SCREENING FOR CONGENITAL HYPOTHYROIDISM IN THE NETHERLANDS

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SCREENING FOR CONGENITAL HYPOTHYROIDISM IN THE NETHERLANDS

PROEFSCHRIFT

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GERARDA DERKSEN-LUBSEN

geboren te Amsterdam

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Prof.Dr. G.A. de Jonge

Co-referenten: Prof.Dr. H. Galjaard
Prof.Dr. G. Hennemann

VOORWOORD

Dit proefschrift is een weerslag van de werkzaamheden van de zeer velen die bij de screening op congenitale hypothyreoïdie in Zuid-Holland waren betrokken. Uiteraard ben ik aan hen veel dank verschuldigd op deze wijze gebruik te mogen maken van hun werk. Enkelen wil ik in het bijzonder noemen.

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CONTENTS

ABBREVIATIONS

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CHT	congenital hypothyroidism
FTI	free thyroxine index (100 x T4/TBG test)
T3	triiodothyronine
rT3	reverse T3
T4	thyroxine
TBG	thyroxine binding globulin
TBPA	thyroxine binding prealbumin
TRH	TSH releasing hormone
TSH	thyroid stimulating hormone
P	percentile (e.g., P20 = 20th percentile)
s.d.	standard deviation
$\bar{x}$	mean

1. INTRODUCTION

Screening provides a means for "filtering disease from the population", until then unrecognized by patient or physician. In an increasing number of diseases, early detection is helpful in preventing serious consequences, by treatment or by genetic counseling on the recurrence risk of congenital disorders.
New developments in the early detection of genetic metabolic diseases and other congenital disorders, which are a frequent cause of infant morbidity and mortality, have proceeded rapidly during the last decades (see Galjaard, 1980). Neonatal screening is one of these developments and contributes to the improvement of the prognosis of several diseases in early infancy. Screening for phenylketonuria is, at present, a common procedure in many countries. Other diseases such as maple syrup urine disease, homocystinuria, histidinemia, galactosemia and congenital hypothyroidism (CHT), have been recommended as suitable for screening or have already been included in existing programs (Levy, 1973; Bickel et al., 1980).
This study deals with the institution of neonatal screening for CHT in the Netherlands. Screening for this disorder was first introduced in some North American areas in 1974 and, from then on, also in many other countries, either in the form of trial studies or nation-wide, and mostly in combination with the existing PKU programs (Newborn Committee of the European Thyroid Association, 1979; Fisher et al., 1979). In the Netherlands, PKU screening was introduced on a nation-wide scale in 1974. In the following year, the Government asked the Health Council (a governmental advisory board) for advice on the need for extension of the PKU screening program with other early detection methods for congenital disorders. To come to a decision, the Health Council took into consideration, among other things, the frequency and the severeness of the congenital disorders, and the possibilities for diagnosis and treatment at the time of neonatal screening in our country; only screening for CHT met the criteria posed (Gezondheidsraad, 1980).
In 1977, the Dutch Pediatric Association established a national committee for CHT to prepare for the practical introduction of CHT screening. It was decided that nation-wide screening should be based on the results of screening in a defined trial area. The program was started in the Rotterdam area (the southern part of the province of Zuid-Holland) in 1978. It was organized and supervised by a local committee. The nation-wide program was started in the first week of 1981.

Rationale for screening for CHT
Congenital hypothyroidism is a serious health problem for the individual patient. Hypofunction of the thyroid gland during fetal life and early infancy, as it occurs in CHT, causes damage to the central nervous system and can result in mental retardation and other neuropsychological sequelae. These determine the prognosis of the disease.

Clinical studies and examination of cases detected by neonatal screening suggest that the detection and start of treatment during the first month(s) of life improve this prognosis (Klein et al., 1972; Wolter et al., 1979; Dussault et al., 1980a).
Few CHT patients show clinical manifestations which indicate the diagnosis during the neonatal period. Signs and symptoms are seldom specific and can even be completely absent. Consequently, early detection should not depend on clinical parameters. Microradioimmunoassays for thyroid hormones and thyroid stimulating hormone have been developed. The levels of these hormones reflect the thyroid status of the child. These tests can be performed in blood samples collected on filter paper by heel puncture as in the screening for PKU.
The frequency of CHT is relatively high: a screening prevalence of about one patient per 4,000 infants screened has been found (see Ch. 2) as compared to a screening prevalence of PKU of one per 16,000.

Aims of the study
The aim of this study is the evaluation of the screening in the trial area in order to assess whether the screening procedure chosen is the optimal procedure for nation-wide institution under the present circumstances and with the presently available information on CHT. Screening should not be undertaken without considering general principles of an ethical and practical nature. The benefits derived from early detection by the individual patient should outweigh both immaterially and, - if possible - financially, the burdens for the group which is screened but proves to be healthy and for the society at large. Criteria for planning case finding programs based on the possibilities for detection and treatment, the influence of early detection on the natural history, the acceptability of screening by the population, the costs and the health care facilities were formulated by the World Health Organization in the ten, well-known principles of Wilson and Jungner (1968). Founded on these principles, McKeown (1968) constructed a scheme for evaluation of screening programs wich will be used as a guide-line for this study:
- the definition of the problem: what condition is sought, what therapy is to be offered, which group is screened, at what stage and by what tests?
- review of the position before screening: evidence concerning prevalence, natural history, medical significance and effectiveness of previous methods of detection and treatment;
- review of evidence concerning the screening procedure: evidence concerning the diagnostic method and treatment proposed;
- conclusions concerning the state of evidence on the problem as a whole: the evidence concerning the effects of the screening and treatment, and comparisons with alternative approaches;
- proposals for acquisitions of further evidence;
- proposals for initial applications.

This study will be mainly confined to the screening procedure as such. The trial period is too short to be able to assess the long

term effects of screening and early treatment. For the present, experience acquired elswhere will have to provide this information.

A second objective of this study is to assess whether early clinical manifestations could contribute to early diagnosis of CHT. Although the clinical manifestations are not specific for CHT, the frequency of certain signs and symptoms or a specific combination of particular clinical findings may distinguish CHT patients from healthy individuals, even in a so called asymptomatic or subclinical stage of the disease. For this purpose, the clinical manifestations in patients with CHT were compared with those in a healthy control group.

Outline of the study
Literature pertaining to CHT and screening for CHT will be given in Chapter 2 and 3.
The design of the program in the trial area and the laboratory methods used are the subject of Chapter 4.
In the next chapters, the results of the screening tests and follow-up (Ch. 5), the comparison with methods for early detection other than used in the trial area (Ch. 6), data on cases of CHT detected (Ch. 7) and the early clinical manifestations in known cases with permanent primary CHT (Ch. 8) are described. Conclusions on the screening procedure have been formulated in a final chapter.

2. CONGENITAL HYPOTHYROIDISM

Literature data on prenatal and early postnatal thyroid function as well as literature data on the impact of thyroid deficiency as it occurs in congenital hypothyroidism (CHT) will be discussed in this chapter. The data will be focused only on those aspects of thyroid function and thyroid hypofunction which seem to be important in the context of neonatal screening.
CHT has been chosen as a collective term for a group of disorders which is either genetic or prenatally acquired or postnatally acquired and already present in the neonatal period. Although the latter is not congenital, the abbreviation CHT has been used in such cases as well.

2.1 *Thyroid function*

2.1.1 *Fetal thyroid function and fetal maternal relationship*

The first anlage of the thyroid is visible from the third week of gestation. The thyroid gland, of endodermal origin, grows down from the tongue base and reaches its final position in the seventh week of gestation. Formation of follicles and hormone production is demonstrated to begin between the eighth and twelfth week. The regulation system of the thyroid function, the hypothalamic-pituitary-thyroid axis, develops from the twelfth week and undergoes a rapid maturation at mid-gestation (Fisher et al., 1970; Greenberg et al., 1970; Fisher, 1976). The fetus has to depend mainly on its own thyroid function. The thyroid hormones - thyroxine (T4) and 3,3',5-triiodothyronine (T3) - can pass the placental barrier (Grumbach and Werner, 1956; Myant, 1958; Fisher et al., 1964; Raiti et al., 1967); however, the amounts of maternal hormones are insufficient for the fetal needs (see also review by Goslings, 1975). Neither fetal hypothalamic-pituitary hypofunction can be substituted for by maternal thyrotropin releasing hormone (TRH) or thyroid stimulating hormone (TSH). Although passage of TRH through the placenta has been shown in rats (D'Angelo et al., 1971), the serum levels are not likely to be sufficient for fetal pituitary stimulation. The placenta acts as barrier for TSH (Refetoff et al., 1974).

2.1.2 *Thyroid hormones and regulation of thyroid function*

The thyroid function is regulated by a feedback system between the hypothalamus and pituitary gland and the thyroid gland. TRH, produced in the hypothalamus reaches the pituitary gland through the portal vascular system and stimulates the production and the release of TSH by the pituitary gland. TSH action is required for sufficient

iodine uptake in the thyroid and for the synthesis and the secretion of thyroid hormones; in addition, TSH stimulates the cell multiplication in the thyroid gland. An increase in circulating thyroid hormones results in a decrease in the TRH-mediated TSH release, while a decrease in thyroid hormone levels has the opposite effect. Normal thyroid hormone production depends also on sufficient dietary iodine intake. Iodine is trapped as an anion (iodide) in the thyroid and after oxidation by peroxidase, incorporated into the tyrosine residues of thyroglobulin. Coupling of monoiodotyrosine residues and diiodotyrosine residues results in the formation of T4 and T3. The thyroglobulin-linked T4 and T3 is stored in the thyroid colloid. Absorption into the follical cell and hydrolysis of thyroglobulin results in secretion of T4 and T3 into the circulation, in a molar secretion ratio of 85 : 9 (Westgren et al., 1977).
Circulating T3 has the highest biological activity of the two thyroid hormones. T3 is mainly produced by monodeiodination of T4 (Surks et al., 1973) in peripheral tissues.
Both T4 and T3 circulate bound to several transport proteins. The biologically active free parts approximate 0.03% of the total T4 concentration and 0.3% of the total T3 concentration. The bound parts which are biologically inactive are mainly bound to thyroxine binding globulin (TBG) and in a smaller portion to thyroxine binding prealbumin (TBPA) and albumin (Nicoloff, 1978).
Further metabolism follows different pathways. After the release of T3 and T4, thyroglobulin as well as iodine which is liberated by dehalogenase activity from the tyrosine residues left, are mainly reutilized. Metabolism of T4 and T3 occurs primarily by deiodination. Deiodination of T4 yields T3 and 3,3',5'-triiodothyronine (reverse T3, rT3); the latter is biologically inactive. Further deiodination follows. Other pathways of metabolism are excretion of conjugated thyroid hormone in bile and stool or direct deamination and decarboxylation.

2.1.3 *Thyroid hormone action*

Thyroid hormones influence many processes of metabolism. Effects have been demonstrated on growth and development of the central nervous system, on oxygen consumption, heat production, nerve function and cardiac output as well as on metabolism by activation of many enzyme systems. The action at the cellular level is beyond the scope of this study.
Deficiency of thyroid hormones can lead to serious consequences, especially if such a lack occurs in fetal or early postnatal life. The effects of hypothyroidism on growth become evident only after birth, if treatment is delayed. Prenatal growth is not dependent on the fetal thyroid function, which is indicated by the relatively high-normal birth weight and birth length for gestational age (Mäenpää, 1972).
Hypothyroidism results in a retardation of the skeletal maturation. If retarded at birth, it indicates a prenatal onset of hypothyroidism.

The most serious consequence of hypothyroidism during the fetal or early postnatal period is the damage to the central nervous system which is the cause of mental retardation and other neurological manifestations. The rapid growth and maturation of the central nervous system in the fetus and neonatal infant explain the vulnerability of the neural development. In the human brain, neuronal multiplication has been demonstrated from the 10th to 18th week of gestation. Brain growth as measured by an increase in DNA content (deoxyribonucleic acid) starts prenatally and continues in the second postnatal year, while myelinization continues even longer; the cerebellum has a shorter and more rapid growth period (Dobbing and Sands, 1973; Dobbing, 1975).
Although this rapid development of the central nervous system explains why insults in this period can have such serious consequences, little is known concerning the underlying damage caused by hypothyroidism in humans. The effects have been extensively studied in animal models, especially in rats. The newborn rat is in a stage of development roughly comparable to the human fetus at mid-gestation. Research has been mainly focused on the cerebellum. Thyroid deficiency results in an increased ratio of glial cells to neurons, a decrease in basket cells, a delay in dendritic arborization, synaptogenesis, development of astrocytes and biochemical development; eventual synatic organization changes qualitatively (Balazs, 1975; Brasel and Boyd, 1975). The effects on the rat forbrain are manifested as a decrease in the perikarya of the cortical neurons, a decrease in length and branching of pyramidal neurons, in density of axons and in number and distribution of dendritic spines. The effect of treatment on the development of dendritic spines appears to be dependent on the age at which therapy is started; treatment after a certain age is no longer effective (Morreale de Escobar and Escobar del Rey, 1980). Clinical sequelae such as behaviour disorders have been described, among others by Eayrs (1971).
A question is whether the changes observed in the hypothyroid animals are really due to hypothyroidism or result from undernutrition which accompanies the hypothyroidism. However, differences between these two conditions have been shown (Balázs, 1976).

2.1.4 *Neonatal thyroid function*

In screening for CHT, mostly levels of T4 and/or TSH are measured; both reflect directly the thyroid status of the infant screened. For this reason, it is important to note what changes occur physiologically during the neonatal period and to recognize the differences between full term infants and preterm infants and between small-for-dates infants and infants with a birth weight appropriate to their gestational age. These events, typical for the early neonatal period (the period in which screening and follow-up is performed) are discussed below.

Thyroxine. The total serum T4 level in cord blood is high as compared with adult levels and, during the first two days of life, a

rapid increase is even seen; a slower decline follows (Abuid et al., 1973; Erenberg et al., 1974; Cuestas, 1978) and another 20% decrease occurs during the 3rd and 4th weeks of life (Jacobsen and Hummer, 1979). The slow decrease continues during the first 15 years of life (Fisher et al., 1977).
Apart from these time dependent changes, the T4 values are correlated with gestational age and birth weight. The T4 in cord blood increases significantly with gestational age (Bernard et al., 1977). In full term but small-for-dates infants, T4 is slightly decreased as compared to the full term infant with normal weight (Bernard et at., 1977; Jacobsen et al., 1977b). The postnatal course of T4 in preterm babies is the same as described above, although the decrease is smaller and slower; after approximately six weeks of life, the differences between preterm and full term infants have disappeared (Jacobsen and Hummer, 1979; Cuestas, 1978).

Triiodothyronine. The T3 concentration in cord blood is very low, but there is a rapid and, compared to the T4 increase, relatively large increase during the first day of life (Erenberg et al., 1974; Jacobsen et al., 1977b). Lower T3 values have been found in preterm infants, though the postnatal course of T3 levels is the same as in full term infants (Jacobsen et al., 1977b; Isaac et al., 1979). After the first week of life, Jacobsen and Hummer (1979) found an increase of 50 - 70%, with a maximum at the end of the second month. The maximum level in preterm babies was found later. During the first 15 years of life, a slow decrease amounting to 30% occurs (Fisher et al., 1977).
The T4/T3 ratio also depends on gestational age and birth weight. The ratio decreases with increasing gestational age and birth weight; this means that, in full term infants with a birth weight appropriate to their gestational age, relatively more biologically active thyroid hormone is available than in small-for-dates infants or preterm infants (Jacobsen et al., 1977b).

Reverse triiodothyronine. In contrast to the relative deficiency in T3 in the neonate, the rT3 levels are high. Mean values eight times the adult level have been found in cord blood and no overlap of neonatal and adult values could be demonstrated (Burger et al., 1976; Byfield et al., 1978). Cord blood rT3 decreases with increasing gestational age (Isaac et al., 1979).

Thyroid stimulating hormone. The initial rise in T4 and T3 follows the considerable increase in TSH in the first hours immediately after birth. Sack et al. (1976) found peak values combined with a prolactin peak 30 minutes after birth; since prolactin release from the pituitary gland is stimulated by TRH, the prolactin peak could indicate that the neonatal TSH peak is due to a TRH surge.
The TSH peak is at the same height in preterm as in full term infants and is followed by a rapid decrease; after 5 days, the values are normalized (Jacobsen et al., 1977b). Oddie et al. (1978) assume a recovery of the disordered hypothalamic-pituitary-thyroid axis by oscillation of the hormone concentrations, in which T3 lags behind

T4 and T4 lags behind TSH. The capacity for T4 to T3 monodeiodination is decreased in neonates; therefore, the initial T3 rise is assumed to be derived from the TSH surge (Erenberg et al., 1974; Cavallo et al., 1980).

Thyroid hormone binding proteins. Attemps have been made to explain differences between full term and preterm T4 values by differences in TBG concentration. However, TBG is not gestational age dependent (Oddie et al., 1977), and is constant in the first eight months of life (Stubbe et al., 1978; Jacobsen and Hummer, 1979). Since both the free thyroxine index (FTI) * (Redding and Pereira, 1974) and the directly measured free T4 (Klett et al., 1979) are the same in preterm infants as in full term infants, a reduced T4 binding affinity seems more probable. The T4 decline during childhood can be largely explained by the TBG decrease during the first 15 years of life (Fisher et al., 1977).
The other binding proteins (albumin and TBPA) increase gradually during the first months of life (Jacobsen and Hummer, 1979).

2.2 *Classification of CHT*

CHT is a group of disorders with different underlying causes (Table 2.1). The two main categories, primary CHT and secondary/tertiary CHT, refer to the site of disturbance in the hypothalamic-pituitary-thyroid axis: in primary CHT, the defect is in the thyroid itself; in secondary hypothyroidism, the function of the pituitary gland is deficient, while tertiary hypothyroidism represents a hypothalamic disorder.
The relative frequencies of the different forms of primary CHT (except for transient cases and endemic cretinism) are summarized in Table 2.2.

2.2.1 *Primary CHT*

Defective organogenesis of the thyroid. Abnormalities in the thyroid anlage are the most frequent causes of the sporadic forms of hypothyroidism (see Table 2.2). Defective organogenesis results in either total aplasia of the thyroid gland or hypoplasia, in which the thyroid can be normally situated or has an ectopic position (at the tongue base or along the thyroglossal duct). In hypoplasia, a residual thyroid function can often be demonstrated.
The underlying cause of defective organogenesis is unknown. Various etiological factors have been suggested. Blizzard et al. (1960) found a positive association between circulating maternal antithyroid antibodies and the occurrence of functional athyroidism. Sutherland et al. (1960) described three siblings suffering from primary CHT whose

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* A correction of the total T4 level for the TBG concentration. The TBG level is approximated by measurement of the unbound fraction of TBG.

Table 2.1 The causes of CHT

Primary CHT

- defective organogenesis
  - aplasia (athyroidism)
  - hypoplasia, often combined with ectopia
- dyshormonogenesis
  - trapping defect
  - iodine organification defect
  - dehalogenase defect
  - coupling defect
  - plasma iodoprotein defect
  - abnormal synthesis of thyroglobulin
- peripheral resistance to thyroid hormones
- TSH nonresponsiveness
- exogenous causes
  - iodine intoxication
  - maternal treatment with antithyroid drugs
  - maternal autoimmune thyroiditis
  - iodine deficiency
- transient primary CHT of unknown origin

Secondary and tertiary CHT

- morphological malformation
- idiopathic

Table 2.2 Relative frequencies (%) of the causes of sporadic permanent primary CHT

	clinical studies			screening		
	I (n=67)	II (n=41)	III (n=43)	IV (n=127)	V (n=41)	VI (n=106)
athyroidism	31	20	51	63	46	35
hypoplasia	5	59	21	23	2	58
ectopia	36		12		41	
CHT with normal or enlarged gland	28	21	16	14	10	7

I Mäenpää (1972); II Van Gemund and Laurent de Angulo (1971); III Jacobsen and Brandt (1980); IV Fisher et al. (1979); V Connelly et al. (1980); VI Delange et al. (1980a)

mother had an autoimmune thyroiditis. Recent findings in patients by screening reveal that, if maternal antithyroid antibodies are at all a cause of athyroidism, they are in any case not frequent etiological agents. In a series of 104 patients, microsomal antibodies were found in only one (Dussault et al., 1980c).
A genetic etiological factor is implied by familial occurrence (Greig et al., 1966; Safar et al., 1977; Kaplan et al., 1978) and the positive association of athyroidism with a certain type of human leucocyte antigen (HLA) (Miyai et al., 1980).

Dyshormonogenesis. The synthesis of thyroid hormones can be interrupted almost anywhere along the production pathway. Most variants of dyshormonogenesis are familial and are supposed to have an autosomal recessive pattern of inheritance (for a detailed review, see DeGroot and Stanbury, 1975).
The dyshormogenesis can be subdivided into the following disorders: 1) *iodine accumulation defect (trapping defect)*; the accumulation of inorganic iodide into the thyroid and the salivary glands is disturbed; 2) *iodine organification defect*; the oxidation of iodide to iodine (a peroxidase activity) is diminished. The disorder can be due to a real peroxidase defect or to defective oxidation with normal peroxidase activity (e.g., the Pendred syndrome); 3) *iodotyrosine dehalogenase defect*; iodinated tyrosines leave the thyroid and deplete the store of precursors of thyroid hormones due to a defect deiodination of iodotyrosines; 4) *iodotyrosyl coupling defect*; the coupling of iodotyrosines into triiodothyronine and thyroxine is insufficient; 5) *plasma iodoprotein defect*; abnormal iodinated peptides circulate in the serum; 6) *thyroglobulin synthesis defect*; iodine incorporation, coupling and hormone release is disturbed.
It is doubtful whether the last three disorders represent actual separate disorders or belong to a group of diseases in which the thyroglobulin synthesis is defective or aberrant.

Peripheral resistance to thyroid hormones. Peripheral resistance to thyroid hormones may cause hypothyroidism (Refetoff et al., 1967) or goiter (Lamberg, 1973), despite high levels of the hormones. Euthyroidism has also been described (Mäenpää and Liewendahl, 1980).

TSH nonresponsiveness. Familial cases of hypothyroidism involving nonresponse of the thyroid to high TSH levels have been described (Stanbury et al., 1968).

Iodine intoxication. Excessive iodine load results in a block of further iodine intake into the thyroid (Wolff and Chaikoff, 1948) sometimes followed by hypothyroidism. Since iodine passes the placental barrier, maternal iodine intake influences the fetal thyroid. Potential dangerous forms of therapy are maternal intake of iodine containing expectorants (Martin and Rento, 1962; Job et al., 1974), iodine containing röntgen contrast as used in amniofetography (Rodesch et al., 1976) or radioactive iodine (Fisher et al., 1963; Green et al., 1971). The latter is especially dangerous because of the radiation hazards for the fetal thyroid. In the neonate, iodone

alcohol skin application can be followed by hypothyroidism (Chrabrolle and Rossier, 1978). In most cases, the Wolff-Chaikoff block is transient. In some cases, probably due to an abnormality in pituitary-thyroid control (Croughs and Visser, 1965), the block persists; the high TSH production which follows the decrease in thyroid hormone synthesis results in a goiter.
Individual susceptibility to iodine intoxication has also been demonstrated by others; Lejeune et al. (1979) found hypothyroidism following amniofetography in one of a pair of twins. Becroft et al. (1980) assume a higher susceptibility in preterm infants.

Maternal treatment with antithyroid drugs. Like iodine, antithyroid drugs pass the placental barrier and influence the fetal thyroid causing hypothyroidism (Elphinstone, 1953). Individual susceptibility is again of importance, as was illustrated by the occurrence of CHT due to maternal intake of antithyroid drugs in one of a pair of twins (Refetoff et al., 1974).

Maternal autoimmune thyroiditis. Blizzard et al. (1960) showed a correlation between the occurrence of functional athyroidism and the presence of antithyroid antibodies in the mother, whether or not she suffered from thyroid disease. The antithyroid antibodies pass the placental barrier and disappear from the blood of the infant during the first month of life. Matsuura et al. (1980) found a transient hypothyroidism in two siblings due to the transplacental transfer of TSH-binding inhibitor immunoglobulins. Recent data on screened infants show that the frequency of antibodies in CHT is low (Dussault et al., 1980c).

Iodine deficiency. Iodine deficiency is the primary etiological factor in endemic goiter and endemic cretinism (Lancet, 1979). Although goiter and cretinism strike only a part of the population, epidemiological studies on populations living in an iodine deficient area show that iodine deficiency has influence on the total population. In iodine deficient areas, biochemical and clinical thyroid function tests for the non-cretinous part of the population differed unfavourably from a non-iodine deficient control group (Querido and Djokomoeljanto, 1975; Querido, 1975); study of the mental and psychomotor abilities showed differences between both groups with regard to several perceptual and neuromotor abilities but not to mental development (Bleichrodt et al., 1980). Slower development of manual function was also found by Connolly et al. (1979).
It remains a matter for discussion whether the damage to the central nervous system in endemic cretinism is comparable with sporadic CHT in all respects. Apart from fetal and neonatal hypothyroidism for which Delange et al. (1976) found evidence, iodine deficiency could be an additional damaging factor.
Today, severe iodine deficiency is still a problem in many parts of the world; although severe cretinism no longer exists in Europe, iodine deficiency is reponsible for congenital goiter in some parts of Germany (Schuchmann et al., 1974; Heidemann and Stubbe, 1978). Delange et al. (1979) assume that iodine deficiency is an additional

etiological factor in the high neonatal prevalence of transient hypothyroidism in Belgium. This hypothesis is supported by the finding of a low thyroidal iodine content in preterm infants (Ermans et al., 1980).
Historically, parts of the Netherlands were iodine deficient and a high incidence of goiter was found (Gezondheidsorganisatie TNO, 1959). Iodated salt for household purposes was introduced, but at present used only in bread.

