regardless of newborn screening results, serum T₄ and TSH determinations should be carried out.

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