

THYROID TODAY

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SCREENING FOR CONGENITAL HYPOTHYROIDISM

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To establish a neonatal screening program for any disease, one must be able to answer at least three specific questions: (1) What are the consequences of the disease in the undiagnosed infant? (2) Is the disease treatable? (3) Is the screening procedure adequate and cost-effective in the detection of cases?

With respect to congenital hypothyroidism, the answer to the first two questions are apparent. Both prenatal and postnatal periods are critical for brain development. Pickering and Fisher¹ have shown that approximately half of the postnatal brain growth is completed by age 6 months. Since thyroid hormones are known to play an essential role in the development and growth of the brain,² it is clear that institution of early treatment is necessary to prevent the neurological and mental deficiencies that result from thyroid hormone deprivation in early life.³ Recent evidence by Klein et al⁴ confirms this expectation. These investigators showed that when hypothyroidism was detected before 3 months of age and treatment was instituted properly, the IQ was invariably above 85 when measured later. With the longer delay in treatment, 85% of the infants exhibited definite evidence of mental deficiency. Desiccated thyroid, which has been available for more than 80 years, as well as the more recent synthetic hormone preparations, were used in treatment.

We shall now address ourselves to the third question, namely, the adequacy of laboratory screening procedures for the detection of neonatal hypothyroidism. The clinical

difficulties in making the diagnosis of hypothyroidism at birth have been emphasized (see *Thyroid Today*, Vol. 1, No. 8, Hypothyroidism in Childhood, by Delbert Fisher). The laboratory tests used in screening procedures take advantage of several important physiological principles.⁵ The fetal hypothalamic-pituitary axis functions in an autonomous fashion and is relatively independent of maternal influence. There is no substantial transplacental transfer of triiodothyronine (T_3), thyroxine (T_4), or thyrotropin (TSH). The physiological TSH surge in the neonate shortly after birth is responsible for a dramatic increase in T_4 concentration in the first 24 to 36 hours of life. Since T_4 levels do not increase in infants with primary hypothyroidism, the level of T_4 can be used as an extremely sensitive discriminant for the detection of hypothyroidism in the neonate.

In 1972, Laberge and I⁶ developed a simple radioimmunoassay procedure to measure the T_4 concentration in the eluate of blood spots on filter papers used for phenylketonuria screening. After the successful completion of a pilot study, a program was instituted under the auspices of the Quebec Screening Network for Metabolic Diseases⁷ that has succeeded in screening every infant born in the Province of Quebec since April 1974. Soon thereafter, other regional programs were set up in Oregon and New England.^{8,9} At the same time, other groups used blood serum determinations of TSH level as the screening discriminant.^{10,11} Finally, in 1975, both our group and the New England group^{12, 13} were able to

measure TSH concentration in the same blood spot used for assay of T_4 level and thus provided a confirmatory step in the prompt diagnosis of hypothyroidism. Screening procedures using TSH level have also been set up in certain areas of Europe, and others are being started elsewhere. In North America, more than 1 million infants have now been screened, using T_4 concentration as a primary measurement backed up by TSH level determinations on spots yielding low T_4 concentrations. Since the incidence of hypothyroidism and other abnormalities in the various programs appears roughly comparable, we shall use our own data as a reflection of the North American experience to date.

Table 1 summarizes these results according to the various diagnostic entities uncovered. Thyroid scans were performed in a number of the infants. Seventy-five percent of infants showed no thyroid tissue and were classified as having thyroid agenesis or hypoplastic glands. In the remaining 25%, thyroid tissue was clearly visible in the thyroglossal tract, and the neonates were accordingly classified as having thyroid dysgenesis or ectopic glands. Infants with residual thyroid tissue and an elevated TSH generally presented a T_4 concentration in the 3 to 7 $\mu\text{g}/\text{dl}$ range, and in most instances also showed an elevated T_3 level that was presumably due to preferential thyroidal secretion. True congenital hypothyroidism and a congenital disease in thyroxine-binding globulin (hypo-TBG-emia) have been found to occur in one in 5,000 and one in 9,000 infants, respectively.

To decrease the time lapse between diagnosis and treatment, we have devised the following follow-up procedure,¹⁴ illustrated in Fig. 1. If the T_4 concentration is low (less than 2.1 SD below the geometric mean of the day) a serum TSH level determination is performed on the filter paper eluate. (1) If the filter paper spot TSH level is elevated, the infant is immediately referred to a treatment center. If the diagnosis is subsequently confirmed by serum measurements, therapy is begun immediately. Thus, all infants with hypothyroidism receive treatment within one month after birth. (2) If the TSH concentration is normal, the TBG capacity is determined by measurement performed on an eluate of a spot from the same sample. The binding capacity of the eluate is evaluated indirectly by measuring the uptake of radioactive T_4 by charcoal. This assessment of the TBG concentration is subsequently confirmed in serum by radioimmunoassay. If the

TBG level is low, the infant is then classified as having hypo-TBG-emia. (3) If the T_4 level is low with normal TSH and TBG concentrations, another filter paper spot is obtained from the infant and measurement of the T_4 level is repeated. If the T_4 level is now normal, the infant is reclassified as normal. If the T_4 concentration is still low, the patient is referred to a diagnostic center to rule out the possibility of hypothalamic-pituitary disease. To date, most of the infants with this constellation of findings have turned out to suffer from prematurity.