Transient hypothyroidism of unknown origin. Several causes of transient hypothyroidism have been described above: iodine deficiency, iodine intoxication and maternal treatment with antithyroid drugs. In most cases of transient hypothyroidism however, the cause of thyroid dysfunction is unknown. The incidence of transient hypothyroidism seems to be very high amongst seriously ill, often preterm infants (Delange et al., 1978, 1979). In a Belgium screening program, an incidence of 1 per 700 infants has been reported (Delange et al., 1980b). This phenomenon has to be distinguished from hypothyroxinemia which occurs in preterm or ill infants without elevation of the TSH level.
Transient hypothyroidism characterized by transient low T4 values and transient elevation of TSH has also been described in full term healthy infants (LaFranchi et al., 1977; Miyai et al., 1979a). Temporary TSH elevation has been found in infants born by caesarean section (Engberg et al., 1978).
Several hypotheses on the etiology of transient hypothyroidism have been formulated. Fisher (1980) summarizes various possible developmental immaturities of the thyroid system such as a decrease in the TSH response, in the T3 feedback response and in the TRH degradation. The high incidence of transient CHT in Belgium has been related to the relative iodine deficiency in this country (Delange et al., 1979; Ermans et al., 1980). The question of whether to speak of a delayed TSH surge which does not require therapy (Sommer et al., 1979) or of transient hypothyroidism (Delange, 1979) in which treatment is important remains unanswered for the time being.

2.2.2 *Secondary and tertiary hypothyroidism*

Pituitary and hypothalamic disorders causing hypothyroidism (respectively secondary and tertiary hypothyroidism) are often combined with other hypothalamic-pituitary hormone deficiencies, although isolated TSH and TRH deficiencies occur.
Hypothalamic-pituitary disorders can be divided into two main categories: the morphological malformations and the idiopathic forms. The first category is congenital and results mostly in severe and early clinical manifestations. The second is probably often neonatally acquired and is likely to become manifest during childhood.

Morphological malformations. Morphological malformations in the hypothalamic-pituitary area are of varying extent. The most serious is, of course, the anencephaly whether or not combined with pitu-

itary aplasia (Grasso et al., 1980); the condition is lethal. Also pituitary aplasia without other gross malformations of the brain but often accompanied by aplasia of the adrenal cortex and hypogonadism (Reid, 1960; Moncrief et al., 1972) is nearly always lethal. Response to prompt therapy has been described, however, in the second affected infant in one family (Sadeghi-Nejad and Senior, 1974). Other malformations limited to the pituitary region are familial hypoplasia of the sella turcica (Ferrier and Stone, 1969; Sipponen et al., 1978), pituitary hypofunction in an enlarged sella (Parks et al., 1978) and ectopia of the pituitary gland (Ehrlich, 1957). Midline defects can also be found in more extended areas: hypofunction combined with optic nerve hypoplasia whether or not in combination with agenesis of the septum pellucidum (Patel et al., 1975; Kaplan et al., 1970) and hypothalamic deficiency accompanied by a cleft lip and palate (Roitman and Laron, 1978) or by holoprocencephaly (Johnson et al., 1973).

Idiopathic secondary and tertiary hypothyroidism. "Idiopathic" hypopituitarism seems to occur more frequently than the morphological malformations. In the neonatal period, the idiopathic forms are probably of minor importance, although congenital idiopathic hypothalamic deficiency with severe clinical manifestation can occur (Lovinger et al., 1975; Cacciari et al., 1977).
Growth hormone deficiency is the most pronounced defect in idiopathic hypopituitarism, although isolated TSH deficiency has been described (Miyai et al., 1979a; Kramer et al., 1979; Smail et al., 1979). Rona and Tanner (1977) surveyed patients with growth hormone deficiencies in England; an additional TSH deficiency occurred in only 11%. Besides familial factors, an etiological factor seemed to be birth trauma (breech delivery, forceps delivery or caesarean section). Especially in multiple deficiencies did birth traumas occur in a higher frequency. Andler et al.(1978) reached the same conclusions, but found a higher percentage of additional TSH deficiencies. Hypothyroidism seems to develop in a later stage of the disease, sometimes after the institution of growth hormone therapy (Goodman et al., 1968).

2.3 *Frequency of CHT*

2.3.1 *Incidence and prevalence*

The occurrence of CHT is invariably expressed in incidence rates in the literature. To express the frequency found by screening, however, use of a prevalence rate seems more appropriate. The prevalence rate is the proportion of a defined group having a condition at one point of time (Rose and Barker, 1978). Neonatal screening measures at a defined age of the infant; thus, the frequency found by screening represents the frequency *at the age of screening* and will be referred to in this text as the screening prevalence. The main reason for doing this is the fact that a screening prevalence

found could be an underestimation of the actual incidence (the proportion of a defined group developing a condition within a stated period; Rose and Barker, 1978). At the age of screening, severely affected CHT patients could have died; mild forms of hypothyroidism can be manifest at an age above the age of screening and transient forms could have been normalized into euthyroidism. Therefore, the screening program can inform us only about the occurrence of CHT which is present at the age of screening.
It is important to be aware of this fact in comparing screening prevalences with each other. The prevalence found in cord blood can be higher than that found at the age of two weeks, because of transient hypothyroidism. Such a difference is not due to a difference between populations but to a difference in age at screening.
In epidemiological studies on patients diagnosed by clinical criteria, the frequency found refers to new cases diagnosed during a defined period; then, the use of an incidence rate is appropriate.

2.3.2 *Clinical incidence*

To assess the clinical incidence of CHT, clinical studies have been performed in the Netherlands (De Jonge, 1976 and 1977), Sweden (Alm et al., 1978) and Denmark (Jacobsen and Brandt, 1980).
The difficulty in defining "congenital" hypothyroidism is illustrated by the different age limits chosen by the investigators: CHT was defined as diagnosed before the end of, respectively, the 4th, 2nd and 6th year.
Table 2.3 summarizes the clinical incidences in the countries mentioned; in this table, only the data on patients diagnosed before the end of the second year have been included. In none of the studies, the incidence of secondary or tertiary CHT has been separately mentioned. The differences among the incidences found are not significant; the mean incidence is 1 patient per 6900 newborns.
Both the Dutch and the Danish study show a higher incidence in the oldest cohorts investigated. This suggests that the age of clinical diagnosis falls beyond the age of two years in some of the patients.

Tabel 2.3 Clinical incidence of CHT diagnosed before the end of the 2nd year in the Netherlands, Sweden and Denmark (for references, see text)

country	years of birth	newborns	CHT	incidence	95% confidence limits*
the Netherlands	1972-1974	594,951	90	1/6,600	1/5,400-8,400
Sweden	1969-1975	767,698	112	1/6,900	1/5,800-8,400
Denmark	1970-1975	436,959	60	1/7,300	1/5,700-9,500

* Poisson distribution

Table 2.4 Screening prevalence of primary CHT

screening method	center/ country	age at screening (days)	infants screened	patients with primary CHT
T4 + TSH	Toulouse	5	61,451	18
	Louvain	5	24,895	5
	Stockholm	5	20,000	6
TSH	Japan	5	295,000	55
	Copenhagen	5	107,700	28
	Zürich	5	92,603	31
	Bern	5	90,890	22
	London	7	87,444	26
	Lyon	5	86,149	26
	Antwerp	5	54,062	8
	Osnabrück	5	51,000	16
	Angers	6	44,053	9
	Reims	5	38,700	8
	Caen	5	37,500	8
	Heidelberg	5	31,008	12
	Oslo	3-5	28,983	8
	Dillenburg	5	20,000	7
T4 + TSH (TSH in case of a low T4)	Québec	3-5	475,126	110
	New England	3-5	463,521	111
	Australia	6	349,390	63
	Oregon (North West America)	1-5*	299,666	66
	Ontario (Toronto).	5	102,000	19
	Israël	2-4	83,493	18
	Japan	5	21,595	2
T4	Vienna	5	132,000	12
TSH (cord)	Berlin	0	24,052	4
T4 + TSH (cord; TSH in case of a low T4)	Toronto	0	115,000	32

* second heelpuncture at the age of 4-6 weeks
** Poisson distribution

screening prevalence (95% confidence limits)**	references
1/3,400 (2,200-6,800)	Rochiccioli and Dutau (1979); Rochiccioli (1980a)
1/5,000 (2,300-)	Beckers et al. (1977); Delange et al. (1980a)
1/3,300 (1,600-20,000)	Delange et al. (1980a)
1/5,400 (4,200-7,400)	Irie (1980)
1/3,800 (2,700-6,300)	Delange et al. (1980a)
1/3,000 (2,200-4,600)	Illig et al. (1977); Illig and Torresani (1980)
1/4,000 (2,800-7,600)	Illig and Torresani (1980)
1/3,400 (2,400-5,400)	Hulse et al. (1980)
1/3,300 (2,300-5,400)	David et al. (1978); Delange et al. (1980a)
1/6,757 (3,600-27,000)	Adriaenssen (1977); Delange et al. (1980a)
1/3,200 (2,000-6,400)	Delange et al. (1980a)
1/4,900 (2,800-14,700)	Daver et al. (1978); Delange et al. (1980a)
1/4,900 (2,600-19,300)	Delange et al. (1980a)
1/4,700 (2,500-18,800)	Delange et al. (1980a)
1/2,600 (1,600-6,200)	Klett et al. (1978); Delange et al. (1980a)
1/3,600 (1,900-9,600)	Lie (1980)
1/2,900 (1,400-20,000)	Delange et al. (1980a)
1/4,300 (3,600-5,300)	Dussault et al. (1978); Dussault et al. (1980d)
1/4,200 (3,500-5,100)	Mitchell et al. (1978); Mitchell and Larsen (1980)
1/5,500 (4,400-7,400)	Connelly et al. (1980)
1/4,500 (3,600-6,000)	LaFranchi et al. (1979); Dussault et al. (1980d)
1/5,400 (3,500-10,200)	Walfish (1980)
1/4,600 (3,000-9,300)	Sack (1980)
1/11,000 (3,600-)	Irie (1980)
1/11,000 (6,600-26,400)	Fritzsche et al. (1977); Delange et al. (1980a)
1/6,000 (2,700-)	Zabransky (1976)
1/3,600 (2,600-5,800)	Walfish et al. (1979); Walfish (1980)

therefore, these clinical incidences could be an underestimate of the real incidence.

2.3.3 *Screening prevalence*

Far more data are available on the prevalence of CHT found in the different screening programs all over the world. Data published recently have been summarized in Table 2.4 in which data only on centers where more than 20,000 neonates have been screened are included. The centers were grouped under the different screening methods used (see Ch. III). Only those accepted as permanent cases or primary CHT have been included. The cord blood programs represent a separate category.

The mean overall prevalance of *primary CHT* is 1 per 4,400 screened neonates. Considering the random variation in the incidences found (95% confidence limits in a Poisson distribution), no actual differences among the various countries appear. An exception is the incidence found in Vienna (1 per 11,000) that falls beyond the confidence limits of most others mentioned; whether an explanation for the difference has to be sought in methodological aspects of screening, in geographical differences or in random variation remains a matter for further investigation.
The neonatal screening prevalence of *transient forms* of hypothroidism is not easy to establish. Delange et al. (1980b) found a prevalence of transient hypothyroidism of about 1 per 700 neonates screened; most were preterm infants. In the North American programs (Fisher et al., 1979), the prevalence of transient hypothyroidism was 1 per 37,000 neonates; there, the cause was mostly the use of antithyroid drugs or iodine medication by the mothers. Connelly et al. (1980) found an incidence of 1 per 70,000 in Australia.
A few screening programs aim to detect *secondary and tertiary CHT* as well. The screening prevalence found in North America is 1 patient per 110,000 infants (Dussault et al., 1980b). This prevalence is lower than the prevalence earlier reported by the same screening center (Fisher et al., 1979). This is due to the fact that three infants with neonatal hypothyroidism were initially diagnosed as having tertiary hypothyroidism; in the neonatal period, low TSH values were found. In a reevaluation of the diagnosis, elevated TSH levels were found and the diagnosis was changed to primary CHT (Dussault, personal communication). The European incidence was also found to be 1 patient per 110,000 infants (Delange et al., 1980a).

2.3.4 *Discrepancy between incidence and screening prevalence*

The overall incidence and prevalence are summarized in table 2.5. For references, see the two preceding sections.
It appears that the clinical incidence in the first two years of life as estimated in the three different countries is significantly lower than the prevalence of primary hypothyroidism in the neonatal period

Table 2.5 Clinical incidence and screening prevalence

	births/ infants screened	patients*	incidence/prevalence (95% confidence limits)**
clinical diagnosis	1,799,608	262	1/6,900 (6,100-7,800)
screening	3,237,281	730	1/4,400 (4,100-4,800)

* Data on patients found by screening concern only primary CHT. The exact number of primary CHT patients in the clinical studies is not known; several patients with secondary or tertiary CHT were probably included
** Poisson distribution

as found in screening programs.
Four explanations are possible. The first is that the difference is due to geographical differences in incidence among three countries in Western Europe and the rest of the world. It is an unlikely explanation, contradicted by the higher screening prevalence also found in these countries.
Secondly, screening detects patients formerly missed by clinical diagnosis despite the presence of clinical manifestations. This would mean there are many untreated CHT patients. Thirdly, the fact has to be considered that, in screening, cases of (biochemical) hypothyroidism are detected which probably would never have led to clear clinical manifestations or which are merely transient. Whether treatment in such cases is unnecessary or even harmful, remains a matter for further investigation.
A fourth explanation concerns the method of the clinical studies. The age limit of two, four or six years is probably too low to include every infant with CHT.
Which factor of factors account for the discrepancy is not known. The third possibility, that in screening infants are detected with harmless biochemical abnormalities, stresses the need for careful follow-up and evaluation of the diagnosis.

2.4 *Clinical manifestations and prognosis*

In the neonate with *primary CHT,* the clinical syndrome varies to a great extent. Two factors hinder early diagnosis based only on clinical signs and symptoms. Firstly, the disease can be asymptomatic for a long time or lead to merely a few abnormal signs or symptoms. Secondly, if clinical manifestations are present at all, the nonspecificity of the findings will seldom directly indicate the diagnosis. Studies on the age at which the diagnosis is established illustrate this. Clinical diagnosis was established in about 20% of the cases before the end of the first month of life in the Netherlands, Sweden and Denmark (De Jonge, 1976 and 1977; Alm et al., 1978; Jacobsen and

Brandt, 1980). Data from screening programs reveal that the percentage of cases already diagnosed before screening was performed, is only 3 to 8% (Fisher et al., 1979; Illig and Torresani, 1980; Hulse et al., 1980).

Various clinical manifestations can be present in the early stage of CHT. As mentioned, none of the signs or symptoms is specific for the disease. For example, icterus prolongatus will often be an expression of many other diseases. Only combinations of several findings can sometimes be indicative for CHT.
Which clinical findings belong to the early clinical picture of CHT has been thoroughly investigated (Raiti and Newns, 1971; Mäenpää, 1972; Smith et al., 1975). Early symptoms are respiratory distress, hypoactivity, poor feeding and constipation. Birth length and weight can be high for the gestational age, which is sometimes prolonged. Raiti and Newns (1971) point to the fact that these early symptoms precede the development of the signs of the disease: signs which may become obvious are hypothermia, edema, prolonged icterus, peripheral cyanosis, large fontanels (Smith and Popich, 1972), hoarse cry, umbilical hernia, a dry and mottling skin, abnormal proportions, a typical facies with a low nasal bridge, and a large protruding tongue. Occasionally, a congenital heart block has been described (Syed, 1978). Deafness is a symptom accompanying the Pendred syndrome and endemic cretinism. In dyshormonogenesis a goiter can be present. If treatment is delayed, growth retardation appears during the first years of life. In older patients, muscular hypertrophy can occur (Najjar, 1974). David et al. (1979) described a delayed puberty in children who were insufficiently treated.
The prognosis of primary CHT is determined by the mental development and additional neuropsychological disorders. Somatic manifestations other than neurological manifestations improve rapidly after beginning of treatment.
The intellectual development of infants clinically diagnosed varies from severe retardation to the achievement of a normal IQ. In literature reviews, a mean IQ of 76 was found (Klein, 1980); the percentage of infants with an IQ higher than 90 was estimated at 42%, and that of those with an IQ lower than 50 at 13% (Smith and Morris, 1979).
Factors which can influence the IQ eventually reached, are the time of onset of hypothyroidism, the age at which treatment is begun and the severity of the hypothyroidism. In view of the possibilities to improve the prognosis by early diagnosis through screening and by early treatment, it is important to know whether a better mental development can be achieved by earlier treatment and to assess the influence of the time of onset of hypothyroidism and the severity of hypothyroidism.
Many clinical studies have been performed to investigate the influence of the age at which treatment is begun on the IQ eventually reached. All of them give evidence for the fact that treatment before the age of three to four months results in a better prognosis as compared to infants in whom treatment began after that age (Smith et al., 1957; Andersen, 1961; Man et al., 1963; Collip et al., 1965;

Raiti and Newns, 1971; Klein et al., 1972; Zabransky et al., 1975), although a delay in diagnosis and treatment does not invariably result in severe retardation in mildly affected cases (Van Gemund and Laurent de Angulo, 1971). Andersen (1961) and Mäenpää (1972) also included in their studies the severity of hypothyroidism: a better prognosis was found for infants in whom the CHT was due to an ectopic thyroid; in such cases, the hypothyroidism is mitigated by an functioning thyroid remnant.
The influence of both the onset of hypothyroidism and the age of onset of treatment has been investigated by Wolter et al. (1979). In this study, it was assumed that the bone age as measured at the time of clinical diagnosis indicated the time of onset of hypothyroidism. A skeletal maturation comparable to that of a preterm infant was considered as an indication of the prenatal onset of the hypothyroidism. The onset of hypothyroidism was assumed to be postnatal if the skeletal maturation had reached a postnatal age at the time of diagnosis. A normal mean intellectual development was found in infants with a postnatal onset of hypothyroidism. Prenatal hypothyroidism resulted in a normal development only if treatment was started before the age of three months or, even better, in the first month of life.

Apart from the retardation of the mental development, neurological and psychological disorders can represent severe handicaps for the child. Clumsiness, behaviour disorders, speech disorders, learning disorders, squint, nystagmus, minor motor disorders, enuresis, cerebellar ataxia and spastic diplegia can prevent the child from functioning normally (Van Gemund and Laurent de Angulo, 1971; Zabransky et al., 1975; Wiebel, 1976; MacFaul et al., 1978). MacFaul et al. (1978) found at least one sign of impaired neurological function in 77% of a group of clinically diagnosed patients. Wiebel (1976) observed a higher frequency of neurological disorders in more severely mentally handicapped infants and in infants in whom the hypothyroidism became manifest early. Wolter et al. (1979) (see above) also investigated neuropsychologic sequelae of hypothyroidism. Prenatal hypothyroidism treated late resulted in severe disorders. In the early treated cases and in postnatal hypothyroidism, only minor disorders were found.

Very interesting are, of course, the first results published on patients detected by neonatal screening who received early treatment. Follow-up studies at the ages of 12, 18 and 24 months have been published. Mean developmental scores were within a normal range (Dussault et al., 1980a; Reed and LaVecchio, 1980; Rochiccioli, 1980b), although Dussault et al. found a significant decrease in the score at the age of 18 months as compared to the age op 12 months.
All developmental scales used for the follow-up studies contained scales for neuropsychological development. The New England group of patients (Reed and LaVecchio, 1980) scored lower on the psychomotor development scales, suggesting a delay in development of motor skills. These results agree with those of Rochiccioli (1980b), who found lower postural and coordination scores in comparison with scores for language and sociability. In contradiction, Dussault et al. (1980a) could make a discrimination between the hypothyroid

group and the control group by the scores on hearing, speech and performance; influence of sociocultural factors, however, could not be excluded.

The clinical picture of *secondary and tertiary hypothyroidism* is probably even more variable than that of primary CHT. Little is known about the neonatal manifestations. In the literature, many severe cases have been described in which multiple hormone deficiencies often are present. Lethargy, cyanosis, symptoms of hypoglycemia, prolonged jaundice, liver dysfunction (Herman et al., 1975; Drop et al., 1979) and microphallus predominate the signs and symptoms of hypothyroidism. In anatomical malformations, a cleft lip or palate and optic nerve hypoplasia can occur (for references, see section 2.2.2). Mental retardation is nearly always reported in these severe cases. However, possible etiological factors for brain damage are numerous: hypothyroidism, hypoglycemia, hyperbilirubinemia and anatomical malformations.
The clinical onset of the disease may also be later. Since the hypothyroidism with a late clinical onset accompanies a growth hormone deficiency in most cases, growth impairment is the predominating sign. The mental prognosis for these children is good (Rosenbloom et al., 1966; Bucher and Illig, 1980). If mental deficiency is present, birth injury could often not be excluded as the cause (Van Gemund and Laurent de Angulo, 1971; Bucher and Illig, 1980).
Certainly, the relation between early treatment and an improvement in the prognosis is less clear in secondary and tertiary hypothyroidism than in primary CHT. In screening however, only cases can be found in which hypothyroidism is already present in the neonatal period and hypothyroidism in this early stage of life is a strong indication for treatment.

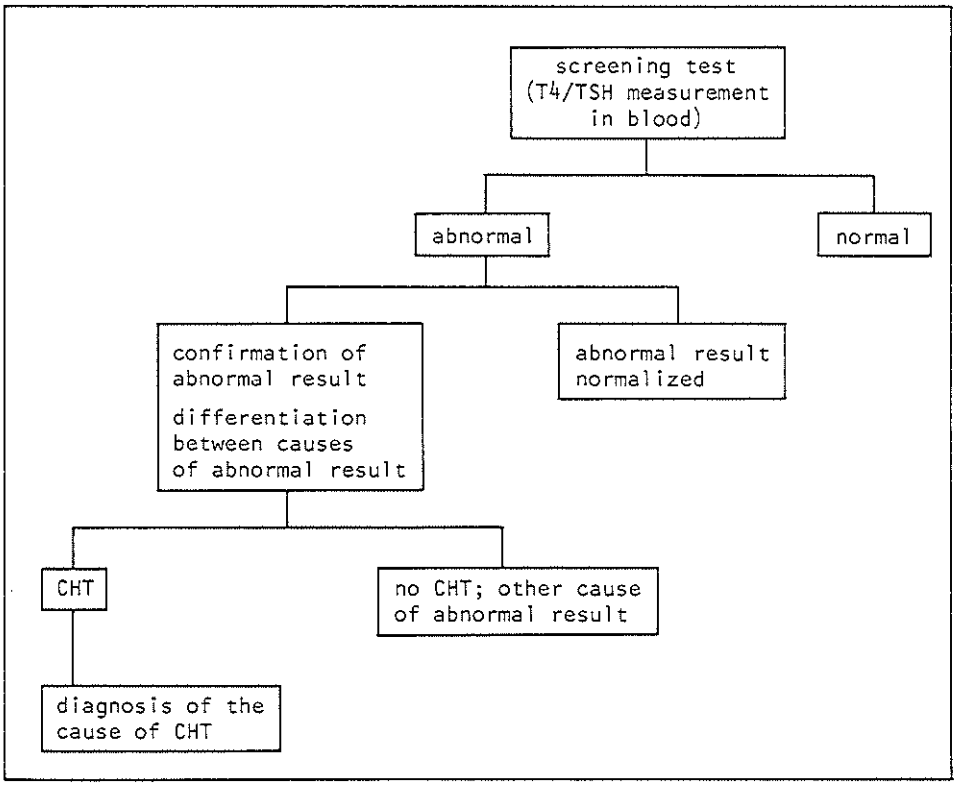
2.5 *Diagnosis in a screening procedure*

The diagnostic pathway in CHT screening is outlined in Scheme 2.1. Hypothyroidism results in a decline in blood thyroid hormone levels which are followed by an increase in pituitary TSH secretion in primary hypothyroidism. The important hallmarks in primary CHT are, therefore, a low T4 level and a high TSH level. The TSH production in secondary and tertiary CHT is decreased; in these cases, the T4 level is the only diagnostic tool in screening.

2.5.1 *Confirmation of an abnormal screening result*

An abnormal screening result requires further investigation. The test will seldom directly distinguish between disease and health; additional tests will be required to establish the diagnosis CHT. In addition, transient abnormalities in the screening values and laboratory and adminstrative errors have to be excluded. The latter reasons for confirmation require only a second screening. However,

Scheme 2.1 Diagnostic pathway following a screening result



if abnormal values have been repeatedly found or if serious suspicion of CHT has been aroused, additional examination of the thyroid status will be necessary: serum measurements of T4, T3, TSH and, in order to exclude a deficiency in the TBG (see below), TBG or measurement of the unbound binding sites of TBG.

2.5.2 *Differential diagnosis*

Abnormal screening results can be caused by various conditions which are summarized in Table 2.6.
A high TSH level is the most sensitive indicator for primary CHT (Barnes, 1975). The neonatal TSH surge immediately after birth has to be considered if high values are found. Sack et al. (1976) observed peak values as early as 30 minutes after birth; the peak is followed by a rapid decline and values normalize within approximately 5 days (Jacobsen et al., 1977b). In addition, elevation of TSH has been reported to continue for a long time without clinical consequences (Miyai et al., 1979a; Jacobsen, 1980).
Czernichow et al. (1980) and Gendrel et al. (1980) observed TSH elevation in neonates which was persistent for several months, in com-

Table 2.6 Causes of an abnormal screening result

high TSH	biological variation in normal infants physiological neonatal TSH surge maternal TSH-like plasma substance primary CHT
low T4, normal TSH	biological variation in normal full term infants low T4 in preterm infants respiratory distress of the newborn acute illness TBG deficiency secondary and tertiary CHT primary CHT

bination with elevated TSH values in the mother. They suggest placental transfer of a TSH-like maternal plasma substance.
Elevated TSH levels are also described in hypothalamic hypothyroidism (Illig et al., 1975); the values, however, are in a lower range than those in primary CHT.

Several conditions such as preterm birth, acute illness and respiratory distress in the newborn lead to low T4 levels without elevation of the TSH level (Redding and Pereira, 1974; Chopra, 1976; Cuestas et al., 1976; Cuestas and Engel, 1979, Klein et al., 1977 and 1979).
In TBG deficiency, the total T4 level is low because of the decreased binding of thyroid hormones. TBG deficiency has various etiologies: medication with androgens, anabolic steroids, prednisone or diphenylhydantoin, major illness or surgical stress, nephrotic syndrome, overt acromegaly and a genetically determined deficiency (Fisher, 1973). In the neonatal period, the genetic disorder is probably the most important. An incidence of 1 per 7,000 to 8,000 infants has been reported (Dussault et al., 1977 and 1980d). The pattern of inheritance has been described as X-chromosomal, although an autosomal dominant pattern can not always be excluded (Refetoff et al., 1972; Dolman et al., 1974; Dussault et al., 1977). TBG deficient persons are clinically euthyroid; lowered free T4 levels are found (Hennemann et al., 1971), but high free T3 levels (Ross et al., 1980).
If the low T4 value (without elevation of TSH) is due to CHT, this will be mostly of a secondary or tertiary type. In the diagnosis of these disorders, a *TRH-test* (measurements of the TSH response to TRH administration) can be helpful (Costom et al., 1971). In case of hypofunction of the pituitary gland, the TSH response will be decreased; in hypothalamic dysfunction the response can be delayed, exaggerated and prolonged in comparison with a normal response (Foley et al., 1972b). In euthyroid full term neonates, the response is equal to that in older children and adults (Jacobsen et al., 1976), and to that in preterm infants and infants small-for-dates (Jacobsen et al., 1977a). TRH injection also stimulates prolactin secretion (L'Hermite et al., 1972) which follows the same pattern as TSH; basal

prolactin levels can be elevated (Foley et al., 1972a; Lovinger et al., 1975) in hypothalamic disorders. On the other hand, Drop et al. (1979) found low basal levels and a subnormal response in two infants with idiopathic hypopituitarism in whom a normal TSH response suggested a hypothalamic deficiency.
Low TSH values do not completely contradict the diagnosis of primary CHT. Several infants with initially low TSH levels have been described (Jackson et al., 1975; Dussault et al., 1976a; Mitchell and Larsen, 1980; Miyahira, 1980).

Clinical examination including assessment of bone age (Von Harnack, 1965; Senécal et al., 1977), serum measurements of T4, T3, TSH and TBG (or unbound TBG binding sites) and - if necessary - a TRH test, should give enough information for the diagnosis of the underlying condition of the abnormal screening result.

2.5.3 *Tests in case of CHT*

Additional tests will be necessary in order to establish the definite diagnosis of the etiology of CHT. The cause and severeness of the hypothyroidism will be of importance for the prognosis. In hereditary disorders, knowledge on the recurrence risk will be used in genetic counseling.

Thyroid scanning. The location and size of the thyroid can be estimated by a scanning of the neck region after injection or ingestion of radioactive iodine (I^{123}) or sodium pertechnetate technetium 99m (Bauman et al., 1976). Endogenous TSH stimulation in primary CHT facilitates uptake of the radioactive anions into the thyroid. Since most cases of CHT are due to defective embryogenesis of the thyroid, thyroid scanning very often provides a definite diagnosis.

Thyroglobulin. The presence of thyroid tissue is reflected by the blood concentration of thyroglobulin (Osotimehin et al., 1978).

Diagnosis of the type of dyshormogenesis. In most types of dyshormonogenesis, extensive investigations will be required which will interfere with an early start of therapy in the neonatal period. A description of the diagnostic possibilities in later infancy are beyond the scope of this study (for a review, see DeGroot and Stanbury, 1975).
Urine measurements of iodohistidine, sometimes found in abnormal thyroglobulin synthesis and in a dehalogenase defect (Gons et al., 1978 a and b), will not cause delay in the beginning of treatment.

Serum PBI and iodine excretion in urine. The iodine status of the infant is estimated by measurement of serum PBI (protein bound iodine) and urine excretion of iodine. In a defect of the thyroglobulin synthesis, the presence of abnormal iodoproteins results in an elevation of PBI compared to the T4 level.

Antibodies against thyroid tissue. Antibodies derived from the maternal circulation are detectable shortly after birth only (Blizzard et al., 1960). As the relationship between circulating antibodies in the neonate and CHT is not yet fully understood, the diagnostic significance for the individual patient seems to be doubtful.

Diagnosis of additional defects in secondary and tertiary hypothyroidism. In hypothalamic-pituitary disorders, deficiencies in other pituitary hormones can occur; this requires further endocrinological investigations.

2.5.4 *Timing of the diagnostic procedure and treatment*

It is clear that diagnosis and treatment (if necessary) have to be carried out as soon as possible. Further impairment of brain function may occur if treatment is delayed in the hypothyroid child.
If primary CHT is suspected on the basis of the screening result and the clinical manifestations, treatment can be started immediately after collection of serum (Landelijke Begeleidingscommissie CHT, 1980). Additional diagnostic tests can be performed during the first days of treatment without influencing the test results. If CHT is ruled out by the results of the serum measurements, treatment will be stopped. Generally, the diagnosis of secondary or tertiary CHT will be less easily made. Except for cases in which very clear clinical manifestations are present, the beginning of treatment will be delayed until the diagnostic tests have been completed.

2.6 *Treatment*

2.6.1 *Substitution with thyroid hormones*

Correction of the deficiency in thyroid hormones results in a prompt improvement in the clinical manifestations. For substitution, there are several possibilities. Desiccated thyroid or purified thyroglobulin contain T4 as well as T3, though with variable biological activity. Synthetic sodium-L-thyroxine (L-T4) is now generally accepted as optimal replacement therapy and probably represents the most physiological method of treatment, since the thyroid produces mainly T4. With L-T4 substitution, (high) normal T4 and normal T3 levels can be achieved.
Abbassi and Aldige (1977) and Rezvani and DiGeorge (1977) investigated the optimal dose to be used in infancy by estimating the lowest dose needed to suppress the TSH elevation in primary hypothyroidism*. The optima found were in the lower range of the dose recommended by the Committee on Drugs (1978); L-T4 is given orally, though parental

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* 2.5-5 µg per kg per day.

administration at 75% of the oral dose is possible. Levotriiodothyronine (liothyronine; L-T3) can also be used as a replacement. Since the biological activity is higher and more rapid than that which is obtained with L-T4 treatment, attention should be given to possible intoxication.
There are two possibilities for the initiation of therapy in the neonatal period. L-T4 is used in many centers as the drug of choice and initiation at a full dose of 25 - 50 µg per day in full term neonates has been advised (Committee on Drugs, 1978). The second possibility is rapid induction by using L-T3, which sooner ensures euthyroidism and is therefore preferred in certain circumstances. The risk of intoxication and of cardiac failure makes close monitoring necessary. Little has been published on induction therapy with L-T3. Petricciani et al. (1971) report treatment in several older infants and consider it safe; they gradually replaced L-T3 by L-T4. Guyda (1980) uses combined L-T3 (5 µg per day) and L-T4 (25 µg per day) for two weeks in neonates with CHT detected by screening; after two weeks, L-T3 is discontinued and L-T4 increased.
Another use for L-T3 has been found in the treatment of certain forms of transient hypothyroidism. Delange et al. (1978 and 1980b) treated preterm infants with transient hypothyroidism with L-T3, which was stopped when a normal T4 value was found; the T4 increase is independent of the T3 treatment and reflects an improvement in thyroid function.

2.6.2 *Control of treatment*

For dose adjustment, biological parameters such as the levels of T4, T3 and FTI can be used. The TSH level is of importance in primary hypothryoidism. In adults, the TSH value is the main parameter (Stock et al., 1974; Evered et al., 1973); the TSH level in infants can remain sightly elevated for a long time, when other parameters already indicate euthyroidism (Abbassi and Aldige, 1977; Guyda, 1980; Schultz et al., 1980). Clinical parameters are the presence of signs and symptoms of hypo- or hyperthyroidism and data on normal growth and development and normal bone maturation.
Not only has a continuation of the state of hypothyroidism to be avoided but overtreatment also has its harmful side effects (Weichsel, 1978). Penfold and Simpson (1975) reported premature craniostenosis in treatment of hypothyroidism. Hollingsworth and Mabry (1975) investigated the long term effects of neonatal thyrotoxicosis and found hyperactivity and perceptual motor problems. Studies in hypothyroid rats treated with a high dose of liothyronine revealed a decrease in cell number in the cerebellum combined with an advanced cell differentiation; behaviour disorders were seen (Eayrs, 1971).

2.6.3 *Breast feeding*

Some investigators claim that breast feeding prevents impaired neurological development in CHT because of T4 and T3 contents in breast

milk (Bode et al., 1978). However, the amounts of T4 and T3 vary considerably (Bode et al., 1978; Sack et al., 1979; Varma et al., 1978) and, in any case, are not sufficient for complete substitution. Rather, breast feeding may delay the clinical recognition of CHT. In a group of screened patients, no differences could be demonstrated between the breast fed and formula fed infants with respect to levels of T4, T3 and TSH, to bone maturation and to psychological performance at the age of one year (Letarte et al., 1980b).

2.6.4 *Iodine supplementation*

Insufficient dietary iodine has to be supplemented for. However, there is no consensus on the treatment of neonatal goiter due to iodine deficiency. Some prefer iodine application (Schuchmann et al., 1974; Heidemann et al., 1979), while this method is rejected by others because of the risk of iodine intoxication (Homoki et al., 1975) and the consequences of hypothyroidism in the neonatal period (Wiebel et al., 1976).
In some types of dyshormonogeneses such as in the iodine trapping defect and the dehalogenase defect in which there is, respectively, a shortage in iodine supply in the thyroid and a iodine leak from the thyroid, high doses of iodine could probably be used as therapy; in a thyroglobulin synthesis defect in goats (Van Voorthuyzen et al., 1978; De Vijlder et al., 1978), achievement of euthyroidism has been described by use of an excess of iodine supplementation only.

2.6.5 *Intrauterine treatment*

Intrauterine treatment has been attempted but is in an experimental stage. Van Herle et al. (1975) treated a hypothyroid fetus (the hypothyroidism was due to radioablation of the maternal thyroid in the 11th week of pregnancy) with a weekly intramuscular dose of L-T4 from the 35th week of gestation. Biochemical signs of hypothyroidism were present immediately after birth, although the bone age was normal. The dose used was small. Lightner et al. (1977) injected L-T4 intra-amniotically in a case of suspected CHT resulting from an inadvertently given dose of radioactive iodine in early pregnancy. Rising rT3 in the amniotic fluid proved a fetal uptake of T4.

2.6.6 *Treatment of secondary and tertiary hypothyroidism*

Thyroid hormone substitution in secondary and tertiary forms of hypothyroidism does not differ in essence from that in primary hypothyroidism. In case of other hormonal deficiencies, additional supplementation will have to be provided for.
Experimental treatment with oral TRH has been described by Stolecke (1974). Euthyroidism was achieved, although the dose required increased during the first months of therapy.

3. SCREENING FOR CHT; LITERATURE DATA

The introduction of a screening program for a certain disease requires that the pros and cons of early detection by screening are weighed; a screening program has to meet basic criteria. These criteria and the screening procedure as such are discussed in this chapter, but are focused on screening for CHT.

3.1 *Criteria for screening*

A definition of screening generally accepted was given by the American Commission on Chronic Illness: *Screening is the presumptive identification of unrecognized disease or defect by the application of tests, examinations or other procedures which can be applied rapidly. Screening tests sort out apparently well persons who probably have a disease from those who do probably not. A screening test is not intended to be diagnostic. Persons with positive or suspicious findings must be referred to their physicians for diagnosis and necessary treatment* (Commision on Chronic Illness, 1957).
Identification of CHT can only be effective as far as prevention of the serious consequences is concerned, if screening is performed in the neonatal period. The nature of the disease is such that screening cannot be limited to a high risk group within the neonatal population, but has to be a mass screening program.
The character of the screening also has to be defined. A difference can be made between case finding programs and programs where the aim is to gain epidemiological information and where case finding is only a "by-product". By the time screening was prepared in the Netherlands, some epidemiological information was available, for example on the incidence and on the natural history of the disease. The methodological aspects of case finding were of higher importance in this project. In a Public Health Paper of the World Health Organization, Wilson and Jungner (1968) formulated basic guidelines for planning case finding programs. These guidelines ("for ease of description rather than from dogma called principles") will be dicussed here in view of CHT screening.

*Planning of a case finding screening program for CHT judged by the principles of Wilson and Jungner**

(1) *The condition sought should be an important health problem*

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* The literal text of the principles is given.

There is no doubt on this point. As discussed in Chapter 2, the prognosis if CHT is grave in many cases, especially that regarding the mental development and the neurological effects. This means that CHT is often a serious disease for the individual patient.
Another indicator for the importance of a health problem is the prevalence expected to be found. Epidemiological studies to establish the prevalence in a group similar to the one selected for screening should serve as a basis for determining a screening procedure (Whitby, series of articles on screening in the Lancet, 1974). CHT is a rare disease but, in comparison to other diseases to be considered for neonatal screening or to PKU already screened for, it is relatively frequent: in the Netherlands, a screening prevalence of CHT of 1 per 6,000 was expected (De Jonge, 1977). Other known frequencies in the Netherlands are, for example, the incidence of PKU of 1 per 16,000 (Anders et al., 1973; Landelijke Begeleidingscommissie Phenylketonurie, 1978), the incidence of cystic fybrosis of 1 per 3,600 infants (Ten Kate, 1979) and the incidence of galactosemia of 1 per 50,000 infants (Derksen-Lubsen, 1980).
The importance of the health problem can be reduced by screening, because of the effect of screening on the population screened (Holland, 1974). Probably, an indirect influence of screening for CHT is to be expected as well: screening will result in an increase in knowledge on some preventable causes of CHT; primary prevention in such cases will diminish the yield of the screening.

(2) *There should be an accepted treatment for patients with recognized disease*

The substitution treatment of CHT with thyroid hormone is relatively easy and without overt side effects. An important question is whether early treatment provides for a better prognosis; introduction of screening should be based on evidence that the natural history of the disease can be influenced in an appreciable proportion of those screened (Cochrane and Elwood, 1969). Wilson and Jungner divide this problem into two questions:

a) does treatment at the presymptomatic borderline stage of a disease affect its course and prognosis?
b) does treatment of the developed clinical condition at an earlier stage than normal affect its course and prognosis?

The latter question can be answered positively. Based on various studies, it can be expected that earlier diagnosis and treatment affect the course and the prognosis of the disease in such a way that both somatic manifestations and the mental development are favourable influenced (see Ch. 2).
To answer the question what is to be expected from earlier treatment of presymptomatic cases or of borderline cases, two subproblems have to be solved:

a) is every biochemical or pathological change a permanent change which results in a symptomatic stage?
b) if not, do these transient forms result in irreversible damage which is preventable by early detection and therapy?

Little is known about the natural history of the borderline cases and transient forms of CHT. Such cases are a "by-product" of screen-

ing; evaluation of patients screened will give more information about this subject (Raine, 1974).

(3) *Facilities for diagnosis and treatment should be available*
The fulfilment of this criterion depends on local facilities. In principle, these facilities were present in the trial area. Part of the preparation before the beginning of the program was to ensure the adequacy of the services.

(4) *There should be a latent or early symptomatic stage*
Early pilot studies of screening for CHT have shown the existence of an early recognizable stage (Klein et al., 1974; Dussault et al., 1975). Abnormal TSH or T4 values were found in infants who were later proved to have CHT.
Two problems remain. The first is whether all cases of CHT have a presymptomatic but recognizable stage *during the neonatal period*, so that no patients will be missed. A second problem is whether there are biochemical abnormalities similar to those found in CHT, which are harmless. These problems were unresolved at the beginning of the screening. Recently, infants with asymptomatic elevated TSH values have been described (Miyai et al., 1979a; Czernichow et al., 1980; Gendrel et al., 1980; Jacobsen, 1980).

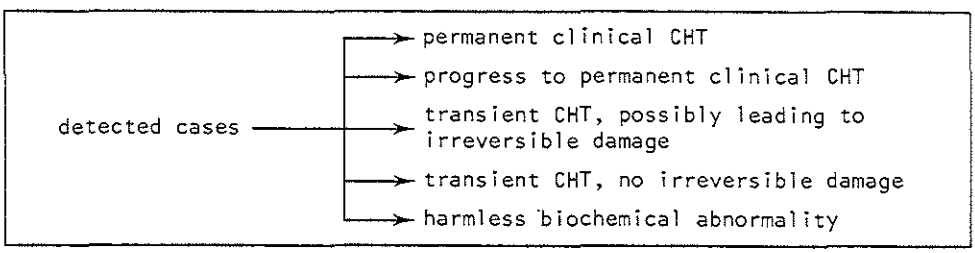
(5) *There should be a suitable test or examination*
Two aspects have to be dinstinguished here. The first is the suitability of the performance of the test as such. The collection of blood has to be easily and rapidly performed and safe for the person tested. In the case of collection of cord blood, these conditions are certainly fulfilled. A heel puncture is probably less easy. Osteomyelitis following frequent heel punctures in preterm ill infants has been occasionaly described (Fernandez-Fanjul et al., 1979), but mostly no side effects are seen (Blumenfeld et al., 1979). As far as we know, no side effects of a heel puncture performed once or twice for screening purposes have been described. The performance of the laboratory test has to be suitable for application on a large scale, an objective which can also be reached (see Section 3.2).
The second aspect concerns the validity, reliability and accuracy of the screening method proposed. Before beginning the program, it could be expected from the literature data, that the qualities of the screening test for CHT would be adequate.

(6) *The test should be acceptable to the population*
The participation of more than 99% of the population in the PKU screening indicates a good acceptance of neonatal screening using a heel puncture procedure, which can also be expected for a combined PKU-CHT screening. The consequences of the higher follow-up percentages in CHT screening will require further attention.

(7) *The natural history of the condition, including development from latent to declared disease, should be adequately understood*
This question has been discussed by Wilson and Jungner under the heading "Need for Survey", which includes their opinion that, in many

diseases which can be considered for early detection by screening, the natural history requires further investigation. In cases detected on clinical grounds (a clinical diagnosis), the natural history is fairly well understood. They are the patients formerly described in the studies on signs and symptoms and mental development in CHT. The situation is different for some of the cases detected by screening. Is the case found by screening a patient who sooner or later would have been diagnosed in a symptomatic stage of the disease? Is it a case in which the abnormal screening result and the ensuing diagnostic tests indicate a transient hypothyroidism, whether or not combined with clinical manifestations but in which the laboratory results cannot be distinguished from a real and permanent hypothyroidism? On the final outcome of such cases little is known. Therefore, while the natural history of patients in whom a clinical diagnosis has been made is known, this is not true in screened cases. The theoretical possibilities for the outcome in a screened case has been given in Figure 3.1.

Figure 3.1 Natural history in cases detected by screening



When additional investigations indicate the cause of CHT, for example, as in athyroidism, no doubts will arise about the natural history. In an ectopy, the outcome is more difficult to predict: is the hypothyroidism transient and will it be compensated for in the near future or, will it be progressive? It will be even more difficult if no clear cause of CHT can be demonstrated in the neonatal period.

It seems plausible to expect that the values for the biochemical parameters will show a considerable overlap in the five possible outcomes of a detected "case". The value for a parameter is not necessarily a prediction of the natural history.

More information on cases detected by screening has became available in the past few years. The prevalence in screening was much higher than would be expected from epidemiological studies based on clinical manifestations (see Ch. 2). Reasons for this are, among others, either that epidemiological studies missed patients, although they had clinical manifestations, or that screening detects cases without clear clinical manifestations (which does not necessarily mean these infants do not need therapy) and who therefore will be missed in such epidemiological studies. In the latter group, we can expect all possible outcomes listed in Figure 3.1. If there is even a small

chance of irreversible damage, it will be unethical to withhold therapy from such an infant and to carry out a survey of the prognosis in infants whose natural history seems unclear. It emphasizes rather the need for evaluation of the thyroid status after a few years of therapy, at an age when the rapid growth of the central nervous system has ceased.

(8) *There should be an agreed policy on whom to treat as patients*
From what has been mentioned under (7), it will be clear that there is a strong inclination to start therapy in all cases where abnormal values found in screening are confirmed. Progressive abnormality or nonprogressive but persistent abnormality in the biochemical parameters will be reason to start therapy.

(9) *The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole*
Wilson and Jungner distinguish an immediate economic aim (the time saved by highly trained people) and a long term economic aim (the lengthening of the productive life of population at risk). The first aim does not apply here. Though the screening test is relatively cheap and easy to perform, there are in fact no other possibilities for early detection. Thus, screening for CHT adds an additional cost to medical care; these are, however, relatively low (Illig, 1978). The second long term aim is likewise hardly applicable. It is not a lengthening of the productive life which is achieved by early diagnosis and treatment but rather an improvement in the quality of life, although this of course brings an improvement in productivity.
An economic advantage is the reduction in long term confinement in institutions for mentally handicapped persons. Layde et al. (1979) computed that the costs for traditional methods of detection and treatment were about 9 times as high as those for screening and subsequent treatment.
Roughly estimated, the expected cost-benefit analysis in the trial area was as follows, before beginning the program.

Cost of the screening for two years in the pilot area (including laboratory costs, screening of 60,000 infants and administration)	*f* 540,000,-
Cost of treatment of patients screened is equal to cost of treatment of patients diagnosed in the period before screening	--
Cost of follow-up investigation of 3% of the newborns (see Ch. 4)	*f* 437,400,-
Minimal benefits (no institutionalization of one patient for a duration of 30 years in an institution for mentally handicapped)	*f* 1,500,000,-

(10) *Case finding should be a continuing process and not a "once and for all" project*
Continuous screening of virtually all newborns in a certain area

fulfils this criterion. The fact that the screening procedure fits in the existing system of public health - which can be considered as a condition for the initiation of screening (de Waard-Preckel, 1979) - facilitates continuation of such a project.

Before the beginning of the project in the trial area, the state of evidence towards screening for CHT could be summarized as follows: CHT could be considered as an important health problem, although the expected prevalence was low. A better prognosis could be anticipated from early detection and treatment. The cost-benefit analysis was favourable. Organizational requirements could be fulfilled, especially because of the fact that a PKU screening program already existed. The screening test could be easily performed, was relatively cheap and well accepted by the population.
Four questions remained to be answered: (1) Is every detectable stage followed by a clinical stage? (2) If not, are minor subclinical damages to be expected? (3) Is every clinical CHT preceded by a detectable stage *during the neonatal period*? (4) And finally, are there harmless biochemical abnormalities similar to those found in CHT? The magnitude of these problems will be discovered by screening. Ethical considerations will prevent the performance of a survey on the prognosis of (untreated) borderline cases but emphasize the need for evaluation of the thyroid status of the patient found by screening at an age when this can be done without risk for the cerebral development.

3.2 *Screening methods for CHT*

3.2.1 *Screening tests*

A basic condition for every test is the reliability and the accuracy of the test. The *reliability* is the measure of similarity between the results of a series of measurements in the same person or sample (including both the variability caused by the laboratory method and the variability dependent on the skill of the person who performs the test); the *accuracy* is the potential to give a true measurement of the variable tested. Every screening test must have an acceptable reliability and accuracy. Apart from this, it must have the diagnostic potential to sort out "apparently well persons who probably have a disease from those who propably do not". Of course, this will be greater, the more the test is directly aimed at the underlying pathological changes involved in the disease.
The potential to separate persons who have a condition from those who do not is called the *validity* of the test; the Commission on Chronic Illness (1957) defined validity as the measure of the frequency with which the result of that test is confirmed by an acceptable diagnostic procedure. Thus, the validity of the test can be determined only when every screening result is confirmed by another acceptable diagnostic test. The relation between screening and diagnosis is demonstrated in a contingency table (Thorner and Remein, 1961)

(Table 3.1).
True positive and true negative results are those results which are confirmed by a diagnostic test, either positive (indicating the disease) or negative (denying the disease). A false-negative result is found when the screening test is negative, while the confirmatory diagnostic test is positive; a false-negative result means that a patient is missed by the screening. False-positive is the result in which the screening is positive, while the diagnostic test does not indicate the condition sought. A high validity is determined by a high frequency of correct (true) results.

Table 3.1 Contingency table of screening results and results of a confirmatory diagnostic test

		diagnosis +	diagnosis -	
screening test	+	true positive (a)	false-positive (b)	a+b
	-	false-negative (c)	true negative (d)	c+d
		a+c	b+d	a+b+c+d

The validity - or predictive value of a positive or negative test - can be expressed in terms of probability:
predictive value of a positive test: the probability of CHT given a positive screening test;

$$P(CHT \mid test^{+}) = \frac{n(a)*}{n(a+b)}$$

predictive value of a negative screening test: the probability of not suffering from CHT given a negative screening test;

$$P(CHT^{-} \mid test^{-}) = \frac{n(c)}{n(c+d)}$$

The predictive value of the test result informs on the diagnostic potential but not on the measure of frequency with which the test gives a positive result in CHT or a negative result in infants not suffering from CHT or, in other words, on the percentage of the group of CHT patients founds by screening and the percentage of healthy infants indeed indicated to be healthy. These qualities of a screening test are illustrated by Figure 3.2. A T4 screening has been chosen as an example; in both the normal population and the CHT population, the T4 is assumed to have an unimodal distribution. The patient distribution is known to considerably overlap the distribution of the

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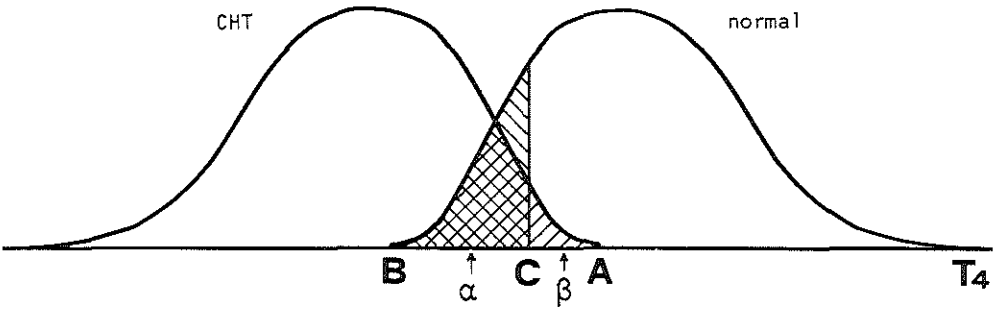
* n(a): number of infants in cell (a).

Figure 3.2 Relative frequency distribution of T4 in a normal population and a CHT population



normal population
The *sensitivity* is the potential to give a positive result in those who really have the condition. If the T4 *cut-off point* is A, it means that all values found equal to or lower than A are positive. From Figure 3.2, it can be easily seen that the sensitivity is virtually 100%. A lower cut-off point, for example, point C results in a decrease in sensitivity; in terms of probability, in which the surface of each distribution is equal to 1, the sensitivity decreases from 1 to 1-β.
The *specificity* of a test indicates the potential to give a negative result in those who do not have the condition. Is the cut-off point equal to B, the specificity is 100% or 1; is the cut-off point equal to C, the specificity is 1-α.
On the analogy of the definition of the predictive value, sensitivity and specificity are defined as follows:
sensitivity: the probability of a positive test given CHT;

$$P(test^{+}|CHT) = \frac{n(a)}{n(a+c)}$$

specificity: the probability of a negative test given the infant is not suffering from CHT;

$$P(test^{-}|CHT^{-}) = \frac{n(d)}{n(b+d)}$$

It is obvious that sensitivity and specificity are counteractive qualities: in overlapping distributions, an increase in sensitivity results in a decrease in specificity and vice versa.