As indicated above, the hallmarks of primary hypothyroidism are a low T_4 concentration and an elevated spot TSH level. When these measurements are repeated on a recall spot sample, the T_4 level is generally even further decreased. In contrast, infants with hypo-TBG-emia will have the same low filter paper T_4 levels and the same normal TSH values in the subsequent repeated spot tests. Similarly, infants with pituitary or hypothalamic hypothyroidism or low birth weight will show stable low T_4 and TSH determinations on the repeated spot tests.

Table 1 shows that, as in the adult, measurement of serum T_3 concentration is of very limited practical value in the diagnosis of hypothyroidism. Determination of the TBG concentration, however, helps to segregate the group of patients with low T_4 concentrations and normal TSH values into those who have a decrease in circulating binding proteins and those who may have a pituitary or hypothalamic basis for their abnormalities. In the latter group, injection of thyrotropin-releasing hormone (TRH) (see *Thyroid Today*, Vol. 2, No. 2, Thyrotropin Releasing Hormone—Physiology and Clinical Use, by Robert Utiger) has always evoked a normal TSH response. The basis for the low T_4 values in these patients therefore appears to be a reflection of a hypothalamic abnormality or an alteration in the set point of the TSH feedback system. All such patients had normal birth weights and T_4 levels less than 3 $\mu\text{g}/\text{dl}$, compared to infants with a low birth weight in whom the T_4 level was borderline low and the TSH concentration normal. We have also detected cases of transient hypothyroidism secondary to maternal drug ingestion, primarily ingestion of antithyroid drugs. In addition, two infants with goiter secondary to an organification defect of iodine were uncovered.

Of those infants diagnosed as hypothyroid, less than 5% were suspected clinically. Three weeks after the laboratory

Table 1
Types of Thyroid Diseases Detected
by Quebec Screening Programs for Congenital Hypothyroidism

Diagnosis	T_4 (Spot) (ng/40 λ Blood) (Normal, >0.8)		TSH (Spot) (μU) (Normal, <1)	T_4 (Serum) ($\mu\text{g}/\text{dl}$) (Normal, 6-16)	TSH (Serum) ($\mu\text{U}/\text{ml}$) (Normal, 0-10)	T_3 (Serum) (ng/dl) (Normal, 70-220)	TBG (Serum) (mg/dl) (Normal, 2-5)
	First Sample	Second Sample					
Primary							
Hypoplastic (N=71)	0.493 \pm 0.023	0.23 \pm 0.03	8.97 \pm 0.98	1.62 \pm 0.21	605.77 \pm 50	60.97 \pm 9.4	4.26 \pm 0.16
Ectopic (N=7)	0.667 \pm 0.049	0.29 \pm 0.14	5.5 \pm 0.7	4.4 \pm 0.83	268 \pm 79	269.2 \pm 82.4	...
Hypothalamic (N=8)	0.5 \pm 0.09	0.46 \pm 0.14	0.52 \pm 0.21	3.5 \pm 0.64	9.14 \pm 1.39	133.29 \pm 32.4	3.24 \pm 0.46
Hypo-TBG-emia (N=38)	0.43 \pm 0.03	0.45 \pm 0.03	0.31 \pm 0.05	3.07 \pm 0.24	7.06 \pm 0.89	66.25 \pm 5.2	0.73 \pm 0.09

diagnosis was made, a group of hypothyroid infants was reexamined in an effort to determine the presence of any significant physical signs that might provide an early clue to the clinical diagnosis of hypothyroidism. A number of signs and symptoms were uncovered that may be of potential usefulness, especially in areas where there are now no screening procedures in operation. Table 2 lists these signs and symptoms and provides a score for each as an index of its relative importance in distinguishing hypothyroidism from a normal population of infants of the same age. In increasing importance are the following: feeding problems, dry skin, hypotonia, an open posterior fontanel, constipation (one stool or less per day), an enlarged tongue, inactivity, skin mottling, edematous facies, and an umbilical hernia larger than 0.5 cm. The sum of these factors add to the total of 20. There was an excellent inverse correlation between the T_4 and T_3 concentrations and the hypothyroid index. Thus, infants with very low hormonal concentrations had the highest indexes. In the absence of available screening programs, such an index can serve as the equivalent of the "Apgar score" in nurseries. Infants with an index greater than 4 should be suspected of having congenital hypothyroidism, a diagnosis that can easily be verified or eliminated by mea-



Figure 2 Congenital hypothyroid infants at age 3 weeks. Infant A has an index of 4 and very few stigmata of the disease. Infant B has an index of 14 and many clinical features of the disease.