In the evaluation of screening, the sensitivity, the specificity and the predictive value of a positive test are considered as the important characteristics of a certain screening method. Of course, the latter can be directly derived from the screening result, but can also be calculated if the sensitivity, the specificity and the screening prevalence is known. Using Bayes theorem of conditional probability (van der Helm and Hische, 1979), the calculation is as

follows:
predictive value of a positive test:

$$P(CHT|test^+) =$$

$$\frac{P(CHT)}{P(test^+)}.P(test^+|CHT) =$$

$$\frac{P(CHT).P(test^+|CHT)}{P(test^+ \text{ and } CHT)+P(test^+ \text{ and } CHT^-)} =$$

$$\frac{P(CHT).P(test^+|CHT)}{P(CHT).P(test^+|CHT)+ (1-P(CHT))\{1-P(test^-|CHT^-)\}} =$$

$$\frac{prevalence.sensitivity}{prevalence.sensitivity + (1-sensitivity)(1-specificity)}$$

It is clear that the predictive value of a positive test depends on the specificity and the sensitivity and on the prevalence, which is illustrated by the following example. Let us assume that both sensitivity and specificity have a value of 0.9. Is the prevalence of the condition sought 10 patients per 100,000 infants screened, then 9 patients will be found per 10,008 positive screening results (the predictive value of a positive test is 0.0009; example A in Table 3.2). Is the prevalence 100 patients per 100,000, it can be calculated that the predictive value increases to 0.0089 (example B in Table 3.2). This makes clear, that with constant values of sensitivity and specificity, both parameters which are determined by the choice of the cut-off point(s), the predictive value of a positive test increases with increasing prevalence.

Table 3.2 Variation of the values in the contingency table caused by variation in prevalence. In the examples, both the sensitivity and the specificity is 0.9

A	diagnosis			B	diagnosis		
screening	+	-	total	screening	+	-	total
+.	9	9,999	10,008	+	90	9,990	10,080
-	1	89,991	89,992	-	10	89,910	89,920
total	10	99,990	100,000	total	100	99,900	100,000

3.2.2 *Methods for screening for CHT*

In screening for CHT, different approaches can be distinguished. The first one uses *clinical parameters*. For example, the search for CHT in infants suffering from icterus prolongatus is a form of selective screening in a high risk group. It is, however, a marginal area between clinical diagnosis and screening and, as far as we know, no research has been done on the validity of this kind of early detec-

tion or other forms of case finding dependent on nonspecific clinical findings. The screening for CHT on the basis of delayed skeletal maturation uses a *radiological parameter*. Serious attempts at solving the problem of early CHT detection have been made in this area. Dacou-Voutetakis (1973) and Taranger et al. (1973) reported screening for the presence of ossification centres in the knee, which are generally absent at birth in children with athyroidism. Of course, this method is applicable only when the infant is born at term and will detect only cases with a delayed skeletal maturation. This aspect is one of the principal objections against this method (Ehrlich and McKendry, 1973).
A more appropriate approach than the use of these parameters which are too nonspecific, is the use of *biochemical methods* in which the present thyroid status of the infant is determined. Methodological differences among the biochemical screening methods are expressed in the following aspects:
a) the parameters measured
b) the age at the screening date
c) the method of sample collection
d) the cut-off points

Screening parameters
The thyroid status is reflected by the level of thyroid hormones, either biologically active or nonactive (such as reverse T3), and by the level of TSH (measurement of TRH is not applicable for diagnostic purposes). Screening methods measuring one or more of these parameters have been developed.
T4 measurement. The first reports on screening for the thyroid function using T4 date from 1975. Development of a microradioimmunoassay had made T4 measurement possible on larger scale (Dussault et al., 1975).
The problems to be expected in T4 screening are firstly the fact that there are other causes of a low T4 value (see Section 2.5.2) and also important is the fact that T4 values within the normal range can be found in CHT patients (Lindstedt et al., 1975; Newborn Committee of the European Thyroid Association, 1979; Walfish et al., 1979; Illig, 1979). This lessens the sensitivity of the method or, if all infants with a T4 value within the low-normal range have to be recalled, the specificity. For this reason, a valuable improvement in the T4 screening is supplementary TSH measurement (see below).
The T4 value is influenced by the length of gestation and, to a minor degree, by the birth weight of the infant (Section 2.1.4). Dussault et al. (1976b) apply a correction factor for birth weight in their program which improves the specificity of the method. Another way to do this is TBG measurement in low T4 values; a normal FTI will be found in infants in whom the low T4 is explained by a low TBG level (Robertson et al., 1980).
T4 in human amniotic fluid does not reliably reflect the thyroid status of the fetus (Sack et al., 1975) and therefore cannot be used as a parameter in selective screening for CHT.
T3 measurement. T3 measurement is not suitable for screening pur-

poses. The values reported in patients with CHT overlap considerably with the normal range, although T3 probably reflects the real thyroid status and the severeness of the hypothyroidism (Klein et al., 1976; Hulse et al., 1979).

TSH measurement. The development of microassays for TSH lagged behind the development of T4 assays. Firstly, serum assays were improved and were tried in cord blood screening (Klein et al., 1974; Zabransky, 1976). Assays on filter paper blood made it possible to use TSH screening on wider scale in combination with PKU screening (Irie and Enomoto, 1975; Illig and Rodriquez de Vera Roda, 1976; Torresani et al., 1976). Enzyme immunoassays were recently developed (Kato et al., 1979) and are experimentally used in CHT screening (Naruse, 1980). Since the TSH values are very high in most cases of CHT and the TSH distribution is skewed to the right in the normal population (Klein et al., 1974), the specificity and the sensitivity of the method is high. Cases of primary CHT in which the neonatal TSH level is normal or only slightly elevated (Dussault et al., 1976a; Delange et al., 1977; Mitchell and Larsen, 1980; Miyahira, 1980) and cases of secondary and tertiary CHT will be missed in a TSH screening.

T4 measurement with supplemental TSH measurement. In many programs, the T4 screening was supplemented by TSH measurements, for several reasons: rapid confirmation of the diagnosis of primary CHT (Dussault et al., 1976c; Farriaux et al., 1979), improvement of the validity of the method by avoiding false-negative results in patients with a T4 in the normal range (Walfish, 1976), confirmation of the significance of an apparently low T4 result (Buist et al., 1975; Mitchell et al., 1978). With this combined method, it is possible to detect all forms of hypothyroidism, including the secondary and tertiary forms. When a program is aimed at detecting these forms as well, the advantage of increased specificity of the method is lost.

Reverse T3 measurement. RT3 is known to be elevated in neonates in comparison to adult values, while low values can be found in CHT (Burger et al., 1976; Klein et al., 1978). Two Italian screening programs used rT3 in addition to TSH or T4 in order to increase the specificity (Newborn Committee of the European Thyroid Association, 1979). Besides the use in screening, a progressive decrease in rT3 in the amniotic fluid is probably an indicator for fetal hypothyroidism (Filetti et al., 1977). Examination of amniotic fluid is applicable, of course, only to selective screening of a high risk group.

Age at screening

In neonatal screening programs, two methods can be distinguished: screening in cord blood and screening in the first days or weeks of life using dried blood on filter paper. Cord blood has the advantage that an ample quantity of blood can be collected. However, in programs where sending of the samples by post is necessary, difficulties will arise.

If screening is performed in the postnatal period, most programs aim for screening at the 3rd to 5th day of life. In this, two problems arise. Postnatal screening in the first week of life means screening in a period of life in which rapid changes in the thyroid function

Table 3.3 Cut-off points used in screening programs for CHT (see also Table 2.4)

screening method	center/ country	T4 cut-off point	TSH cut-off point mIU/l
T4 + TSH	Toulouse	$\bar{x}$ - 2.0 s.d.	25
	Louvain	$\bar{x}$ - 2.0 s.d.	50
	Stockholm	$\bar{x}$ - 2.0 s.d.	30
TSH	Japan	-	25
	Copenhagen	-	25
	Zürich	-	50
	Bern	-	50
	London	-	25
	Lyon	-	40
	Antwerp	-	25
	Osnabrück	-	?
	Angers	-	50
	Reims	-	25
	Caen	-	30
	Heidelberg	-	20
	Oslo	-	50
	Dillenburg	-	20
T4 + TSH (TSH in case of a low T4)	Québec	$\bar{x}$ - 2.6 s.d.*	1 (µIU/40µl)
	New England	4 µg/dl**	20
	Australia	60 - 70 nmol/l***	30 - 50
	Oregon (North West America)	6 µg/dl	25
	Ontario (Toronto)	-	25
	Israël	-	?
	Japan	-	25
T4	Vienna	$\bar{x}$ - 2.0 s.d.	-
TSH (cord)	Berlin	-	50
T4 + TSH (cord; TSH in case of of low T4)	Toronto	-	45

* Standard deviations from the geometric mean of a log-normal distribution.
** Follow-up in case of low T4 only mentioned by Mitchell and Larsen (1980).
*** Two heel punctures are performed. Follow-up if TSH is elevated or if T4 is low twice.

T4 cut-off point (for TSH measurement)	references
-	Rochioccioli and Dutau (1979); Rochioccioli (1980a)
-	Beckers et al. (1977); Delange et al. (1980a)
-	Delange et al. (1980a)
-	Irie (1980)
-	Delange et al. (1980a)
-	Illig et al. (1977); Illig and Torresani (1980)
-	Illig and Torresani (1980)
-	Hulse et al. (1980)
-	David et al. (1978); Delange et al. (1980a)
-	Adriaenssen (1977); Delange et al. (1980a)
-	Delange et al. (1980a)
-	Daver et al. (1978); Delange et al. (1980a)
-	Delange et al. (1980a)
-	Delange et al. (1980a)
-	Klett et al. (1978); Delange et al. (1980a)
-	Lie (1980)
-	Delange et al. (1980a)
$\bar{x}$ - 2.1 s.d.*	Dussault et al. (1978); Dussault et al. (1980d)
6 µg/dl	Mitchell et al. (1978); Mitchell and Larsen (1980)
P10	Connelly et al. (1980)
P3	LaFranchi et al. (1979); Dussault et al. (1980d)
P10 - 15	Walfish (1980)
5 µg/dl	Sack (1980)
?	Irie (1980)
-	Fritzsche et al. (1977); Delange et al. (1980a)
-	Zabransky (1976)
P8 - 10	Walfish et al. (1979); Walfish (1980)

take place (see Section 2.1.4). These changes should be taken into account. A second problem arises if the screening is combined with the PKU screening, which could result in false-negative measurements for PKU when carried out too early (Holtzmann et al., 1974).

Sample collection
Sample collection for screening purposes has to be easy. Of course, collection of cord blood fulfils this criterion and creates the possibility of measurement in serum. Capillary blood is collected by heel puncture, which is a safe procedure if performed correctly (Blumenfeld et al., 1979). The blood is collected on filter paper, in preprinted circles and is air-dried or is collected in tubes.

Cut-off points
The distribution of biochemical values for healthy infants and for CHT patients may be considered as two separate distributions. The distribution found in screening is the sum of these two distributions. The cut-off point for a distribution is the limit of values considered as normal. All values below (in case of T4) or above (in case of TSH) the cut-off point are considered as positive values. Theoretically, the only rational basis on which a cut-off point can be chosen is on grounds of information on both the distribution in patients and the distribution in the normal population. In that case, we can choose an acceptable sensitivity and specificity. Complete knowledge about these distributions is seldom available; therefore, other ways of choosing the cut-off point will have to be found.
For clinical purposes, "normal limits" are often used. In this assumption, a biochemical parameter has a normal distribution; two standard deviations (or more exactly, 1.96 standard deviations) subtracted from or added to the mean represent the normal limits. If the distribution is indeed normal, the values outside these limits will be found in the defined percentage (5%).
However, for most biological variables, the distribution is smooth and unimodal but skewed and the fixed percentage of 95 will not be found within the normal limits (Elveback et al., 1970).
The objective of the choice of the cut-off point is to select a defined part of the population. In smaller series, the most accurate way to do this, is the calculation of percentile values; in larger series, given that the distribution can be considered as normal, standardization of the distribution is permitted (Rümke and Bezemer, 1972 a and b). In methods with a high reliability, the percentile or standardized value chosen can be converted into a fixed value.
In a screening program for CHT, three different cut-off points have to be distinguished:
a) the cut-off point for the T4 distribution
b) the cut-off point for the TSH distribution
c) the cut-off point for the T4 distribution for TSH measurements (in programs where TSH is measured, only when the T4 values fall below a certain cut-off point).

The cut-off points chosen in the programs which were mentioned in Table 2.4 have been summarized in Table 3.3.

4. DESIGN OF THE STUDY IN THE TRIAL AREA

The design of the study in the trial area resulted from the existing PKU screening program developed several years ago within the framework of the health care system in the Netherlands. It seems to be useful to give a brief description of the Dutch health care system as such before going into details of neonatal screening.
The characterization of the health care system requires various explanations concerning institutions, authorities or functions which are well known in the Netherlands but are difficult to translate for the foreign reader. To avoid confusion, brief definitions are given in footnotes, in which the Dutch words are also given.

4.1 *Some information concerning health care in the Netherlands*

The health care system in the Netherlands is probably best described by showing the relation between the various *echelons* into which the system can be subdivided. Doeleman (1980) distinguisghes 5 such echelons: the basic echelon (public health), the first echelon (primary care), the second echelon (out-patient care by specialists), the third echelon (hospital care by specialists) and the long term care (care of chronic illness). We will confine ourselves mainly to child health care.

Public health for children is to a large extent in the hands of the Home Nursing Organizations*. In local sections and supervising provincial organizations and in an overall national organization, they organize the maternity home help and the welfare centers for babies and toddlers. The heel punctures for screening are in many cases performed by health visitors** or nurses employed by a maternity help center. To make use of these services, membership in the organization is obligatory except for the services of screening.
The welfare centers are concerned with preventive health care, including vaccinations and health education for infants and toddlers. School health services organized by municipalities or local authorities provide this service during the school years.
Curative care is not the task of the basic echelon. Most problems of

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* Private bodies for domiciliary care, both preventive and curative. *Kruisverenigingen.*

** Nurse, employed by a Home Nursing Organization, who has both a curative and a preventive task. *Wijkverpleegkundige.*

physical or psychosocial nature which require treatment will be handled within the echelon of primary care by the general practitioner. The specialist is a consulting physician whose help has to be requested by the general practitioner. Care in the second and third echelons will always be provided by a specialist, but in collaboration with the general practitioner. Every specialist is attached to a hospital.

The system depends mainly on private initiative, guided by the three tiers of the government: the municipality, the province and the central government. The municipalities are active in the field of public health. In addition, hospitals which are mostly private organizations, are sometimes municipal services. Provinces are mainly concerned with planning and have a certain degree of authority over the municipalities. The central government agency which is in charge of health care is divided into two bodies: the Department of Public Health and Environmental Protection for controlling, coordinating, financing and planning of health care and the Chief Inspectorate for the State Supervision of Public Health* which is in charge of supervising and advising on health care. The Department works under the responsibility of the minister for Public Health and Environmental Protection and his Parliamentary Secretary.
There are various sources for finances. Curative care is mainly paid for by health insurance. Practically all households are insured, either compulsory - if the wage is below a certain threshold - or privately. Several social funds are available in case of excessive expenses not provided for by insurance. Government subsidies legislated by various acts are other important funds. For example, the laboratory and administrative parts of the neonatal screening are financed by the Act for Exceptional Sickness Expenses**. The Home Nursing Organization recently also came under the heading of this act, although a contribution by the individual remains obligatory for most services.

4.2 *Neonatal screening for PKU in the Netherlands*

The existence of a well-functioning neonatal screening program for phenylketonuria (PKU) was the starting point for CHT screening. The PKU screening was instituted in 1974 (Landelijke Begeleidingscommissie Phenylketonurie, 1978) after six years of study in a pretest area (Haverkamp Begemann, 1974). The organization is directed by the provincial Home Nursing Organizations; on the national level, the screening is organized by the national Home Nursing Organization and

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* *Hoofdinspectie van het Staatstoezicht op de Volksgezondheid.*
** Collective form of health insurance. *Algemene Wet Bijzondere Ziektekosten.*

the State Institute for Public Health* (which is particularly in charge of the laboratory part) and is supervised by the Chief Inspectorate of the State Supervision of Public Health. The screening tests are performed in 17 Regional Laboratories for Public Health** and in the State Institute for Public Health.
The test used is the Guthrie test; the blood is collected by heel puncture on filter paper, preferably in the second week of life. The heel puncture is performed at home in about 63% of the cases; in the Netherlands, about 40% of the children are born at home (Centraal Bureau voor de Statistiek, 1979). The puncture itself is carried out by a variety of persons: the health visitor (27%), the midwife (12%), the general practitioner (9%), an employee of a maternity nursing center (15%) or an employee of the hospital (37%) if the child is an inpatient (Landelijke Begeleidingscommissie Phenylketonurie, 1978). Testing of newborns for PKU is not compulsory, although the government provides by law for the funds to screen. There is an extensive check system in order to ensure good compliance. Until 1980, financing of the screening was a complex affair. The screening tests and the test materials were paid for under the Act for Exceptional Sickness Expenses. The Home Nursing Organizations were paid by different funds: membership payments (membership in the organization is not obligatory for the PKU screening), subsidies by the state, province or municipality and private foundations. Since the first of January 1980, the Act for Exceptional Sickness Expenses has also provided the funds for the Home Nursing Organizations. The performance of the heel puncture by others than employees of the Home Nursing Organizations is part of the normal child health care; no additional fee can be charged.

In 1975, the Parliamentary Secretary for Health and Environmental Protection asked the Health Council*** for advice on the need for extension of the PKU screening with screening for other genetic diseases or sporadic diseases. The Council investigated the possibilities existing within the framework of the PKU screening. In 1979, the Council gave positive advice (Gezondheidsraad, 1980).
The Dutch Pediatric Association established a National Steering Committee for CHT (Appendix 1), in which all persons and institutions involved in the neonatal screening program were represented. This committee recommended the institution of a screening program in a defined trial area under the supervision of a local Working Party (Appendix 1).
The most important reason for combining the CHT screening with the PKU screening was the increase in efficiency of the PKU screening, while the time of performance and the sample seemed appropriate for CHT screening. Moreover, there was the advantage of a functioning

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* Government laboratory and research institute. *Rijksinstituut voor de Volksgezondheid.*

** *Regionaal Laboratorium voor de Volksgezondheid (streeklaboratorium).*

*** Advisory board for the Minister and State Secretary. *Gezondheidsraad.*

organization and a good acceptance of the screening by the population, which was reflected by the coverage of more than 99% of the infants by screening.

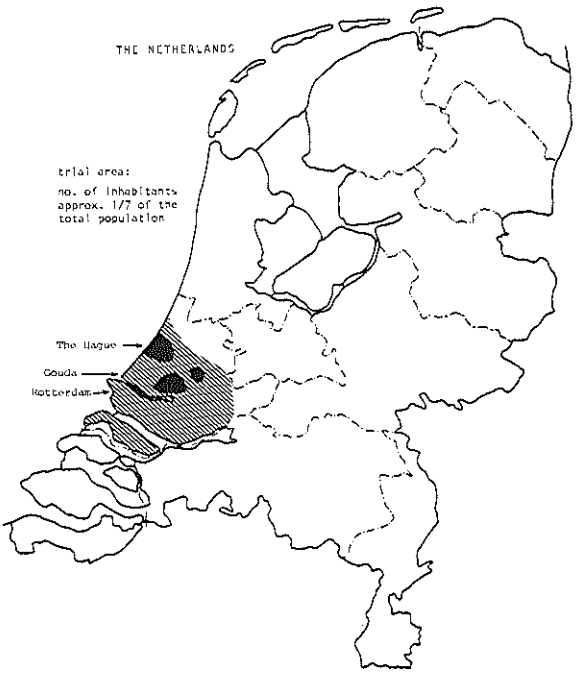
4.3 *The trial area*

A few demands had to be made concerning the pretest area:
a) geographical conformity with one or more regions served by the Regional Laboratories for Public Health should exist because of the organizational unity within such an area;
b) the incidence of CHT should not be lower than that in other regions (according to the incidence study; De Jonge, 1977);
c) laboratory facilities for screening for CHT should be available, with respect to both qualitative and quantitative aspects;
d) close cooperation between the future CHT laboratory and the Regional Laboratories for Public Health had to be possible; the Regional Laboratories are mostly microbiological/serological laboratories in which radioimmunoassays cannot be carried out. For this reason, it is seldom possible to provide for both the PKU and the CHT screening in one laboratory;
e) good relations had to exist within the area between the pediatricians connected with the local hospitals and one or more hospitals with pediatric endocrinologists.

Other supporting arguments were of an arbitrary nature. The final choice was the southern part of the province of Zuid-Holland (see Fig. 4.1). The number of births in this area is about 30,000 per year. The screening was introduced into the area in three successive phases. On the first of May 1978, screening began in the area of the Regional Laboratory in Rotterdam, on the first of September 1978, in the PKU Laboratory of Gouda (a division of the Regional Laboratory in Dordrecht) and, finally, on the first of June 1979, in the area of the Regional Laboratory in The Hague. The CHT tests were carried out in the Endocrinological Laboratory of the Bergweg Hospital (Dr. W. Schopman) in Rotterdam.

The Rotterdam Working Party made preparations for the screening in the trial area. These consisted of the following:
a) laboratory studies in the endocrinological laboratory of the Bergweg Hospital in Rotterdam in order to develop microradioimmunoassays for blood eluted from filter paper spots;
b) preparation of a protocol for all organizations involved (Nederlands Instituut voor Praeventieve Geneeskunde/TNO, 1977);
c) preparation of a protocol for follow-up investigations and therapy (Appendix II), intended for the participating pediatricians;
d) instructional meetings and preparation of information booklets for all performers of the heel puncture and for those members of the medical profession who are concerned with neonatal health care;
e) preparation of an information brochure for parents for distri-

Figure 4.1 Trial area



bution at the time of registration of the birth of a child.

The project was planned for a duration of two years, from the first of May 1978. In fact, the project continued until the institution of the nation-wide screening at the first of January, 1981. Subsidy was provided by the Prevention Fund*.

4.4 *Organization*

4.4.1 *Organization scheme*

The organization of the CHT screening followed that of the existing organization for screening for PKU in the province of Zuid-Holland and in Rotterdam. The main points are summarized below (see also Scheme 4.1).

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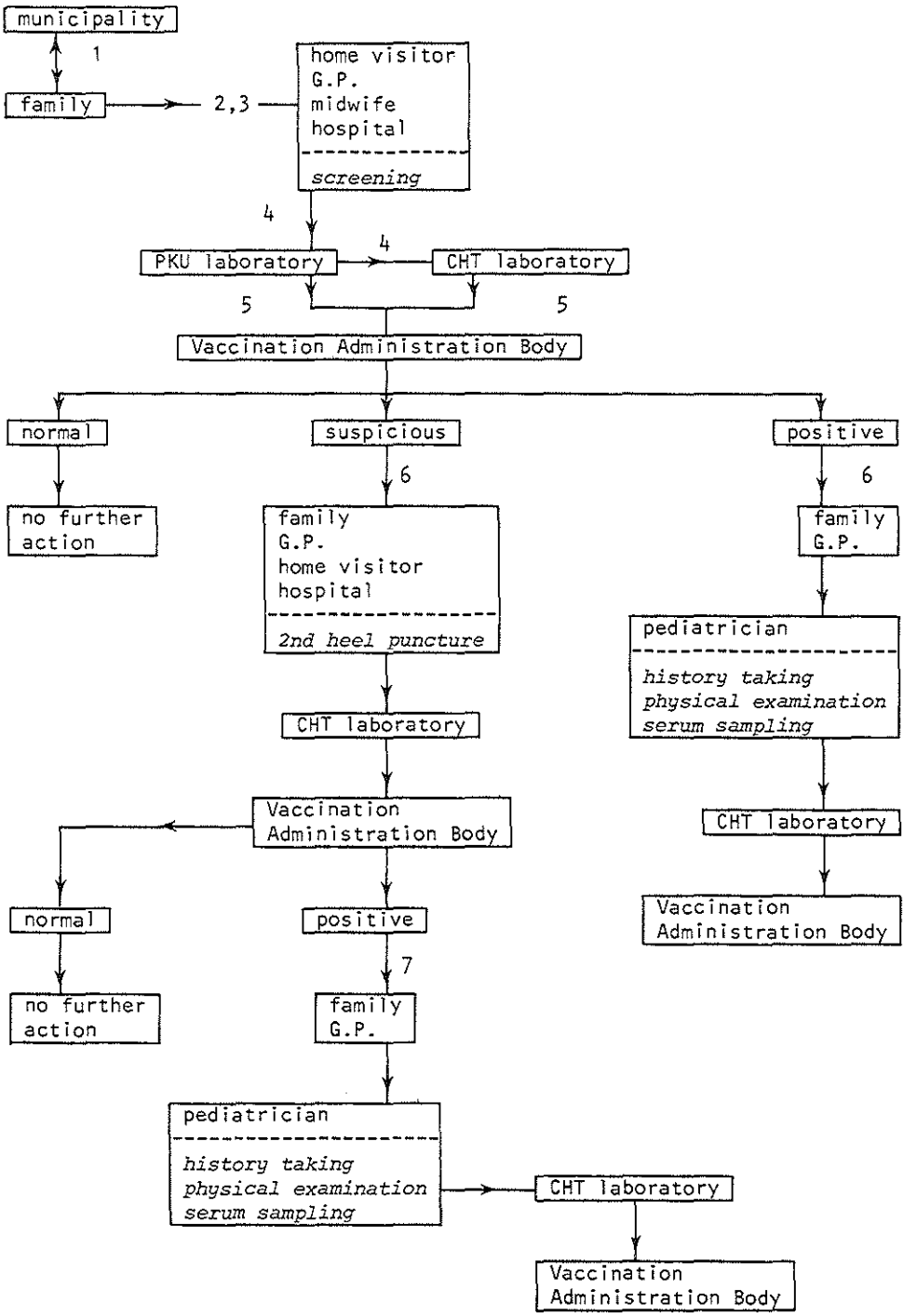
* A fund instituted by law for the stimulation of research in the field of preventive health care. *Praeventiefonds*.

Scheme 4.1 Scheme of the screening program
(the numbers refer to the points discussed in section 4.4.1)



1. The births were registered by the parents at the municipal administration in the municipality where the child was born; this is obligatory by law. At the time of registration, the parents received an information brochure on the screening and received the PKU/CHT test set. The test set consisted of a filter paper and materials needed for the heel puncture, a reply envelope and forwarding the blood and a triplicate application form, all included in a covering envelope to be kept by the parents afterwards as evidence of the performance of the heel puncture.
   The covering envelope, filter paper and application form were numbered with a code which indicated the PKU laboratory concerned and served as a serial number. In most cases, this code was known at the municipal administration as well, in order to be able to trace incomplete forms.
2. The heel puncture was to be performed preferably at the age of 6, 7 or 8 days. If this proved to be impossible for the performer of the heel puncture, it was advised that it be performed in any case before the end of the second week.
   The Guthrie test for PKU can result in false-negative values when measurements are made in blood collected within the first days of life (Holtzmann et al., 1974). A safe margin of a minimum of 120 hours after delivery was recommended.
3. The heel punctures were performed by either the general practitioners, the midwives, the health visitors or by an employee of the hospital. The parents themselves had to notify one of these persons, which was facilitated by the fact that the health visitors routinely visited the parents.
4. The routing of the filter paper was as follows: the performer of the heel puncture forwarded the filter paper and application form to the PKU laboratory. There, the two blood spots which were the best filled and the appropriate part of the application form were forwarded to the CHT laboratory by express delivery or by a messenger.
5. The screening results were handled in the Vaccination Administration Body* (supervised by the Provincial Pediatrician** of the provincial Home Nursing Organization or, if the child was born in Rotterdam, in the Vaccination Administration Body in Rotterdam (supervised by a physician of the Municipal Health Service).
   The birth registration forms received from the municipalities were compared with the forms of the screening results. If no result was received, an enquiry was sent to either the general practitioner and the parents or to the home visitor.

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* Provincial administration body for vaccination and screening results, responsible to the Provincial Pediatrician (see next footnote; Amsterdam and Rotterdam have their own Vaccination Administration Bodies, responsible to a physician of the municipal Public Health Service *(Gemeentelijke Geneeskundige en Gezondheidsdienst). Entadministratie.*

** Physician, employed by the provincial Home Nursing Organization, in charge of the preventive health care for infants. *Provinciaal kinderarts.*

A second examination was carried out either by a pediatrician or, if only a second heel puncture had to be performed, by the general practitioner, health visitor or employee of the hospital. The general practitioner was informed about the need for a second examination by the provincial pediatrician or by the physician of the Municipal Health Service (in Rotterdam).
In the first period of the screening, the parents were directly informed. In a later period, they were informed by the general practitioner in case of a referral to a pediatrician, or by letter from the Vaccination Administration Body, in case of a second heel puncture.

7. If the second heelpuncture revealed abnormal values, the infant had to be referred to a pediatrician.

4.4.2 *Follow-up*

From May 1978 to April 1979, inclusive, every infant whose screening result was considered abnormal was *referred to a pediatrician*, preferably within 24 hours. After that period, a second heel puncture was considered to be sufficient in most cases with an abnormal result; depending on the values found, only a small percentage was referred to a pediatrician.
All pediatricians working in hospitals within the trial area or in near adjacent areas were participants in the project (Appendix III). The total number of hospitals amounted to 31 including two children's hospitals (one of these is part of the University Hospital of Rotterdam).
The pediatricians examined the infants referred according to a protocol for history taking and physical examination and for laboratory examinations (Appendix II) which was drawn up by members of the National Steering Committee and the Rotterdam Working Party. The laboratory examinations had to be preferably carried out in the CHT laboratory, in order to be able to compare the follow-up result with the screening result and to compare the follow-up results with each other.
The general practitioner who was to make referral to a specialist was informed by the Provincial Pediatrician or the physician of the Municipal Health Service (Rotterdam). The CHT laboratory forwarded the results of the follow-up to the Vaccination Administration Bodies; when no results were received, an inquiry was sent to the general practitioner. When CHT was diagnosed, therapy following a recommended protocol (Appendix II) was advised.
The pediatricians forwarded their findings of history taking and physical examination to the Netherlands Institute for Preventive Health Care.

The possibility to perform a *second heel puncture* was introduced to the screening procedure in May 1979; the decision to do a second heel puncture instead of referring the child to a pediatrician depended on the values found (see Scheme 4.2).
The general practitioner was informed about the abnormal screening

result and a repeat PKU/CHT set was forwarded to the parents or the health visitor. A normal result on this second examination was reported to the parents; abnormal results led to a referral to a pediatrician.

4.5 *Laboratory methods*

The screening test chosen consisted of measurements of T4 in all blood samples; TSH was measured in the same blood sample if the T4 value was among the lowest 20% of values for the series of that day. In the beginning of the screening (from May 1978 to October 1978, inclusive), TSH was measured if the T4 value was among the 10% lowest values; this percentage was raised because of the fact that the T4 value of the first patient found by screening was only slightly below the 10th percentile.
The T4 assay was performed 5 days a week, the TSH assay twice a week. All measurements were performed in the Endocrinological Laboratory of the Bergweg Hospital in Rotterdam (Dr. W. Schopman). Heel puncture blood was collected on filter paper (Sleicher and Schultz 2992). Two nearly circular spots with an inside diameter of about 9 mm were available for the CHT screening.
For the *T4 measurement* a 3 mm punch was taken from each spot; each punch contained a mean quantity of approximately 1 µl of serum (see Section 5.3). T4 was assayed by a radioimmunological method in duplicate (one measurement in the eluate of each of the two punches). The antiserum used was non-commercial*. The assay variation is given in Section 5.3. For a more detailed description of the laboratory method, see Schopman (1979).
Because of the variation in the amount of serum in the filter paper spots, the values were expressed per punch and not per liter of serum. To avoid the variation which results from the between-assay variations, the daily distributions were standardized; the values were also expressed by number of standard deviations from the daily mean.
For the *TSH measurement* in duplicate, punches around the original punches were taken. The outside diameter was 6.5 mm. The values were expressed in µIU/punch; 0.10 µIU/punch is equivalent to about 25 mIU/l. TSH was determined by radioimmunoassay in a double antibody system adapted from the method of Sluiter et al. (1972), with a lower detection limit of 0.02 µIU/punch. For the calibration curves, Medical Research Council standards (68/38) were used. The assay variation is given in Section 5.4.

The *cut-off points* of both the T4 and TSH distributions were changed during the trial period as well as the indications for a referral to a pediatrician and for a second heel puncture (see Scheme 4.2).

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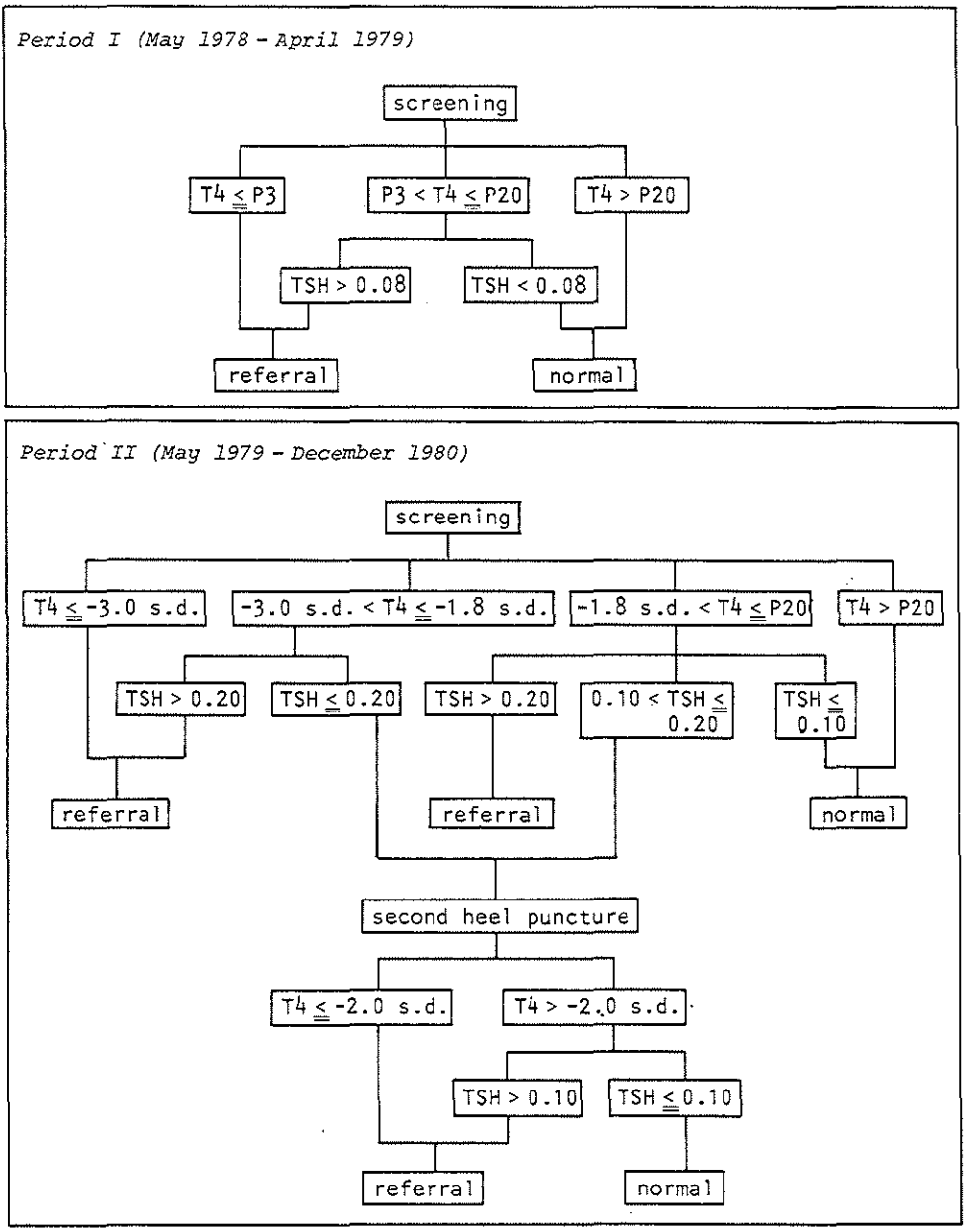
* Made by A.P.M. Schellekens, University Hospital Wilhelmina Gasthuis, Amsterdam

Scheme 4.2 Flow sheat for screening and follow-up*



* The T4 value is expressed in either percentiles or number of standard-deviations from the daily mean; the TSH value is expressed in µIU/punch.

In fact, in the beginning of period II, a TSH level between 0.11 and 0.20 µIU/punch was also an indication for referral. In practice, a second heel puncture was nearly always recommended.
Although a cut-off point based on percentile values is more appropriate theoretically, this practice was discontinued. In T4 screening, a cut-off point based on percentile values introduces too many sources of inaccuracy. Firstly, the number of infants had to be rounded off upwards every day. For example, if the daily series consisted of a number of 80 samples, 3 percent would be 2.4 infants. Rounding off the next higher number means selection of 3 infants or 3.8% of 80 infants, which is higher than the percentage chosen. Secondly, there is the influence of the physiologically low T4 levels found in preterm infants. Incidental screening of three or four preterm babies having a low T4 in a series of about 100 measurements could together constitute the lower third percentile. This would mean a considerable reduction in the chance to be selected because of a low T4 in full term infants. The influence on the mean and standard deviation, although certainly existing, is less far-reaching.
The indications for a follow-up examination on the basis of the result of a *second heel puncture* were the following: pediatric examination if the T4 value was lower than or equal to $\bar{x}$ - 2.0 s.d. and/or the TSH value was higher than 0.10 µIU/punch. Results with a T4 value higher than $\bar{x}$ - 2.0 s.d. and a TSH value lower than or equal to 0.10 µIU/punch were considered as normal.

Serum measurements of T4, T3, the unbound TBG binding sites and TSH were performed in the Bergweg Hospital in most of the cases.
To approximate the TBG level, the unbound TBG binding sites were saturated with I^{125}-T3 (TBG-test); bound and free I^{125}-T3 were separated by a method using anti T3 antiserum. The values of the TBG test were expressed as the reciprocal of the free I^{125}-T3 fraction and were normalized (the mean of the normal population is 100%). The FTI was calculated as follows: 100 x T4/TBG test.
For the T4 and T3 measurements and the TBG test, an automated cauted tube technique was used (Micromedic Systems, Autopak reagents). The method of Sluiter et al. (1972) using rabbit TSH antibodies was adapted for the TSH measurement.

5. RESULTS OF THE SCREENING IN THE TRIAL AREA

In this chapter, the results of the screening in the trial area will be outlined. The first part (Section 5.1 - 5.4) will be focused on the screening test as such and on several factors which influence the results of the test. The second part (Section 5.5 - 5.11) is a description of the general functioning of the screening program such as participation in it, the performance of follow-up, the time course of the different steps in the screening procedure and the results of the follow-up examinations.
The findings in the patients will be described in a separate chapter (Ch. 7) as well as the calculations and considerations on the validity of the procedure (Ch. 6).

The results described in this chapter concern infants screened in the trial area and born during the months May 1978 to February 1980, inclusive. Data were collected on both screening results and follow-up examinations; if the infant was referred to a pediatrician, information on clinical history and physical examination was requested. The group in which a second examination was required after screening (either a second heel puncture or a referral to a pediatrician) is called the *group selected by screening*. In this text, the word "screening" is reserved for the first heel puncture.
Information on the total population of newborns was required for several purposes. A sample of all infants born in the trial area during the first two weeks of March 1980 was taken; in the following text, this sample (consisting of 1136 infants) will be referred to as the *sample of the total population*.
During the course of the trial period, the indications for follow-up were changed (see Scheme 4.2): the limit of normal of the TSH level was raised from 0.09 µIU/punch to 0.10 µIU/punch and the T4 cut-off point was changed from the 3rd percentile to values equal to the mean minus 1.8 standard deviation. The first situation will be referred to as *period I* and the second as *period II*.
The values found in heel puncture blood will be expressed in the following way: T4 is expressed either in a percentile (P) or in number of standard deviations from the mean (s.d.); both values were calculated from the daily T4 distribution. TSH is expressed in µIU/punch (0.10 µIU/punch approximates 25 mIU/l of serum). Values measured in serum have been expressed in nmol/l for T4 and T3, in mIU/l for TSH and in % for the TBG test.

5.1 *Number of infants screened*

During the months of May 1978 to February 1980, inclusive, 43,554 infants were screened in the trial area. This represents about 99.3% of the total number of newborns. It was stated in Chapter 4 that the number of newborns in the trial area amounted to 30,000 per year. Since the screening program did not start at the same time in the three different regions which together make up the trial area, the total of 43,554 infants is slightly less than the numer which would be expected from the birth rate in the entire trial area.

5.2 *Screening values of T4 and TSH*

The T4 and TSH values found up to February 1980 are summarized in Table 5.1 (period I) and Table 5.2 (period II).
During period I, 633 blood samples were considered to have a positive screening result, which is 3.6% of the number of infants screened. A T4 value below the third percentile was found in 3.5%. This percentage is higher than the percentage of 3 that would be expected, which is the result of the daily rounding off to the next higher number of selected infants (Section 4.5). The number of infants showing a positive screening result because of an elevated TSH level represents only a small percentage: 53 of 633 (8.4%). In the remaining 91.6%, a follow-up was requested because of a low T4 level but a

Table 5.1 Screening values of T4 and TSH (period I); positive screening results in *italics*

	TSH (µIU/punch)				
T4 (P)	≤ 0.08	> 0.08	not known	not measured	total (%)
≤ P3	*542*	*40*	*37**	-	619 (3.5)
P4 - P10**	2,760	*13*	154*	-	2,927 (16.5)
> P10	-	-	-	14,190	14,190 (80.0)
not known	-	-	*1****	-	1 (0.0)
total (%)	3,302 (18.6)	53 (0.3)	192 (1.1)	14,190 (80.0)	17,737 (100.0)

* Missing values concern blood samples in which a laboratory error was made (one series of 191 TSH measurements).
** During period I, the T4 cut-off point for TSH measurement was raised from the 10th percentile to the 20th percentile. This is not indicated in the table.
*** No elution of blood was possible; neither T4 nor TSH could be measured.

Table 5.2 Screening values of T4 and TSH (period II); positive screening results in *italics*

T4 (s.d.; P)	TSH (μIU/punch) ≤0.10	0.11-0.20	>0.20	not known*	not measured	total (%)
≤(-3.0)	*70*	*2*	*10*	*2*	-	84 (0.3)
(-2.9) - (-1.8)	*610*	*20*	*1*	*23*	-	654 (2.5)
(-1.7) - P20**	4,658	*31*	*8*	64	-	4,761 (18.4)
>P20	-	-	-	-	20,318	20,318 (78.7)
total (%)	5,338 (20.7)	53 (0.2)	19 (0.1)	89 (0.3)	20,318 (78.7)	25,817 (100.0)

* Missing values concern blood samples in which a laboratory error occurred (one series of 89 measurements).

** The number of values below or equal to the 20th percentile amounts to more than 20% of the total number of infants screened. This is due to daily upwards rounding off of the 20th percentile (comparable to the rounding off of the 3rd percentile during period I, see Section 4.5).

normal TSH level.
During period II, the screening results were considered to be positive in 777 cases (italics in Table 5.2). In another 10 infants, follow-up was requested: two daily series of T4 measurements contained no values below or equal to the cut-off point of $\bar{x}$ - 1.8 s.d.; in these cases, 6 infants with the lowest 3% of the values were selected for follow-up. After that, this practice was discontinued. Another 4 infants were selected whose T4 values were just above the T4 cut-off point, but whose TSH value was unknown. Thus, the group selected by screening during period II consisted of 787 infants. T4 values below the cut-off point were found in 2.5%. In 9.1% of the group selected by screening during this period, the infant was selected because of an elevated TSH (72 infants out of 787).

5.3 *T4 measurement*

Figure 5.1 shows the frequency distribution of the T4 values determined from the first of June 1978 to the 31st of August 1980, inclusive*. The values of May 1978 were not included because, at that time, the laboratory method differed slightly from the methods used from June 1978. In addition, 483 values of which the mean differed

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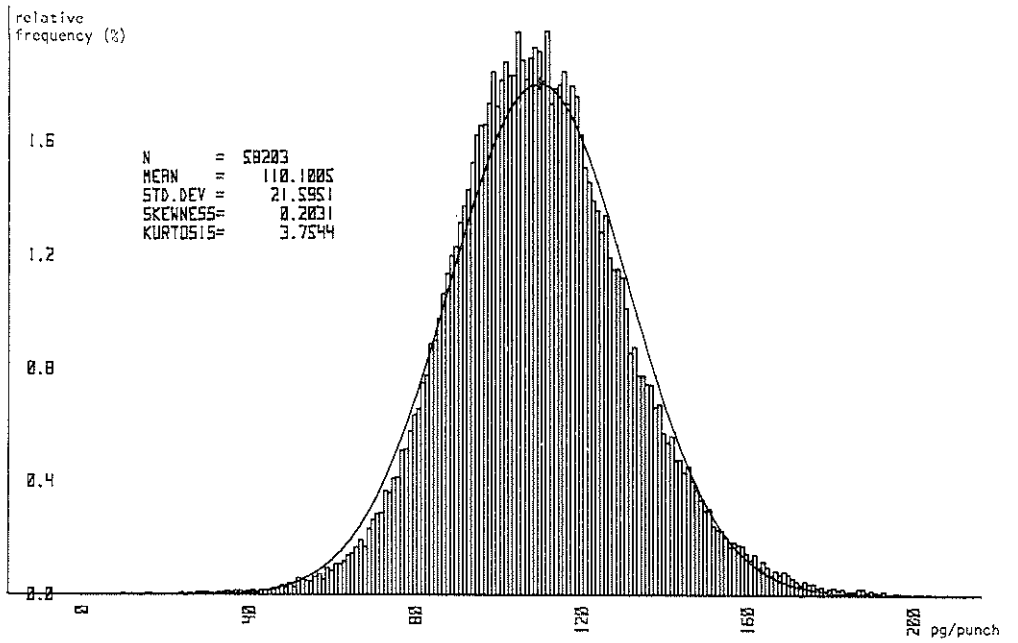
* Since, in the following chapters, results will be presented to August 1980, inclusive, the distribution till this date was given.

Figure 5.1 T4 distribution in the total population of infants screened (1st of June 1979 - 31st August 1980)



by more than 3 standard deviations from the distribution of daily means were excluded from the series; such a deviation was found in six series. Figure 5.2 shows a distribution of a daily series. The variation of both distributions could be due to various factors: (1) the biological variation of T4 within the neonatal population; (2) the assay variation; (3) the variation caused by the variable amount of blood collected on filter paper and the variation in spread of blood on the filter paper*; (4) environmental influences - such as a decline in hormone level by prolonged storage; (5) the random variation in a small daily sample; (6) seasonal influences. For several of these, it was possible to determine more quantitatively the extent of the variation.

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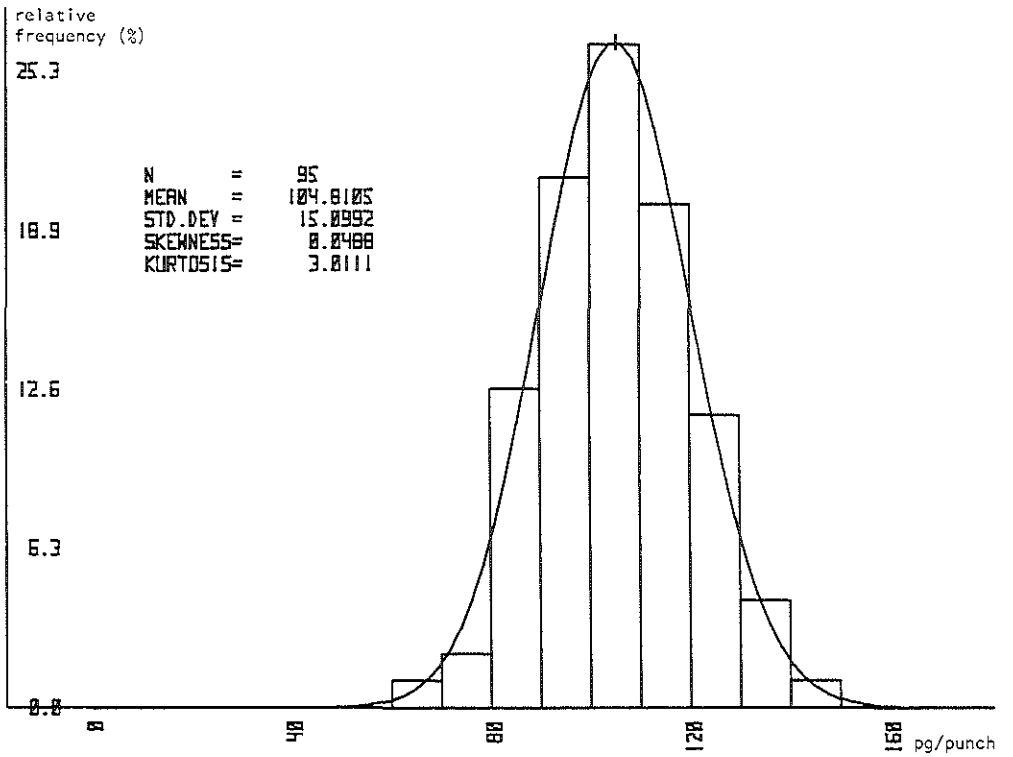
* Schopman, 1979.

Figure 5.2 T4 distribution in a daily series



Assay variation
The within-assay and between-assay variation* in the T4 heel puncture assay was below a variation coefficient of 10%. Four control samples were measured in each daily series. In Figure 5.3, the assay variation for one of the control samples is shown, measured on 31 successive days. The T4 level in this control sample is near the cut-off point.

Amount of serum per filter paper punch
To determine the variation in amount of serum per filter paper punch, in the beginning of the screening period, the pediatricians who examined the infants as a follow-up because of a positive screening

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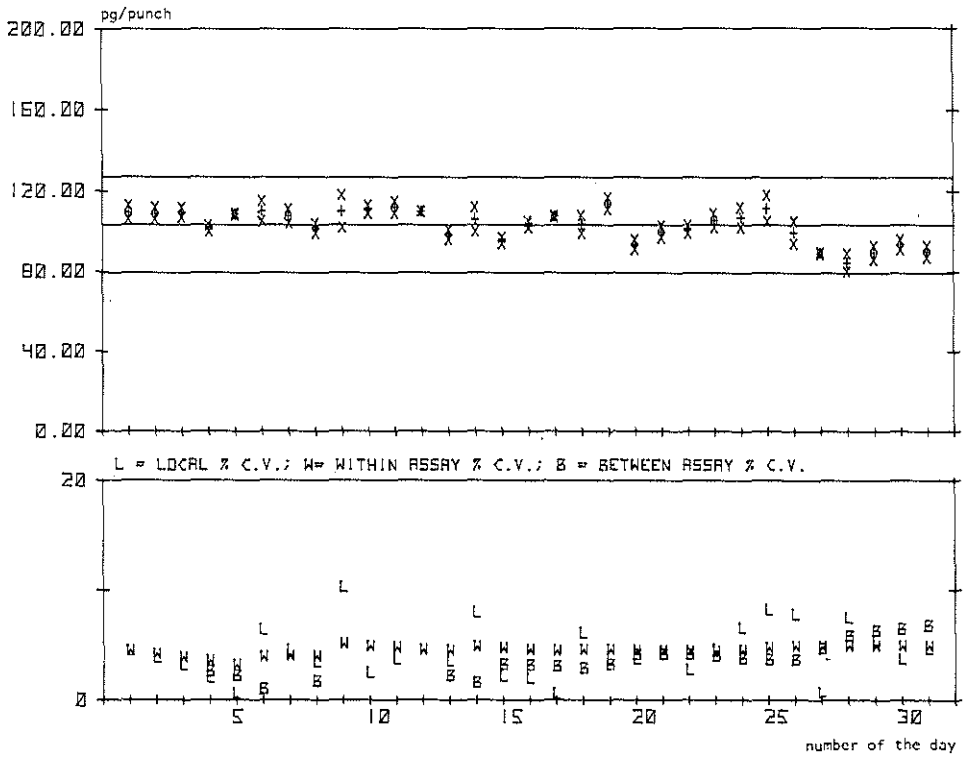
* Within variation: variation between values measured in control samples (which contain the same level of T4) in a single series. Fig. 5.3 the within variation (W) is expressed as the daily calculated mean of the local variation (L), which is the variation between duplicate measurements in one control sample. Between variation: variation between values measured in control samples in different series.