Table 2
Hypothyroid Index

Signs and Symptoms	Score
Feeding problems	1
Dry skin	1
Hypotonia	1
Fontanel	1
Constipation	1
Tongue	3
Inactivity	3
Skin Mottling	3
Facies	3
Hernia	3
Total	20

surement of T_4 and TSH levels. For example, Fig. 2 shows the spectrum of clinical features of the disease, with infant A presenting very few clinical signs and symptoms of hypothyroidism and infant B all the clinical stigmata expected with no circulating thyroid hormone. Infant A had an index of 4, compared to 14 for infant B.

In this series, all infants were initially treated in the same manner. For the first two weeks, $15\mu\text{g}$ of liothyronine sodium and $25\mu\text{g}$ of levothyroxine sodium were administered. Thereafter, $0.5\mu\text{g}$ of levothyroxine sodium was given. Subsequently, the dose was adjusted in light of the clinical response and the serum T_4 concentration. Since in some infants serum TSH concentration is not readily suppressed by thyroid hormones, this index cannot be readily used to assess the daily dose of levothyroxine. To date, all of our treated patients exhibit normal growth and physical development. In 1976, twenty hypothyroid infants born in the Province of Quebec were evaluated psychologically by the Griffith Mental Development Scale and compared to a nor-

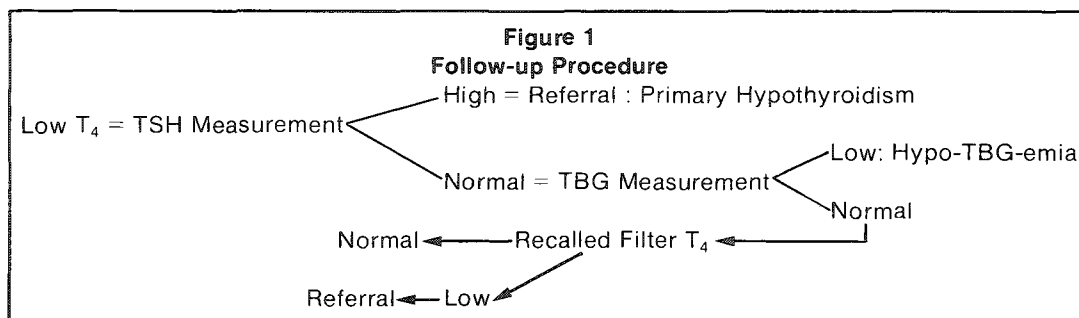


Figure 1 Flow chart of our biochemical follow-up procedure using filter paper spot measurement of T_4 level backed up by measurements of TSH and TBG levels from the same samples.

mal comparable population (Table 3). Test scores were almost identical in the two groups. Although the preliminary results are most encouraging, further studies must be done before any conclusions can be drawn with regard to the final outcome in the treated group. The test will again be administered at ages 3 and 6, together with a complete neurological examination.

We believe that a detection program for neonatal hypothyroidism can be effectively integrated into an ongoing, established screening program for other metabolic diseases. The advantage of such integration is that existing facilities such as a computer system can be readily adapted to monitor the results of day-to-day laboratory determinations and to select automatically those specimens requiring determination of TSH levels. Such a program should effectively reduce the number of patients requiring recall and thus reduce needless anxiety in the families of such patients. Its cost is small when integrated into a regional program. In Quebec, it has been estimated to be 0.65 cents per infant, a value that should be contrasted with the estimated \$8,000 per year for the lifetime institutionalization of a mentally retarded patient. This figure does not encompass the hospitalization and

Table 3
Psychological Development at Age 12 Months
(Griffith Test Scores)*

	Hypothyroid Infants (N=20)	Normal Infants (N=23)
Mean	112	114
SEM	12	8.3

*These infants' IQs were not statistically different.

investigational cost for undetected cases. In Quebec, we have estimated that at least 20% of the hypothyroid infants were institutionalized before the implementation of the screening program. Not all infants required hospitalization; some were treated at about 3 months of age and others died of other malformations. On the basis of the conservative approximation of the incidence of institutionalization and taking into account the cost of medical services and special schooling required for children with borderline IQs (i.e., 65 to 80), we estimate that the cost-benefit ratio for screening vs non-screening is 3:1 over a period of five years. This ratio, of course, is increasing with time since the total of institutionalized patients is increasing every year. It should be emphasized that the screening program in Quebec was set up under the auspices of a nationalized health service and that appropriate modifications in the system will be required to satisfy the requirements of the specific medical care delivery system in the region to be screened.

An important future challenge to screening programs will be a reduction of the current 1% recall rate, which is prompted largely by low T₄ concentrations in low-birth-weight infants. This problem is now under intensive investigation. Although there has been considerable discussion about the relative advantages of the measurement of T₄ and TSH levels as a laboratory screening procedure, we believe

that the most reliable and cheapest method for screening newborns involves the primary determination of T₄ level backed up by determination of TSH level as outlined above. Admittedly, TSH levels have greater diagnostic value; nevertheless, they are technically more difficult to determine on a large scale basis, and their exclusive use would not allow detection of secondary or tertiary hypothyroidism or of hypo-TBG-emia that might subsequently be incorrectly diagnosed as hypothyroidism.

To prescribe any drug mentioned in this article, the readers should consult full prescribing information.

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