Figure 5.3 Assay variation of the T4 measurement (31 series)*



* Calculations following Cernosek and Gutierrez-Cernosek (1978).

result were asked to collect simultaneously serum and heel puncture blood. Venepunctures and heel punctures are not always performed by the same person and at the same time in an inpatient department. For this reason, only the results are presented which were derived from blood collected in an outpatient department, to ensure that the time between serum sampling and heel puncture varied as little as possible.
The mean amount of serum per punch amounted to 0.92 µl (s.d. = 0.30), computed from each of the 180 pairs of serum and heel puncture assays. The spread around the mean is influenced by the assay variation in both of the serum measurements and heel puncture blood measurements. If these were the only source of variability, a standard deviation of 0.10 could be expected*.

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* The expected s.d. is computed by using a variation coefficient of 10% for the filter paper assay and of 6% for the serum assay. Calculations following Mood et al., 1974.

Correlation between serum and heel puncture measurement
The correlation coefficient of the T4 values measured in control samples consisting of blood on filter paper and the T4 values measured in serum known to contain the same T4 concentration, is 0.99 after excluding the assay variation in both measurements*.
In practice, in the comparison of values measured in serum simultaneously collected with capillary blood on filter paper, the correlation coefficient is influenced not only by the variations of the assay but as well by differences between serum T4 and capillary T4 and by differences in the amount of serum on the filter paper samples. The correlation coefficient in 180 simultaneously collected samples under these practical circumstances is 0.49 (Figure 5.4), and is 0.57 for the standardized values, both highly significant. The orthogonal regression equation is T4 (nmol/l) = 1.55 T4 (pg/punch) - 11.65.

Storage of the samples
Storage and transport of the filter paper samples could influence the T4 level; this hypothesis was supported by the fact that the time lapse between screening and T4 measurement was significantly longer in the group selected by screening (which is mainly characterized by low T4 levels) than in the sample of the total population (Table 5.3). This probably means that, in a percentage of the group selected by the screening, the low T4 value is explained by the long time lapse between screening and T4 measurement. Another experience was that

Table 5.3 Comparison of time lapse between screening and T4 measurement between the group selected by the screening and the sample of the total population

time lapse between screening and T4 measurement (days)	group selected by the screening		sample of the total population	
	n	cum.%	n	cum.%
≤ 2	367	28.6	319	30.6
3 - 4	455	64.2	396	68.6
5 - 6	293	87.0	266	94.1
7 - 8	95	94.5	36	97.6
> 8	71	100.0	25	100.0
total	1281		1042	
not known	139		94	

($\chi^2 = 33.13$; df = 5; $p < 0.001$)

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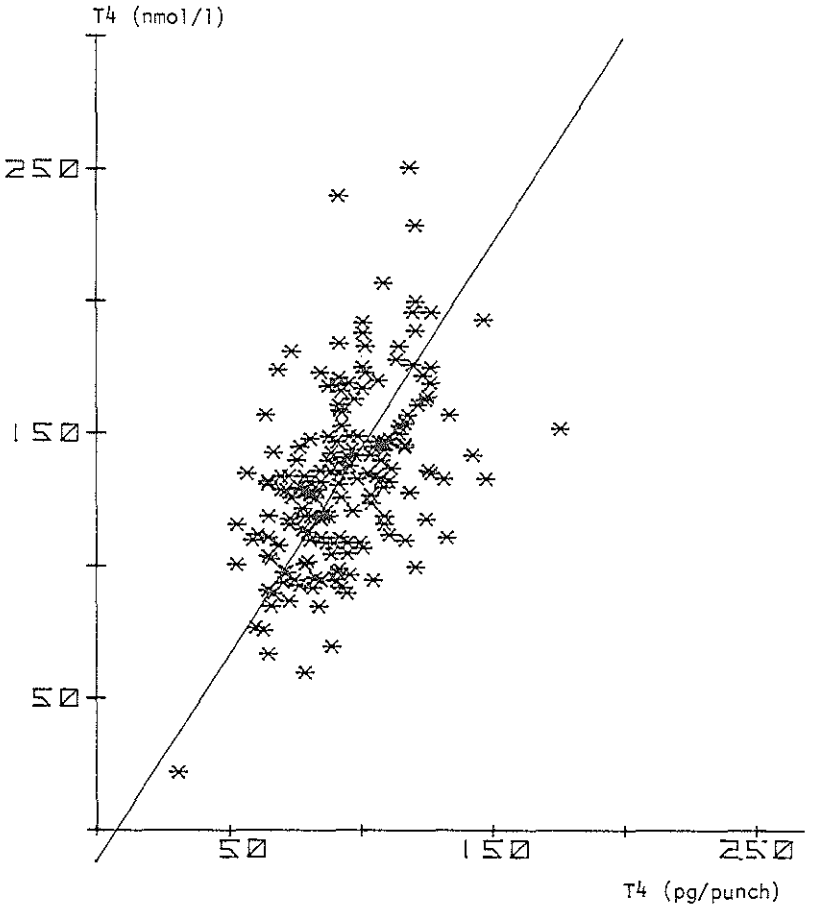
* Schopman, 1979.

Figure 5.4 Correlation between T4 measured in serum (nmol/l) and T4 measured in simultaneously collected heel puncture blood (pg/punch)



several infants in whom this time lapse was very long had very low T4 levels.
However, the correlation between the T4 level and the time lapse was not significant within the sample of the total population ($r = -0.04$; $p > 0.05$).

Biological variation
Length of gestation and birth weight. Data on the association between T4 and length of gestation and between T4 and birth weight were derived from the sample of the total population. The performers of the heel punctures were asked to mention birth weight and length of gestation on the PKU/CHT application forms, which was done for approximately 62% of the infants.
The positive association between gestational age and T4 and between

birth weight and T4 is clear. The correlation coefficient between gestational age and T4 is 0.26, and that between birth weight and T4 is 0.29, both highly significant. The latter - the correlation between birth weight and T4 - cannot be completely explained by lower birth weights in shorter gestational ages. A partial correlation coefficient between birth weight and T4 controlled for gestational age is also positive ($r = 0.19$; $p < 0.001$). The existing correlation means that a relatively high percentage of preterm and small-for-dates infants will be selected in a T4 screening program.

Age at screening. The group selected by screening was screened significantly later than the sample of the total population (Table 5.4). This is probably explained by the fact that preterm infants appear to be screened at an older age than full term infants; in several hospitals preterm infants are usually screened in the third week of life instead of in the second week of life, in order to reduce the chance for a false-negative PKU test.

There was no significant correlation between T4 and age at screening in the age range in which our screening program is performed, if controlled for gestational age ($r = -0.01$; $p > 0.05$).

Sex of the infants. Another source of biological variation seemed to be the sex of the infants. In the group selected by the screening (and thus mainly consisting of infants with low T4 levels), 58.2% of the infants were boys and 41.8% were girls.

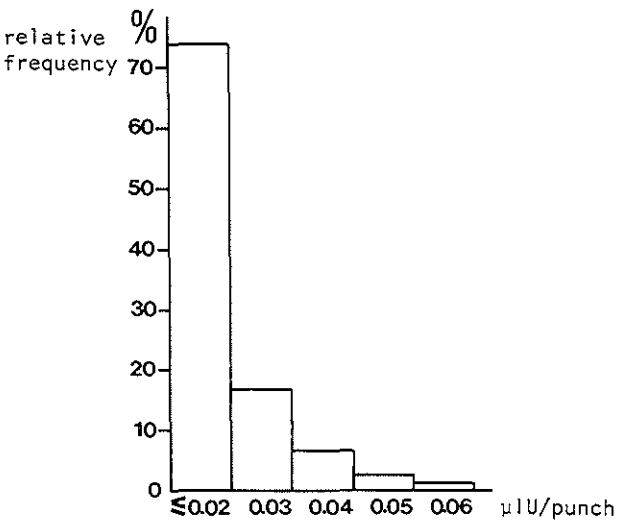
Table 5.4 Comparison of age at screening between the group selected by screening and the total population

age at screening (days)	group selected by screening		sample of the total population	
	n	cum.%	n	cum.%
< 6	9	0.7	7	0.7
6 - 8	572	45.4	648	61.5
9 - 11	379	74.9	335	93.0
12 - 14	176	88.7	45	97.2
15 - 20	85	95.3	17	98.8
> 20	60	100.0	13	100.0
total	1281		1065	
not known	139		71	

($\chi^2 = 142.26$; $df = 6$; $p < 0.001$)

The distribution of TSH values is shown in Figure 5.5. The *assay variation* as determined in 48 subsequent series in a control sample is presented in Figure 5.6. The within-assay variation coefficient is about 11%; the between-assay variation coefficient is about 18%.

Figure 5.5 Distribution of TSH in the sample of the total population (n = 224)*



* At the time the sample of the population was taken, TSH was assessed if the T4 values were below $\bar{x}$ -0.84 s.d., instead of below the 20th percentile. For this reason, the number of measurements is less than 20% (19.7%; 224 infants out of 1136).

To determine the TSH level a new punch is taken with an outside diameter of 6.5 mm around the original punch of 3 mm in which T4 is measured considering the surfaces of both discs of filter paper, the *amount of serum* available for TSH measurement can be calculated. The mean quantity should be 3.7 times as high as the mean amount of serum in the "T4 punch" (0.92 µl) or 3.4 µl. The calculated amount of 3.4 µl is, however, a slight underestimation of the real amount of serum, because of the unequal spread of serum along the surface of the filter paper*. For this reason, the actual amount of serum is approximately 17% higher, or 4.0 µl.

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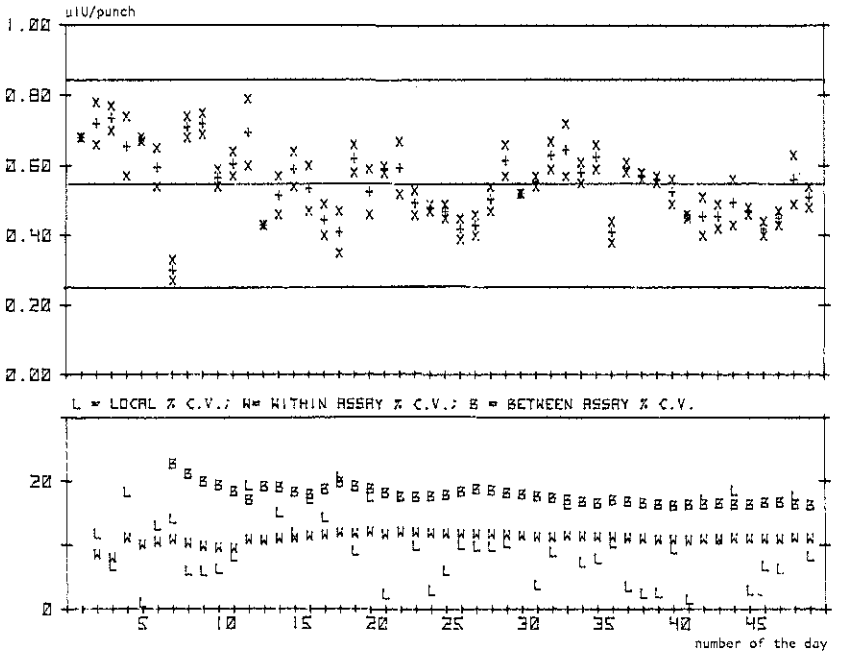
* Schopman, 1979.

Figure 5.6 Assay variation of the TSH measurement (a series of 48 control samples)*



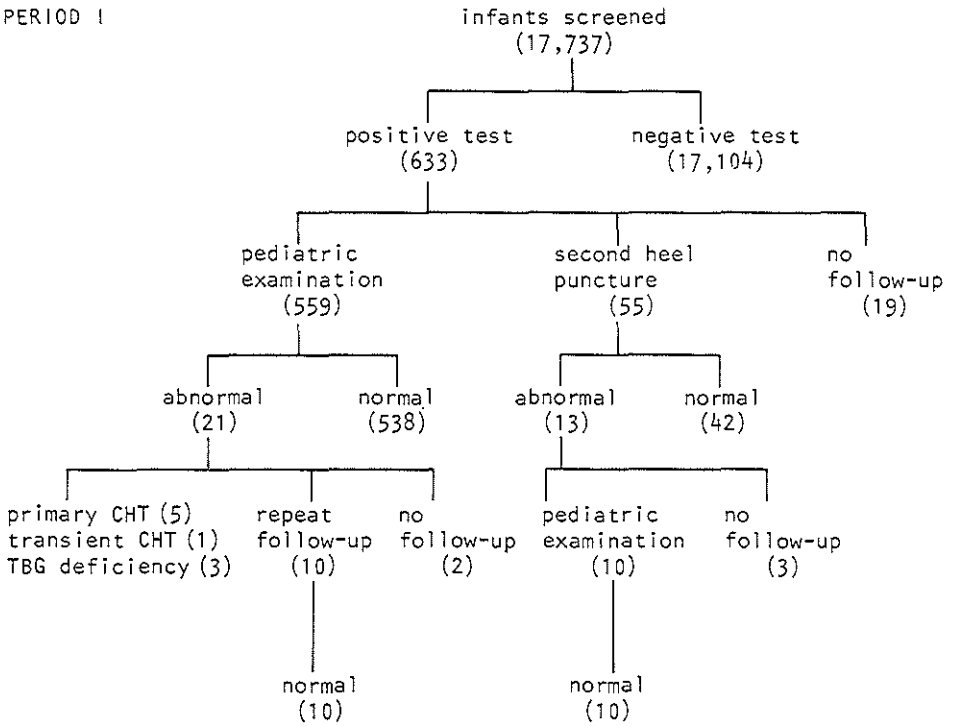
* Calculations following Cernosek and Gutierrez-Cernosek (1978)

Storage of the samples did not influence the TSH values. In the sample of the total population, there was no correlation between the time lapse between screening and measurement and the TSH value ($r = -0.03$; $p > 0.05$).

5.5 *Follow-up testing*

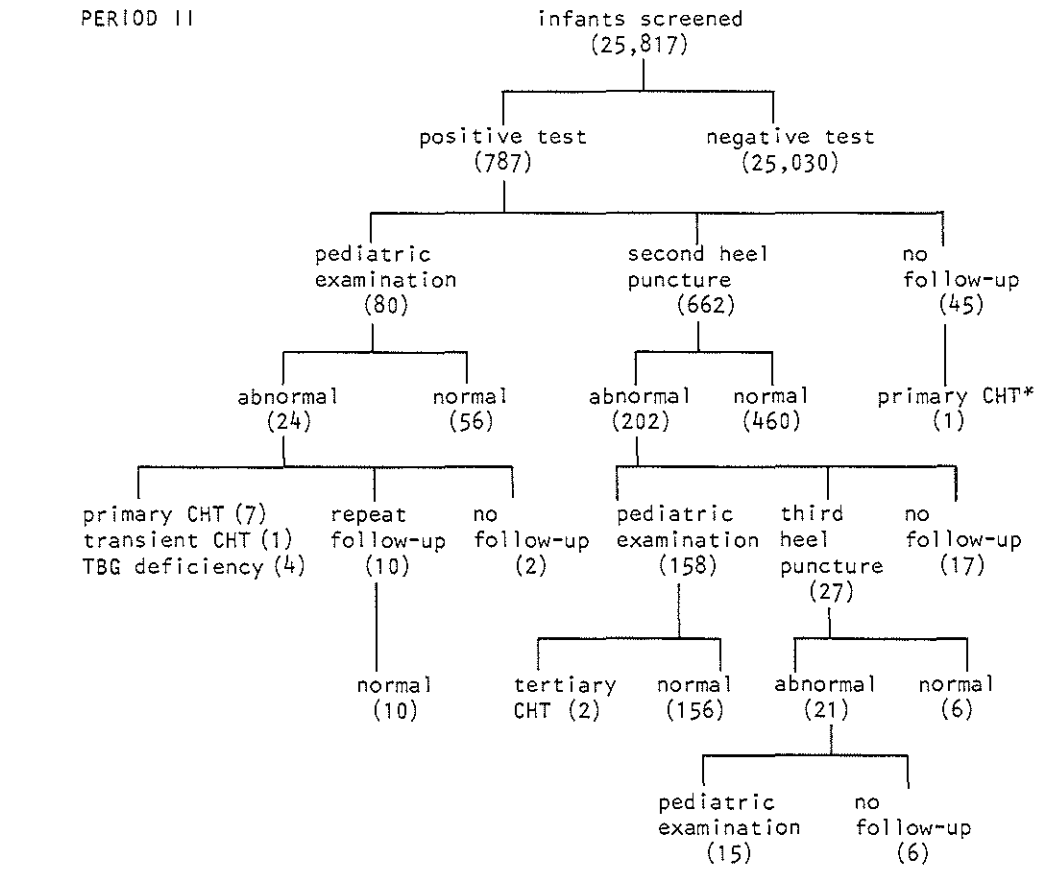
The scheme of follow-up and the main results are represented in Scheme 5.1. During *period I*, reexamination because of a positive screening result was necessary in 633 infants (see Table 5.1). According to the protocol for follow-up, every infant had to be referred to a pediatrician; some organizational problems were the reason for the fact that, in the beginning, a second heel puncture was instead performed several times. The pediatrician examined 559 infants (88.3% of 633), of whom 348 were in an outpatient department; 194 were in a pediatric department of a hospital at the time of the follow-up examination, mostly because of prematurity. In 17 cases is not known whether the infant remained in a pediatric department. A second heel puncture was performed in 55 cases. No kind of follow-up

Scheme 5.1 Scheme of follow-up (periods I and II) and results of the follow-up examinations (number of infants)



was done in 19 (3.0%) infants.
A permanent primary CHT was diagnosed in 5 infants, a transient primary CHT in one and a TBG deficiency in 3 infants. Further investigations were necessary in another 12 infants examined by a pediatrician. In one, a TRH test was performed to exclude a tertiary hypothyroidism; the test was normal. In 9 others, normal values were found in a second serum sample; no samples were received in 2 cases. Of the 55 second heel punctures performed, 13 again showed abnormal results. The pediatrician examined 10 of these, who proved to be normal. In 3 cases, no further information is available. The reasons for the nonparticipation in follow-up are discussed in Section 5.9.

Period II was characterized by other indications for reexamination



* CHT diagnosis based on the screening result; the infant died before further examination was made (see Ch. 7).

(Scheme 4.2). Depending on the T4 and TSH values found, either a referral (in case of very low T4 and/or very high TSH levels) or a second heel puncture had to be done.
The difference between these two schemes of reexaminations is the following: in case of referral to a pediatrician by the general practitioner serum was collected - if possible - and a comprehensive history taken and a physical examination performed. A second heel puncture is merely a second sampling which can be performed at home by the general practitioner or by the home nurse; if the infant remains in a hospital, the second heel puncture is performed there.
A positive screening result was found in 787 infants during period II (see Table 5.2 and related text). The follow-up is outlined in Scheme 5.1. Table 5.5 summarizes the kinds of follow-up done; in ad-

Table 5.5 Follow-up of infants recalled because of an abnormal screening result (period II)

	follow-up actually done		
follow-up required	referral	2nd heel puncture	no follow-up
referral	60	20	13
2nd heel puncture	20	642	32

dition, it is shown whether the indications were acted upon or not. After screening, the pediatrician reexamined 80 infants (10.2%), of whom 45 were in an outpatient department and 24 in a pediatric department of a hospital. For the remaining 11 infants the place of reexamination is not known. A second heel puncture was performed in 662 infants (84.1%). Follow-up was not done in 45 cases (5.7%).
Abnormal values were again found in 202 of the second heel punctures performed, which were indications for an immediate referral. In 17 infants, no third examination has been performed, 158 infants were referred to a pediatrician and a third heel puncture was performed in 27.
It is clear, that the indications for follow-up examinations were not strictly obeyed. Apart from the infants who were not reexamined at all, the first follow-up was not performed according the rules in 40 of the 787 (5.1%) infants with positive screening values. In 27 of the 202 cases in which a third examination was necessary, a third heel puncture was done instead of making a referral (13.4% of 202 cases). The reason for a second heel puncture instead of a comprehensive examination by the pediatrician was a known prematurity, slightly elevated TSH with normal T4 or a personal decision of the pediatrician to deviate from the protocol proposed. The reason for making a pediatric examination instead of doing a second heel puncture was the fact that the infant remained in a pediatric department. In several cases, the results of the reexamination led to further investigations. The 80 pediatric examinations following a positive screening test revealed abnormal results in 24 infants of whom 7 appeared to have primary CHT, one a transient primary CHT and 4 a TBG deficiency; repeat serum measurements were normal in 10 cases. No information was available in two cases.
Pediatric examinations following a second heel puncture (n = 158) were normal in 156 cases and established the diagnosis of tertiary CHT in two cases. The result of the third heel puncture following a second heel puncture indicated further investigations in 21 cases, which were carried out and appeared to be normal in 15 infants. In the remaining 6 infants, no further information was available.
In one case, a CHT was diagnosed on the basis of the screening result. The infant died before further examinations could be made.
Nonparticipation in follow-up will be dealt with in Section 5.9.

5.6 *Time course during screening and follow-up*

The time course has been differentiated into the following steps: (1) age at screening; (2) time lapse between screening and T4 measurement in the CHT laboratory; the day on which T4 is measured is the day on which the report of a positive screening result is sent to the Provincial Pediatrician (see Ch. 4); (3) time lapse between T4 measurement and follow-up (if necessary); (4) time lapse between 2nd heel puncture and 3rd examination (if necessary); (5) age at follow-up.

Age at screening
In the instruction given to the performers of the heel puncture, they were asked to do the heel puncture at the age of 6 to 8 days, or in any case, before the end of the second week. In the group selected by screening, this objective was achieved in 44.7% and, in the sample of the total population, in 60.8%. Screening before the age of 14 days was achieved in 88.7% of the group with abnormal screening values and in 97.2% in the sample of the total population. The median age at which the infant was screened in the sample of the total population was 8.0 days, with a range from 4 to 44 days.
For the difference found between the group selected by screening and the sample of the total population, see Section 5.3.

Time lapse between screening and T4 measurement
This interval consists of two components: the time delay between heel puncture and arrival at the PKU laboratory and the time delay between forwarding of the samples from the PKU laboratory to the CHT laboratory. The latter lasts one to several days; the first is responsible for the greatest part of the total time lapse. The median time lapse in the selected group was 3.2 days; in the sample of the total population, a median of 3.0 was determined. The percentages in which the duration of delay amounted to more than 8 days were, respectively, 5.5% and 2.4%.

Time lapse between T4 measurement and follow-up
If a positive screening result was found during period I, immediate action was taken. The Provincial Pediatrician or the physician of the Municipal Health Service in Rotterdam was informed by telephone; he then informed the general practitioner as soon as possible.
The same procedure was followed during period II in case of a referral; if performance of a second heel puncture was sufficient, only information by mail was forwarded by the CHT laboratory and by the Provincial Pediatrician or physician of the Municipal Health Service. The day on which the T4 was measured was the day on which the report of an abnormal value was sent by the CHT laboratory. (If the T4 value was normal but the TSH value elevated, the report was sent a few days after the T4 measurement, at the time when the TSH result became known).
The data on the time lapse between T4 measurement and follow-up are presented in Table 5.6.

Table 5.6 Time lapse between T4 measurement and follow-up (pediatric examination and 2nd heel puncture)

time gap* (days)	pediatric examination		2nd heel puncture	
	n	cum.%	n	cum.%
≤ 1	13	2.2	12	1.8
2	44	9.6	21	5.1
3	38	16.1	25	8.9
4 - 7	200	49.9	224	43.3
8 - 12	166	78.0	252	82.0
15 - 21	64	88.8	78	94.0
> 21	66	100.0	39	100.0
total	591		651	
not known	46		66	

($\chi^2 = 35.42$; df = 7; $p < 0.001$)

* A pediatric examination was performed before the screening result was known on two occasions

The original objective, to reexamine the infant within 24 hours if a referral to a pediatrician was necessary, was achieved in only 2.2% of the referrals. Pediatric examinations took place earlier than did the second heel puncture: within a week, respectively, in 49.9% and 43.4%. As would be expected, infants remaining at a pediatric department in a hospital were seen earlier by a pediatrician than those referred to a pediatric ward (respectively, 59.7% and 44.6% within a week).
Pediatric examinations during period II were performed sooner than during period I. This is probably explained by the fact that, during period II, the main reason for referral was either a very low T4 value - mostly found in preterm infants who were still remaining in the hospital at the time of the reexamination -, or a very high TSH value - reason for insisting on an early pediatric examination.

Time lapse between 2nd heel puncture and third examination
The median time duration between second heel puncture and a third examination was 7.9 days, with a range from 0 to 138 days (the number of infants is 193, the time duration was known in 182 cases).

Age at follow-up
The aspects mentioned above reflect the way the screening procedure as such was performed in the trial area. Of course, for the individual, the most important variable in the time course is the age at which follow-up is performed and, if necessary, therapy is started. The ages at which the second examinations (either pediatric examin-

ation or second heel puncture) and third examinations (either pediatric examination or third heel puncture) were performed, are shown in Table 5.7. The median age at the time of the second examination was 23.4 days (range 6 - 97 days); if a third examination was necessary, this occurred at a median age of 34.5 days (range 15 - 168 days).

Table 5.7 Age at follow-up (period I and II)

age (weeks)	2nd examination n	2nd examination cum.%	3rd examination* n	3rd examination* cum.%
0 (0-6 days)	1	0.1	-	
1	73	5.9	-	
2	402	38.2	5	2.7
3	415	71.5	39	24.2
4	176	85.6	53	53.3
5	88	92.7	32	70.9
6	36	95.6	18	80.8
7	18	97.0	7	84.6
8	10	97.8	10	90.1
9	6	98.3	5	92.9
≥10	21	100.0	13	100.0
total	1246		182	
not known	110		33	

* CHT patients and infants with TBG deficiency were not included.

5.7 *Laboratory results in follow-up*

Serum measurements

An overview of the serum values found in the follow-up of the screening can be derived only from the data collected during period I. During this period, in the majority of the cases in which a positive screening result was found, a serum sample was collected regardless of the actuel value found in the screening. During period II, serum was, in principle, collected only if the T4 value in screening was very low or, the TSH value was very high or in the cases where abnormal heel puncture values were twice found.

In table 5.8, the values found during period I have been summarized. The total group consisted of 633 infants. The pediatricians examined 559 infants and performed a venepuncture in all, except for two cases in which the venepuncture failed. Dependent on the amount of serum available, the following parameters were measured: T4 (nmol/l), TBG test (%), FTI (100 x T4/TBG test), T3 (nmol/l) and TSH (mIU/l). Values measured in another laboratory than the screening laboratory,

Table 5.8 Serum measurements in follow-up (period I)

	median	95% limits P 2.5 - P 97.5
T4 nmol/l (n = 538)	121.8	57.5 - 194.0
TBG test % (n = 519)	99.1	76.0 - 124.4
FTI (n = 519)	123.0	60.0 - 196.0
T3 nmol/l (n = 509)	2.72	1.09 - 5.61
TSH (n = 520)	3.2	< 2 - 9.8

were excluded. The median age at which the serum was collected was 23.4 days.
Before beginning the screening program, provisional limits were chosen to serve as guidelines for reexamination (see Appendix II). For T4 the lower limit chosen was 60 nmol/l, although - depending on the other values found and on the knowledge of the gestational age of the child - , a reexamination was requested in cases with values between 60 and 70 nmol/l. The limits which were selected for the TBG test, the FTI and the T3 level, were respectively 80 - 120%, 60 - 285 and 1.0 - 3.8 nmol/l. The upper limit chosen for TSH was 20 mIU/l, although, in practice, a follow-up was requested in the case of values between 10 and 20 mIU/l.
Low values of T4, TBG test, FTI and T3 and high TSH values were reason for a second serum sampling. The number of infants in whom this was necessary and the results are given in Section 5.5. Infants with CHT or TBG deficiency will be discussed in detail in Ch. 7.

During period II, lower mean serum values of T4, TBG test, FTI and T3 were found. The respective values found during period I and period II are, for T4, 123.8 nmol/l and 81.1 nmol/l ($p < 0.01$), for the TBG test, 100.2% and 93% ($p < 0.01$), for the FTI, 123.3 and 88.2 ($p < 0.01$) and for T3, 2.9 nmol/l and 2.5 nmol/l ($p < 0.02$)*. This is explained by the lower screening values (T4 in 72% $\leq \bar{x}$ -3.0 s.d.) and by the higher percentage of preterm infants in the group referred to a pediatrician during period II as compared with the group referred during period I. The difference in TBG test is unexplained. Excluding the infants with a known TBG deficiency, the difference is still significant ($p < 0.01$).

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* Two tailed t-test.

Influence of the way of serum sampling
To investigate whether the way in which the serum sampling was performed, could have influenced the values found, the pediatricians were asked whether problems were encountered in performing the venepuncture and the site at which it was performed. The mean T4 values in the various groups were compared.* No significant difference was found between the mean T4 in infants in whom the venepuncture was easily performed and infants in whom a venepuncture was difficult, nor between values found in groups defined by different sites of the venepuncture.

Measurements in second heel puncture blood
The T4 and TSH values found in the second sampling are shown in Table 5.9 and 5.10. Values were included if the follow-up consisted only of a second heel puncture.

Table 5.9 T4 in second heel puncture blood (periods I and II)

	T4 (pg/punch) median	95% limits P 2.5 - P 97.5
period I (n = 57)	86.0	50.0 - 136.2
period II (n = 662)	80.4	45.5 - 130.5

Abnormal values ($T4 \leq \bar{x} - 2.0$ s.d.** or TSH > 0.10 μIU/punch) were found in 245 infants and in principle these should have been referred for further examinations. However, the indications for reexamination were not strictly acted upon in all cases. If the T4 in the second heel puncture was below or equal to $\bar{x} - 2.0$ s.d. but markedly increased as compared to the T4 value found in the first sample and if the TSH was normal, no reexamination was requested. The same occurred in cases in which the TSH was slightly elevated (but less than 0.15 μIU/punch) and the T4 was normal. In this way, the protocol was not strictly followed in 30 cases.

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* Two tailed t-test.
** In second heel puncture the limit of $\bar{x} - 2.0$ s.d. was used instead of that of $\bar{x} - 1.8$ s.d.; the T4 value in the second heel puncture was expressed in pg/punch and in number of standard deviations from the daily mean found in the screening blood samples.

Table 5.10 TSH in 2nd heel puncture blood (periods I and II)*

	TSH median	95% limits P 2.5 - P 97.5
period I (n = 37)	0.03	≤0.02 - 0.15
period II (n = 631)	0.03	≤0.02 - 0.15

* TSH was not measured in each 2nd heel puncture blood sample. In the beginning of the trial period, this was only done if the T4 was below the 10th to 20th percentile.

5.8 *General characteristics of the infants selected by the screening*

In the description of some general characteristics of the group of infants selected by screening, this group was divided into various subgroups, defined by the T4 and TSH values found in screening. CHT patients and infants with TBG deficiency were not included in these.

Group A $T4 \leq \bar{x} - 3.0$ s.d. (T4 ↓↓)
TSH ≤ 0.10 μIU/punch (TSH →)

Group B1 $\bar{x} - 3.0$ s.d. $< T4 \leq \bar{x} - 1.8$ s.d. (T4 ↓)
TSH ≤ 0.10 μIU/punch (TSH →)

Group B2 $\bar{x} - 3.0$ s.d. $< T4 \leq \bar{x} - 1.8$ s.d. (T4 ↓)
TSH > 0.10 μIU/punch (TSH ↑)

Group C $\bar{x} - 1.8$ s.d. $< T4 \leq$ P20 (T4 →)
TSH > 0.10 μIU/punch (TSH ↑)

Group A was defined by very low screening T4 values and normal TSH values. Infants with an elevated TSH level and a very low T4 level ($\leq \bar{x} - 3.0$ s.d.) are not segregated into a separate group. Except for CHT patients, such a group would contain only four infants; clinical information was received on two of them. For this reason, this small group is left out of consideration. Group B1 has low T4 values with normal TSH, while group B2 was defined as having a low T4 and an elevated TSH. Group C was defined as having elevated TSH levels with normal T4 levels. Information on group A includes data received during the entire trial period. In principle, every infant in this group should have been examined by a pediatrician (who would have sent the information to the Netherlands Institute for Preventive Health Care - TNO). In fact, this information is lacking in about 25% of the 94 infants, mainly because no pediatric examination but instead a second heel puncture took place. The data on groups B1, B2 and C were derived from period I. Infants belonging to these groups were only seldom referred to a pediatrician during period II, because of the revised indications for follow-up.

Length of gestation and birth weight

The length of gestation found in the different groups is summarized in Table 5.11. It is clear that the distribution of gestational age differs from that expected in a normal population. In the selected groups A, B1, B2 and C, respectively, 78%, 49%, 61% and 38% had a gestational age of 37 weeks or less. In the sample of the total population in the trial area, this was 10%.

The birth weights in the group selected by screening are summarized in Table 5.12. The birth weights found are lower than would be expected in a normal population. Infants with a birth weight of 2500 g or lower constitute together, respectively, 79%, 43%, 36% and 25% of the different groups. In the sample of the total population, this was 7%.

The high percentage of low birth weights is not completely dependent on the shorter gestational age found in the selected group; this is shown by the fact that the number of infants small for gestational age is relatively high. Birth weights corrected for gestational age are summarized in Table 5.13. For the correction, the standards of Kloosterman (1969) were used. The percentage of birth weights below the 10th percentile is higher than 10 in the four groups.

Table 5.11 Length of gestation in infants selected by screening

length of gestation (weeks)	group A T4↓↓ TSH→		group B1 T4↓ TSH→		group B2 T4↓ TSH↑		group C T4→ TSH↑	
	n	(cum.%)	n	(cum.%)	n	(cum.%)	n	(cum.%)
28	3	(4)	2	(1)	1	(3)	-	
28 - 29	7	(14)	6	(3)	-		-	
30 - 31	17	(38)	15	(8)	1	(6)	-	
32 - 33	15	(58)	28	(17)	3	(15)	1	(6)
34 - 35	10	(72)	43	(31)	4	(27)	-	
36 - 37	4	(78)	52	(49)	11	(61)	5	(38)
38 - 39	5	(85)	80	(75)	5	(76)	-	
40 - 41	9	(97)	64	(96)	6	(94)	8	(88)
≥ 42	2	(100)	11	(100)	2	(100)	2	(100)
total	72		301		33		16	
not known	22		57		2		3	

Table 5.12 Birth weight in infants selected by screening

birth weight (g)	group A T4↓↓ TSH→ n	(cum.%)	group B1 T4↓ TSH→ n	(cum.%)	group B2 T4↓ TSH↑ n	(cum.%)	group C T4→ TSH↑ n	(cum.%)
≤750	2	(3)	1	(0)	-		-	
751 - 1250	18	(26)	14	(5)	1	(3)	-	
1251 - 1750	24	(58)	27	(13)	2	(9)	1	(6)
1751 - 2000	6	(66)	34	(24)	4	(21)	1	(13)
2001 - 2250	7	(75)	31	(34)	3	(30)	1	(19)
2251 - 2500	3	(79)	27	(43)	2	(36)	1	(25)
2501 - 2750	2	(82)	35	(54)	4	(48)	1	(31)
2751 - 3250	7	(91)	64	(74)	10	(79)	4	(56)
3251 - 3750	7	(100)	57	(93)	6	(97)	4	(81)
3751 - 4250	-		19	(99)	1	(100)	3	(100)
≥4250	-		4	(100)	-		-	
total	76		313		33		16	
not known	18		45		2		3	

Table 5.13 Birth weight corrected for gestational age in infants screened by screening

birth weight corrected for gestational age (percentile)	group A T4↓↓ TSH→ n	(%)	group B1 T4↓ TSH→ n	(%)	group B2 T4↓ TSH↑ n	(%)	group C T4→ TSH↑ n	(%)
≤P 10	19	(35)	84	(28)	5	(16)	6	(38)
> P 10	35	(65)	215	(72)	27	(84)	10	(63)
total	54		299		32		16	
not known	40		59		3		3	

Pregnancy, delivery and neonatal period
The course of pregnancy was the same in all groups. An uneventful pregnancy was mentioned in about 70% of the cases; severe disorders were found in about 4%*. Complications of delivery such as caesarean section, breech delivery or vacuum extraction were more frequent in group A (26%) than in group B1 and B2 (16%), but the difference is not significant ($p > 0.05$)**.
Deterioration in the clinical condition in the neonatal period such

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* Following the classification from Kark (1974).
** Fisher's exact test.

as icterus, respiratory distress and infections were more frequent in group A than in group B. The frequencies for icterus (5 days or more) were, respectively, 26% and 13%, for respiratory distress, 49% and 18% and, for infections, 24% and 3% ($p < 0.05$)*. Of course, these differences can be partly explained by the higher frequency of prematurity in group A.
In the total group selected, about 6% suffered from congenital malformations other than CHT: Down's syndrome (5), malformations of the gastrointestinal tract (2), inguinal hernia (2), genetic metabolic diseases (2) (galactosemia and glucose-6-phosphate-dehydrogenase deficiency), microcephalia (2), congenital malformation of the limbs (7) and congenital heart disease (9). The frequency of congenital disease does not seem to deviate from that in the normal population**.

5.9 *Nonparticipation*

5.9.1 *Nonparticipation in screening*

Nonparticipation in the PKU/CHT screening was quite rare. In 1979, 27,433 infants of a total population of newborns in the trial area of 27,637 were screened: a coverage rate of 99.3%. Data on the reasons for not participating were collected at the Vaccination Administration Bodies. The reasons as indicated by the person who should have performed the heel puncture are summarized in Table 5.14 and apply to the entire province of Zuid-Holland in 1979. Separate data on the trial area were not available.

Table 5.14 Participation in the PKU/CHT screening in 1979 (province of Zuid-Holland)

participation	n	%
infants screened	37,030	99.3
infants not screened	251	0.7
reasons for nonparticipation		
deceased	67	0.13
refusal	47	0.18
moved	13	0.03
medical objection	5	0.01
not known	119	0.32

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* Fisher's exact test.
** Galjaard (1976).

Neonatal death was the main reason of the reasons for nonparticipation known. Refusal - often because of religious considerations - was the second. Generally, moving away was not a cause of noncompliance. If the family moved to another part of the country, the infant had to be screened there. It is therefore unlikely that the 13 infants included in the table were not indeed screened (with the reservation that, in other parts of the country, only a PKU screening program is in operation), but exact information is lacking. Medical objection refers to conditions of disease which prevented even a heel puncture.

5.9.2 *Nonparticipation in follow-up*

Nonparticipation in follow-up could occur in different subsequent steps of the screening procedure, which are discussed separately below.

Second examination
During the entire screening period, in 32 cases in which an immediate referral was required, no serum sample or heel puncture blood was received from a pediatrician. There are several reasons for this. Nine infants died. Two families moved; in such cases, follow-up was not done if the screening values were near the limit of normal or if the family left the country. In four cases, the general practitioner refused to collaborate in the second examination. In one case, the parents refused because of religious considerations. No exact reason was known in the remaining cases.
In another 32 cases, the second heel puncture requested was not performed. Once, a refusal by the general practitioner was the reason. Five families moved. An administrative error was twice made, which resulted in not forwarding a second heel puncture set. The screening results in these cases were near the limit of normal and, in order not to upset the parents a long time after the performance of the first heel puncture, it was decided to omit the second heel puncture. The reason was unknown in 24 cases.
In the group in which the cause of the noncompliance with follow-up was unknown, it was remarkable that the percentage of foreign infants was relatively high: 36 against a percentage of 13 in the total group selected by the screening. Comparison of the two percentages shows a significant difference ($p < 0.01$)*.
Especially in the case of a referral is it doubtful whether none of the infants mentioned above were not indeed reexamined. At the termination of this study, an inquiry was sent to every participating pediatrician in order to supply lacking information. The answers on this inquiry revealed that several infants formerly considered to not have participated in the follow-up had been reexamined by a pediatrician; this concerned mostly cases in which the serum sample was

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* Fisher's exact test.

not sent to the screening laboratory but to a local one. However, the inquiry was not answered by all pediatricians. For this reason, it could not be verified in each case of nonparticipation whether the reexamination was performed or not.
The T4 and TSH values for the group which did not participate in the follow-up have been summarized in Table 5.15. The table does not include the values found in an infant considered to be a CHT patient who died before follow-up could take place.

Table 5.15 T4 and TSH values found in the group which was not re-examined

T4 (s.d.)	TSH (μIU/punch)			
	≤ 0.10	0.11 - 0.20	0.21 - 0.40	> 0.40
≤ (-3.0)	11	1	-	-
(-3.0) - (-1.8)	38	2	-	-
> (-1.8)	5*	4	2	-

* $\bar{x}$ - 1.8 s.d. < T4 ≤ P3 (infants screened during period I)

Repeat follow-up
In several infants, a follow-up was performed but not completed. In four cases, the pediatrician saw the child, but no repeat sample was received following the finding of abnormal values. It could not be discovered whether repeat examination took place or not. The same happened in 20 infants in whom a second heel puncture was performed, in spite of the fact that the Provincial Pediatrician or the physician of the Municipal Health Service repeatedly urged the parents or the general practitioner. In addition, in six infants after a third abnormal result, no repeat sample was received. In Table 5.16, the values for the last sample received, if collected by heel puncture (either performed by a pediatrician (n = 2) or at home (n = 26)), are summarized.

Table 5.16 T4 and TSH values (2nd or 3rd heel puncture) for the group in which no repeat sample was received

T4 (s.d.)	TSH (μIU/punch)			
	≤ 0.10	0.11 - 0.20	0.21 - 0.40	> 0.40
≤ (-3.0)	1	-	-	-
(-3.0) - (-2.0)	22	1	-	-
> (-2.0)	-	3	1	-

5.9.3 *The chance of missing a patient due to nonparticipation*

If an equal prevalence of CHT is assumed in the group which was not screened as in the group which was, the chance of missing a patient because of nonparticipation in the screening program is (1) the chance of not being screened (0.007) multiplied by (2) the chance of having CHT - or prevalence - (0.0003). Thus the chance of missing a patient because the infant was not screened is two patients per one million infants, or 0.04 patient during the trial period.
To estimate the chance of having missed a patient because of non-participation in follow-up, the estimated distribution of T4 and TSH values in CHT (Table 6.8) and of the T4 and TSH values in the normal population (Table 6.4) can be used. In addition, two groups have to be distinguished: a) infants with a low T4 level ($\leq \bar{x}$ - 2.0 s.d.) and a normal TSH level ($\leq$0.10 µIU/punch) and b) infants with an elevated TSH level (0.10 < TSH $\leq$ 0.40 µIU/punch; higher values were not found in the group of nonparticipants in follow-up).
The first group consists of 64 infants* and the second of 14 infants. In the first group the chance of CHT was estimated at 0.0007; 64 x 0.0007 = 0.05 patients could have been missed (see below). In the second group the chance of CHT was estimated at 0.02; 14 x 0.02 = 0.3 infants could have been missed. In the following the calculations are explained.

a) T4 $\leq \bar{x}$ -2.0 s.d., TSH $\leq$ 0.10 µIU/punch. The chance of having values in this range given CHT is 0.04 (Table 6.8); in the normal population this chance is 0.02 (Table 6.4). Assuming a screening prevalence of one patient per 2.900 infants (combined prevalence of primary, secondary and tertiary CHT; see Ch. 6), the conditional probability of CHT given the fact of having values in this range is 0.0007.
b) 0.10 < TSH $\leq$ 0.40 µIU/punch. The chance of having values in this range given a CHT is estimated at 0.10 (see Table 6.8; in this table is distinguished between values of 25 - 50 mIU/l, or 0.10 - 0.20 µIU/punch and higher values. Based on the same literature as mentioned in the text related to Table 6.8, the percentage of CHT patients having values between 25 and 100 mIU/l, or 0.10 and 0.40 µIU/punch, is estimated at 10%). In the normal population the chance of having values in the given range is 0.002 (see Table 6.4; no values above 100 mIU/l or 0.40 µIU/punch were found in the normal population). The conditional probability of CHT given TSH levels between 0.10 and 0.40 µIU/punch is 0.02.

5.10 *Anxiety of the parents*

It was attempted in an indirect way to gain insight into the impression the screening and follow-up made upon the parents of infants referred to a pediatrician. For this purpose, the pediatricians were asked to note the reaction of the parents on the form

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* See Tables 5.15 and 5.16; infants with a T4 level >$\bar{x}$ -2.0 s.d. (and normal TSH) were excluded from these calculations.

for history taking and physical examination that they filled in. The question asked was, whether the parents were more anxious about referral than would be reasonably expected in the opinion of the pediatrician. The question was answered in about 70% of the cases during period I, when nearly all infants selected by the screening were referred to a pediatrician. In 65% the answer was negative. It is likely however, that in many cases in which an infant remained in a hospital, the parents were not told about the reexamination. In cases in which the infants was reexamined in an outpatient department, the answer was negative in 50% of the cases. If positive, no further explanation was given in one-half of the cases. The main reason given for anxiety was that the parents felt insufficiently informed about the screening procedure and of the chance that their child would indeed have CHT.Other but less frequent explanations were problems of communication with the parents (foreigners, deafness) or the fact that another member of the family suffered from a serious disease or a thyroid disorder.
It is remarkable that, during period II, when referral often took place after a second examination had already been performed at home, the frequency of anxiety mentioned was not increased.

5.11 *Problems encountered during the trial period*

Most problems met during the trial period have already been mentioned in the preceding paragraphs. Laboratory problems, the influence of age at heel puncture and delay in forwarding, the influence of birth weight and gestational age, the time course of the screening, the anxiety of the parents and nonparticipation, are all problems more or less characteristics for CHT screening.
Two additional problems will be discussed in this paragraph. A difficulty frequently encountered is the insufficient completion of application forms, so that, if reexamination was necessary, tracing the child could be very difficult. A more important problem was the insufficient blood contained in the circles of the filter paper. For PKU screening, this was of minor importance. The Guthrie test requires less blood; in addition, only two of the circles are needed instead of the four required in the combined PKU/CHT screening. Data on inadequate filling applying to the trial area are available from the city of Rotterdam (Table 5.17). Data were also collected in the province of Zuid-Holland as a whole, but were not separated for the trial area.
The percentage of insufficient filling was markedly increased after the institution of the combined screening. A gradual decrease seems to have occurred, but this can be explained by chance ($\chi^2 = 1.93$; $df = 7$; $p > 0.05$). The performers were continuously pressed by the Vaccination Administration Bodies to fill the filter papers more adequately. The effect of this will have to be evaluated after a longer period.

Table 5.17 Insufficient filling of the filter paper circles with blood as a percentage of number of infants screened (Rotterdam)

period	infants screened	% of filter papers insufficiently filled
PKU screening		
1977 and first quarter of 1978	6,787	0.35
PKU/CHT screening		
3rd quarter 1978	1,473	1.02
4th quarter 1978	1,390	1.08
1st quarter 1979	1,301	1.23
2nd quarter 1979	1,452	0.83
3rd quarter 1979	1,384	0.94
4th quarter 1979	1,359	0.81
1st quarter 1980	1,455	0.82

6. THE CASE FINDING OF CHT: COMPARISON OF DIFFERENT METHODS

The screening procedure for congenital hypothyroidism as used in the trial area is, in principle, suitable for permanent and nation-wide institution. However, the central question of whether this procedure is the optimal method of detection of CHT remains. Is it possible, for example, to decrease the number of false-positive screening results without an increase in the number of false-negatives? In spite of the fact that no false-negative results were reported by the participating pediatricians in the trial area, is it possible to postulate a chance that a patient will be missed for reasons other than noncompliance with the screening program, when using the method employed in the trial area?
In this chapter screening will be compared with both the traditional methods of detection and different screening methods. The screening methods will be confined to those which can be combined with the existing PKU screening. An elaboration of the impact of other methods such as the use of cord blood which would allow diagnosis at an earlier age falls beyond the scope of this study. Without a pilot study, it is impossible to predict possible advantages and disadvantages.
In the comparisons made, data from the trial area will be supplemented by data reported in the literature.

6.1 *Screening compared with clinical case finding*

In Chapter 2, the data on the incidence of CHT found in epidemiological studies based on clinical diagnosis and the prevalence of CHT at the age of screening have been summarized. From these data, it could be expected that the prevalence found in the trial area would be, as in other countries, higher than the clinical incidence. The number of patients born in 1972, 1973 and 1974 clinically diagnosed before the end of the 4th year of life in the Netherlands (born in a period before the beginning of the screening program) and the number of patients found by screening in the trial area are given in Table 6.1. Geographical differences in the frequency of CHT within the Netherlands should be taken into account. For this reason, the data of the province of Zuid-Holland (the province in which the trial area is situated) have been separately included.
The frequency found in the trial area differs significantly both from the incidence in the Netherlands (95% confidence limits in a Poisson distribution: 1/5100 - 1/7900), and from the frequency in the province of Zuid-Holland (95% confidence limits: 1/3700 - 1/9700). The interpretation of this difference remains a problem to solve.

Table 6.1 Clinical incidence of CHT in the Netherlands and the province of Zuid-Holland (before the period of screening)* and the screening prevalence in the trial area

	before screening		*during screening*
	the Netherlands	Zuid-Holland	trial area (a part of Zuid-Holland)
period	1972-1974	1972-1974	May 1978 - August 1980
newborns	594,951	127,241	59,455
CHT	95	23	23
clinical incidence	1/6,260	1/5,530	-
screening prevalence	-	-	1/2,600

* Data derived from De Jonge (1976, 1977)

Whether it is due to the fact that patients are missed by clinical diagnosis, or to the fact that screening finds harmless biochemical abnormalities in addition to CHT, or to both has to be a subject of future studies.

The age at the time of diagnosis and at the beginning of treatment has been considerably advanced by screening in comparison with the period before screening. This is shown in Table 6.2 using the same data as in Table 6.1.

Table 6.2 The onset of treatment of CHT before and during treatment

	before screening				*during screening*	
age at onset of treatment	the Netherlands n	(cum.%)	Zuid-Holland n	(cum.%)	trial area* n	(cum.%)
0 - 6 days	5	(5)	-		-	
7 - 13 days	2	(7)	-		6	(27)
14 - 20 days	4	(12)	1	(4)	5	(50)
21 - 27 days	8	(20)	3	(17)	6	(77)
28 - 60 days	15	(36)	4	(35)	5	(100)
61 - 91 days	16	(53)	4	(52)	-	
92 days - 4 years	45	(100)	11	(100)	-	

* In Table 4.2, 22 patients have been mentioned. One infant died before the beginning of treatment

On the basis of literature data a better prognosis of the mental development can be expected from earlier diagnosis and treatment as it occurs in patients found by screening. The follow-up period of the patients screened, however, is too short to make a comprehensive

evaluation of the psychomotor development. The initial results will be given in Appendix IV.

A cost-benefit analysis based on the results is very similar to the expected analysis given in Section 3.1 (see page 33). In only a few aspects the actual analysis contrasted with the expected analysis. The costs of follow-up examinations by a pediatrician were less, because of the replacement of many referrals by a second heel puncture. On the other hand, the costs of diagnosis and treatment of patients were twice those in the period before screening, because of the large number of patients. The principal financial benefit expected is the lesser need for institutionalization. In the group of patients found by screening during the trial period, 14 patients in whom no functional thyroid tissue could be demonstrated or in whom an ectopia and/or hypoplasia of the thyroid was proven were found. From the data collected by Smith and Morris (1979) an IQ lower than 50 could be expected in 13% (1.8 patients of 14 patients). In the Netherlands, infants with an IQ below 50 are nearly always institutionalized. Elimination of the need to confine at least one to two patients for 30 years means a benefit of the screening program in the trial area of at least 2 million guilders. The cost-benefit analysis (clearly positive) will not be discussed in more detail.
Apart from the costs, the most important benefit of screening is in the improvement of the prognosis for the individual patient. Against this, the burden for the healthy population has to be weighed. Judging by the good compliance, formerly with the PKU screening and now with the combined screening, screening for PKU and CHT seems an acceptable procedure; taking into account the benefits, its definite application seems warranted.

6.2 *Comparison of screening methods*

The comparison of screening methods for CHT which can be performed in combination with the existing PKU screening with each other is the principal subject of this chapter. The differences among these methods are found in the difference in hormones that are measured and in the variation in the criteria chosen for a second examination (the variation in the cut-off points chosen).
It will be attempted to estimate the consequences of various screening methods for the sensitivity and the specificity of the screening test and for the predictive value of a positive test. These parameters were explained in Chapter 3 and are shortly summarized below (see also Table 6.3).

Sensitivity: the probability of a positive test in CHT;

$$P(\text{test}^+ \mid \text{CHT}) = \frac{n(a)^*}{n(a+c)}$$

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* n (a): number of infants in part (a) of the contingency table.

Specificity: the probability of a negative test in infants not suffering from CHT;

$$P(test^- | CHT^-) = \frac{n(d)}{n(b+d)}$$

Prevalence: the probability of CHT;

$$P(CHT) = \frac{n(a+c)}{n(a+b+c+d)}$$

Predictive value of a positive test: the probability of CHT given a positive test;

$$P(CHT | test^+) = \frac{n(a)}{n(a+b)} =$$

$$\frac{\text{prevalence} \times \text{sensitivity}}{\text{prevalence} \times \text{sensitivity} + (1-\text{specificity})(1-\text{prevalence})}$$

Table 6.3 Contingency table of screening results and actual diagnosis

		diagnosis +	diagnosis -	total
screening result	+	a	b	a + b
	-	c	d	c + d
total		a + c	b + d	a + b + c + d

T4 and TSH values in the normal population

The calculation of the specificity belonging to different screening methods requires the filling of cells b and d of the contingency table for each of these. This supposes a knowledge of T4 values and related TSH values within the healthy population. From this, the probability of a negative test result (T4 above the cut-off point, TSH below the cut-off point) in healthy infants can be calculated. In the trial area, T4 and TSH values for the population not suffering from CHT were found as shown in Table 6.4. The numbers printed in italics are estimated numbers. Since the method used in the trial area did not provide for information on TSH values in infants whose T4 values were above the 20th percentile, such an estimate was necessary. It was supposed that the TSH values in this group were elevated in the same percentage as in the group in which T4 values lying between $\bar{x} - 1.8$ s.d. and the 20th percentile were found. This extrapolation seemed permissible.

Extrapolation would not be permissable if a relationship existed between T4 and TSH levels in healthy infants. For example, in case of a negative association, the percentage of elevated TSH values would be lower in infants with a high T4 level than in infants with a low T4 level. A computed correlation coefficient showed no association ($r = 0.05$; $p > 0.05$);

these data were derived from the sample of the total population (see Ch. 5) and concern only infants whose T4 was below the 20th percentile. It was assumed that also higher T4 levels were not correlated with the TSH level.

In the table, only data from the period in which TSH was measured if the T4 was below the 20th percentile (instead of the 10th percentile) have been included. Missing values were assumed to be normal.

Table 6.4 Distribution of T4 and TSH values within the normal population (*italics*: see text)

T4 (s.d.; P)	TSH (mIU/l)* ≤25	26-50	>50	total n	(%)	(cum.%)
≤-4.0	9	-	-	9	(0.03)	(0.03)
(-3.9) - (-3.0)	75	2	-	77	(0.21)	(0.24)
-2.9	17	2	-	19	(0.05)	(0.29)
-2.8	26	1	-	27	(0.08)	(0.37)
-2.7	22	-	-	22	(0.06)	(0.43)
-2.6	52	-	-	52	(0.14)	(0.57)
-2.5	39	1	-	40	(0.11)	(0.68)
-2.4	55	2	-	57	(0.16)	(0.84)
-2.3	79	6	-	85	(0.24)	(1.08)
-2.2	91	-	-	91	(0.25)	(1.33)
-2.1	110	2	-	112	(0.31)	(1.64)
-2.0	119	3	-	122	(0.34)	(1.98)
-1.9	150	3	1	154	(0.43)	(2.41)
-1.8	96	6	-	102	(0.28)	(2.69)
(-1.7) - (P20)	6,884	44	10	6,938	(19.28)	(21.98)
>P20	*27,855*	*178*	*40*	28,073	(78.02)	(100.00)
total	*35,679*	*250*	*51*	35,980		
(%)	*(99.16)*	*(0.69)*	*(0.14)*		(100.00)	

* The TSH is expressed in mIU/l, calculated from µIU/punch.

T4 and TSH values in CHT

To calculate the sensitivity, the T4 and TSH levels in CHT patients, including the missed ones, have to be known. Parallel to the calculation of the specificity, the cells (a) and (c) of the contingency table (Table 6.3) have to be filled in for each method.
The values found in the patients diagnosed in the trial by screening,

are given in Table 6.5. This sample is too small to use for calculation of sensitivity. In addition, information on patients missed is lacking. Although from frequent contacts with the participating pediatricians nothing was revealed about CHT patients with a false-negative screening result, this possibility has to be considered. Patients are reported in the literature in whom thyroid hormone levels which would have been considered as normal in the screening

Table 6.5 Distribution of T4 and TSH values in patients found by screening in the trial area (*italics*: secondary/tertiary CHT)

	TSH (mIU/l)				
T4 (s.d.; P)	≤ 25	26-40	40-50	> 50	total
≤ -4.0	-	-	-	11	11
(-3.9) - (-3.0)	-	-	-	7	7
(-2.9) - (-2.0)	*2*	-	-	2	4
(-1.9) - (P20)	?	-	-	1	1
> P20	?	?	?	?	?
total	2 + ?	0 + ?	0 + ?	21 + ?	23 + ?

program in the trial area have been found (see below). It seems likely, however, that such patients represent only a small percentage of the total group of patients; therefore, the chance that such a patient was born during the two-year trial period is small. Furthermore, the thyroid hormone levels in this group are within the normal range, which probably means that clinical manifestations are minimal. This means that, if patients were missed by screening, the chance that they were missed by clinical diagnosis as well is considerable.

It is clear that, for estimation of the sensitivity of a method, information on missed infants is essential. There are several ways to collect this information. For example, T4 values of patients missed in a T4 screening can be estimated by considering the T4 distribution of those found; by extrapolating the curve derived above the cut-off point, the percentage of missed patients can be calculated (Morisette and Dussault, 1979). An objection to such methods is that the position of the T4 curve is not correct, since the values of missed patients are not actually included.

Another approach for supplying information on missed patients is the use and the combination of data from different screening methods. For this purpose, the theoretical possibilities of hormone levels that can occur in CHT patients in the neonatal period have to be considered. They are summarized below:

I primary hypothyroidism

a	low T4	high TSH
b	*normal* T4	high TSH
c	low T4	*normal* TSH
d	*normal* T4	*normal* TSH

II secondary and tertiary hypothyroidism

a	low T4	(low-) *normal* TSH*
b	*normal* T4	(low-) *normal* TSH

In this context, *normal* is defined as "above the cut-off point" for T4 or "below the cut-off point" for TSH. It is obvious that those forms of CHT that have *normal* T4 and *normal* TSH levels in the neonatal period (group Id and group IIb) have to be left out of consideration. They cannot be found by screening; in the calculations, this group will be ignored and *not* considered as missed patients. Information on group Ia (low T4 and high TSH) can be derived from every screening program. The finding of group Ib (*normal* T4 and high TSH) requires TSH measurement irrespective of the T4 level. The discovery of both group Ic and group IIa (low T4 and low-*normal* TSH) requires a T4 screening, whether or not combined with TSH assessment. The different groups are shown in a contingency table of T4 and TSH values which can be used in the sensitivity calculation (Table 6.6).

Table 6.6 Contingency table of T4 and TSH values in CHT patients found in different screening programs (see text)

T4	TSH (low-)*normal*	TSH high
low	group Ic group IIa	group Ia
normal	-	group Ib

Sensitivity of a T4 screening:

$$\frac{n(Ia+Ic+IIa)}{n(Ia+Ib+Ic+IIa)}$$

Sensitivity of a TSH screening:

$$\frac{n(Ia+Ib)}{n(Ia+Ib+Ic+IIa)}$$

The relative frequency of each group can be calculated from (1) the relative frequencies of group Ia versus group Ic and IIa - derived from a T4 screening program - and (2) from the relative frequency of group Ia versus group Ib - derived from a TSH screening program. Of course, screening programs in which both T4 and TSH are assessed in all infants do give information on the relative frequency of every group. Experience with this type of screening, however, is limited. The combination of data derived from various laboratories permits

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* In infants with hypothalamic hypothyroidism, slightly elevated TSH levels can be found (Illig et al., 1975; see also Ch. 7, Table 7.4). Such cases are not segregated in a separate group.

only rather rough estimates when constructing contingency tables like Table 6.6. The estimates of T4 and TSH values in CHT are given in Table 6.7 and Table 6.8; the T4 is expressed in number of standard deviations from the mean or in percentiles as applying for the T4 distribution found in the trial area. The underlying assumptions are explained below.

Table 6.7 *Estimated* T4 and TSH values in primary CHT at time of screening (%)

	TSH (mIU/l)			
T4 (s.d.; P)	≤ 25	26-50	> 50	total
≤ (-2.0)	1	4	83	88
(-2.0) - P20	-	9		9
> P20	-	3		3
total	1	99		100

Table 6.8 *Estimated* T4 and TSH values in *all forms* of CHT at time of screening (%)

	TSH (mIU/l)			
T4 (s.d.; P)	≤ 25	26-50	> 50	total
≤ (-2.0)	4	4	80	88
(-2.0) - P20	-	9		9
> P20	-	3		3
total	4	96		100

Firstly, the distribution of T4 values in CHT patients with elevated TSH will be considered. Data have to be obtained from screening programs in which TSH is assessed in every infant and T4 in an immediate follow-up. For the Rotterdam program, it is important to know whether patients with a T4 value above the 20th percentile were found (no TSH was assessed in that case in the trial program).The 20th percentile corresponds with approx. 94 pg/punch (≈131 nmol/l of serum)*. Only in a few programs T4 values of immediate follow-up have been reported (Illig, 1980; Illig and Torresani, 1980; Hulse et al., 1980). Based on figures collected on 57 patients, the percentage of T4 values above the 20th percentile is esti-

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* The mean T4 value for samples with a T4 level equal to the 20th percentile is 94 pg/punch in our program. The mean amount of serum per punch is 0.92 µl; thus, 94 pg/punch corresponds with 102 pg/µl or 10.2 µg/100ml (= 131 nmol/l).

mated at 3%. The values above the 20th percentile were, respectively, 136 nmol/l and 11.2 µg% (144 nmol/l).
Next, the percentage of low T4 values (here defined as T4 $\leq \bar{x}$ - 2.0 s.d.) in patients with elevated TSH levels has to be known. The mean minus 2 standard deviations in this study corresponds with about 70 pg/punch (97 nmol/l)*. Based on data from the same publications as mentioned above, the percentage of CHT patients with a T4 below or equal to $\bar{x}$ - 2.0 s.d. (in the Rotterdam program) is estimated at 88 (Table 6.9).

Table 6.9 Estimated distribution of T4 in CHT patients with elevated TSH levels

T4 (nmol/l)	%
≤ 97	88
98 - 131	9
> 131	3

Table 6.10 Estimated distribution of TSH in primary CHT with low T4 levels

TSH (mIU/l)	%
≤ 25	1
26 - 50	5
> 50	94

From data of Dussault et al. (1980b), Mitchell and Larsen (1980) and Miyahira (1980) and from those obtained in the trial area, the percentage of TSH values between 25 and 50 mIU/l in primary hypothyroidism is estimated at 5 (6 infants out of 123). In addition, initially normal TSH values in primary hypothyroidism have been found (Miyahira, 1980; Mitchell and Larsen, 1980; Dussault, personal communication), which can arouse the suspicion of pituitary-hypothalamic dysfunction rather than of primary CHT. These cases have been estimated at 1% (Table 6.10).
It is assumed that, in all cases of secondary and tertiary hypothyroidism that can be found by screening, the TSH falls below 25 mIU/l (see also footnote, page 89).
The screening prevalence of secondary and tertiary CHT is estimated at 3% of the total group of patients.

It has to be emphazised that the values summarized in Table 6.7 and Table 6.8 are estimates based on literature data on various screening programs performed in different laboratories. Conclusions based on these figures must be made with reservations. A second remark concerns the number of patients with primary CHT missed and reported in the literature. Fisher et al. (1979) reported 3% of missed cases. Most programs will find nearly all patients and those missed can be presumed to be the cases with less severe forms of primary CHT. In TSH screening, the cases with normal or nearly normal TSH will be missed (and, of course, also the secondary and tertiary forms); in T4 screening with additional TSH assessment, those cases with normal T4 values will be missed. These less severe forms are likely to escape clinical attention.

Prevalence of CHT at the age of screening
In the trial area, the prevalence of primary CHT was approximately

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* $\bar{x}$ - 2.0 s.d. ≈ 70 pg/punch ≈ 7.5 µg/100ml = 97 nmol/l.

1 per 3,000 infants screened. This prevalence is significantly different from the overall prevalence found in the various programs world-wide (1/4,400; the 95% confidence limits of the Poisson distribution are 1/4,100 - 1/4,800; see also Table 2.4). For this reason, the prevalence found in the trial area will be used in the following. In the trial period in the Netherlands, the diagnosis tertiary hypothyroidism was established in two infants. Since the prevalence of this condition is very low, no definite conclusions can be drawn on the basis of our results after screening 60,000 infants. The mean prevalence of secondary/tertiary hypothyroidism found in programs which are aimed at also detecting these forms is about 1 per 100,000 infants screened, the prevalence used here.
The combined prevalence of all forms of CHT is 1 per 2,900 infants (1/3,000 + 1/100,000).

6.2.1 *Sensitivity, specificity and predictive value of different screening methods*

The validity of four different screening methods (Table 6.11) is estimated in this section.
The four methods were chosen for different reasons. Firstly, TSH measurement is thought to be essential in the detection of primary CHT. To detect all cases of primary neonatal hypothyroidism with only T4 would require such a cut-off point that the specificity of the

Table 6.11 Screening methods used in the validity estimates

method	measurement	criteria for follow-up	cut-off point T4	cut-off point TSH (mIU/l)
A	100% T4	↓ T4	$\bar{x}$ - 2.0 s.d.	
	20% TSH	↑ TSH		25
B	100% T4	↓ T4	$\bar{x}$ - 2.0 s.d.	
	100% TSH	↑ TSH		25
C	100% T4	-	-	
	20% TSH	↑ TSH		25
D	100% TSH	↑ TSH	-	25

Method A: T4 is assessed in all samples, TSH only of the T4 value falls below the 20th percentile.
Criteria for follow-up: T4 $\leq \bar{x}$ -2.0 s.d. and/or TSH > 25 mIU/l.
Method B: Both T4 and TSH are assessed in all samples.
Criteria for follow-up: T4 $\leq \bar{x}$ -2.0 s.d. and/or TSH > 25 mIU/l.
Method C: T4 is assessed in all samples, TSH only if the T4 value falls below the 20th percentile. T4 assessment is used only to determine in which samples TSH measurement is necessary.
Criterion for follow-up: TSH > 25 mIU/l.
Method D: TSH is assessed in all samples.
Criterion for follow-up: TSH > 25 mIU/l.

method would be unacceptably low. For this reason, methods in which only T4 is assessed were left out of consideration.
The question of the implications of early detection of not only primary CHT but also the secondary and tertiary forms necessitates the comparison of methods aimed at detecting all forms of neonatal hypothyroidism (methods A and B) with methods particularly aimed at the detection of primary CHT (methods C and D). This was the second reason for choosing these four methods.
The choice of the cut-off points of $\bar{x}$ - 2.0 s.d. for T4 and 25 mIU/l for TSH is a more arbitrary one. The cut-off point chosen for T4 is comparable with the points chosen in other European countries and somewhat higher than the limits used in the North American countries. The cut-off point for TSH was chosen because of CHT reported in the literature with slightly elevated TSH values (25 - 50 mIU/l) in about 5% of the cases.
Based on Table 6.4 (T4 and TSH values in normal infants), Table 6.7 and 6.8 (T4 and TSH values in CHT) and the screening prevalence, the various characteristics of the different methods are calculated and summarized in Table 6.12.

Table 6.12 Validity of different screening methods (screening prevalence of primary CHT: 1/3,000; screening prevalence of secondary and tertiary CHT: 1/100,000)

qualities of the methods	A	B	C	D
measurements T4	100%	100%	100%	-
TSH	20%	100%	20%	100%
criteria for follow-up T4	↓	↓	-	-
TSH	↑	↑	↑	↑
detection of all forms of neonatal hypothyroidism (%)				
sensitivity	0.97	1	0.93	0.96
specificity	0.978	0.972	0.998	0.992
predictive value of a positive test	0.015	0.012	0.138	0.040
detection of primary CHT (%)				
sensitivity	0.97	1	0.96	0.99
specificity	0.978	0.972	0.998	0.992
predictive value of a positive test	0.014	0.012	0.138	0.040

The validities are computed in two different ways. Firstly, it is assumed that the methods are aimed at detection of all forms of hypothyroidism occurring in the neonatal period. Secondly, the methods are considered to be aimed only at the detection of primary hypo-

thyroidism.
Sensitivity, specificity and predictive value were expressed as probability in Table 6.12. What this implies in a nation-wide screening in the Netherlands per year is summarized in Table 6.13. The number of live births in the Netherlands is about 175,000 per year (174,700 in 1979; Centraal Bureau voor de Statistiek, 1980). On the average, 99.1% of the newborns is screened for PKU. The same percentage is anticipated for the combined screening; about 173,000 infants will be yearly screened. The expectancy is that per year 60 patients with CHT can be detected by screening: 58 with primary CHT (screening prevalence: 1/3,000) and 2 with secondary/tertiary CHT (screening prevalence: 1/100,000). In addition, once per two years, a patient can be missed because the infant was not screened. It has been supposed that the criteria for either referral to a pediatrician or a second heel puncture are the same as those used in the trial area:

a) immediate referral to a pediatrician for history taking, physical examination and venepuncture if
   $T4 \leq \bar{x} - 3.0$ s.d. and/or TSH > 50 mIU/l;
b) second heel puncture if
   $\bar{x} - 3.0$ s.d. $< T4 \leq \bar{x} - 2.0$ s.d. and TSH $\leq$ 50 mIU/l or
   $T4 > \bar{x} - 2.0$ s.d. and 25 < TSH $\leq$ 50 mIU/l.

Table 6.13 Expected number (%) of follow-up examinations, patients and missed patients in one year of screening in the Netherlands; difference between screening methods (see Table 6.11 and 6.12). Yearly number of newborns, about 175,000; yearly number of infants screened, about 173,000

methods	A	B	C	D
positive results	3846 (2.2)	4903 (2.8)	402 (0.2)	1440 (0.8)
immediate referrals	526 (0.3)	718 (0.4)	108 (0.06)	297 (0.2)
second heel punctures	3320 (1.9)	4185 (2.4)	294 (0.2)	1143 (0.6)
primary CHT found	56	58	56	57
primary CHT missed	2	-	2	1
sec./tert. CHT found	2	2	-	-
sec./tert. CHT missed	-	-	2	2
CHT missed because of noncompliance in screening	½*	½	½	½

* One infant per two years.

6.3 *Discussion and conclusions*

In this chapter, the validity of various screening methods has been calculated for the Dutch situation. The calculations were based on

estimates of the sensitivity, the specificity and the prevalence; the objective was to assess whether the method chosen in the trial area is the optimal one for nation-wide screening purposes. The validity values given in this chapter illustrate that the aims of screening - to find as many patients as possible with a minimum of follow-up examinations - contradict each other. To support a rational decision about the method, it is necessary to be aware of the principal objective of a screening program and next, to decide whether this objective can reasonably reached.

The principal aim can be the detection of *primary CHT* which is manifested by a severe hypothyroidism leading to severe clinical and biochemical symptoms; the necessity of early detection and treatment of patients suffering from such conditions needs no discussion. Then, screening using a high cut-off point for TSH (50 mIU/l), as for example in Switzerland, is an effective and very efficient method. Applied to our program a follow-up percentage of 0.14% could be expected. Every extension of this method to the discovery of milder variants of primary CHT will find these only at the costs of a considerably higher percentage of follow-up examinations.

An opposite point of view (that which was agreed upon by the performers of the screening in the trial area) is that the aim of screening is the detection of not only primary CHT, but also neonatal secondary and tertiary hypothryoidism, thus the detection of *neonatal hypothyroidism*. It was considered that in every form of neonatal hypothyroidism there is theoretically a risk for cerebral damage, independent of the underlying cause of hypothyroidism. Little is known about the prognosis of infants suffering from neonatal secondary or tertiary hypothyroidism in which treatment was delayed or not instituted at all. The few studies that are available (Rosenbloom et al., 1966; Bucher and Illig, 1980) report on patients with late clinical manifestations of multiple hormone deficiencies in which hypothyroidism often developed only after the beginning of treatment with growth hormone. Whether these infants were hypothyroid in the neonatal period is doubtful.

It is not unusual that, in the beginning of a screening program, one is confronted with conditions of which the clinical significance is unknown. In the PKU screening, it was the (benign?) hyperphenylalaninemia; in the screening for cervix carcinoma the significance of a pre-invasive lesion is not quite understood. The galactosemia screening detected the hitherto unknown and probably benign uridine-diphosphate-galactose-4'-epimerase deficiency. In CHT screening, the problems are in the unexpectedly high prevalence of primary CHT and in the lack of knowledge on the prognosis of neonatal secondary and tertiary hypothyroidism. Following the principles of Wilson and Jungner, no screening program should be instituted for conditions in which etiology, natural history and prognosis are unknown. But, as mentioned, there are theoretical arguments to decide not to limit the screening to the detection of severe primary forms. Low and even low normal, thyroid hormone levels during the neonatal period could lead to irreversible damage to the cerebrum. However, screening for such conditions has, besides the aim of case finding, an epidemiological goal. If the aim of screening is the detection of all forms

of neonatal hypothyroidism it means that a careful evaluation of the screening results, the results of the following diagnostic examinations and of treatment is necessary and that a reevaluation of the diagnosis after a few years has to take place.

Detection of all forms of neonatal hypothyroidism implies application of either method A or B. If we consider method A as described in this chapter, the following conclusions can be drawn (method A: TSH cut-off point = 25 mIU/l; T4 cut-off point = $\bar{x}$ - 2 s.d.; T4 cut-off point for TSH measurement = 20th percentile): (1) for TSH, a cut-off point of 25 mIU/l seems to be necessary; a higher cut-off point could miss a considerable number of the group of patients with primary CHT, although probably not those with the most severe hypothyroidism; (2) for T4, the cut-off point of the mean minus 2 standard deviations is comparable to the points chosen in most of the other European countries (Delange et al., 1980a) but higher than in the North American countries (Dussault et al., 1980d). Our own data suggest that a lowering of the T4 cut-off point would lead to the missing of patients with secondary/tertiary hypothyroidism; the highest value found was $\bar{x}$ - 2.3 s.d. Whether this is an exceptional finding or not can only be learned from future screening; (3) the T4 cut-off point for TSH measurement, which was the 20th percentile in the trial area, will probably require reconsideration. Several authors mention T4 values in CHT which would have fallen above our cut-off point for TSH measurement and would be missed in our program (Hulse et al., 1980; Irie and Naruse, 1980; Illig and Torresani, 1980). An increase in the number of TSH measurements probably leads to the finding of the less severe forms of CHT, although this could be proved only by more information on such patients. The highest T4 value reported in CHT, as far as we know, is 11.2 µg/100 ml (≈144 nmol/l) (Illig and Torresani, 1980). In our program, the finding of such a patient would require TSH measurement in almost 50% of the samples. It also applies here, that it is not known whether such a value is an exceptional finding or indeed constitutes the 3% of the values in CHT as was estimated from literature data (Table 6.9). The availability of more international data and the use of a model such as described in this chapter could solve many of the uncertainties described here. The next step in the decision about the screening method is to assess whether the consequences of method A and B are acceptable for permanent institution. These consequences are mainly determined by the specificity of the method (respectively, 0.978 and 0.972) and the predictive value of a positive test (respectively, 0.015 and 0.012); the expected follow-up percentage of the healthy population is, respectively, 2.2% and 2.8% and 1.5% to 1.2% of the positive tests will concern an actual CHT.

It can be stated that no insurmountable problems have been encountered in the trial area, neither in the laboratory nor in the organization. A decrease in acceptability of the screening as compared to the former PKU screening has not been expressed in a decrease in compliance; further information on this is still lacking. Although a follow-up percentage of 2% is high, the actual burden on the health care system is small. For every general practitioner, it means one

immediate referral per 10 years and a second heel puncture once per two years, if performed as often by the general practitioner as by the home nurse. In addition, the burden on the health care system can be decreased by a slight lowering of the cut-off point for T4, which means a considerable decrease in the follow-up percentage and only a small increase in the chance of missing a patient. Using Table 6.4, the consequences of such a lowering can be easily calculated. Of course, these aspects, the burden of a T4-TSH screening on the performers of the screening and the anxiety of the parents of the infants screened should be subject of constant attention.
Another aspect concerns the necessity for evaluation of screening and follow-up. Especially in disorders which are probably less severe or of which the natural history is not quite understood (for example, in the neonatal tertiary hypothyroidism without other deficiencies or in the infant with a functioning ectopic thyroid) are careful monitoring of clinical manifestations, diagnostic examinations, treatment, follow-up and reevaluation of the diagnosis after several years necessary. Then, a rational decision can be made as to whether such patients should be treated; if not, it can be concluded that screening for such disorders can be discontinued. Continuous evaluation and, based on this, the possibility to modify the screening method should be guaranteed.

In conclusion, screening for all forms of neonatal hypothyroidism seems to be possible within the neonatal PKU screening program as practised in the Netherlands. A provisional choice for this far-reaching aim of screening is a T4 screening with additional TSH measurement (using the cut-off points mentioned in this section) with the reservation that an increase in TSH measurement from 20% to, for example, 50% would be desirable. A strict condition for the performance of such a program is that all participants in the screening including the pediatricians collaborate in a continuing evaluation of screening, diagnostic examinations, follow-up and evaluation of the diagnosis.

7. CHT AND TBG DEFICIENCY FOUND IN THE SCREENING PROGRAM

Data on congenital hypothyroidism and thyroxine binding globulin deficiency obtained in the screening program during the period of May 1978 to August 1980, inclusive, will be presented in this chapter. During this period, 59,455 infants were screened.
The screening procedure chosen was suitable in principle for detection of all forms of hypothyroidism occurring in the neonatal period, both primary hypothyroidism and secondary and tertiary forms. TBG deficiency is discussed, not because of the clinical importance of this condition but mainly because of the experience that the differentiation between TBG deficiency and tertiary hypothyroidism can be difficult to make.
The laboratory data of the individual infants are summarized in several tables. Originally, the measurements in heel puncture blood were expressed in units per punch. To facilitate comparison with the results of other screening programs, the data have been recalculated in nmol/l for T4 and in mIU/l for TSH (T4: 100 nmol/l ∿ 71 pg/punch; TSH: 25 mIU/l ∿ 0.10 µIU/punch).

All infants were under care of one of the pediatricians who participated in the screening program in the trial area. They provided us with the information on the clinical condition of the child and on the diagnostic examinations.

7.1 *Permanent primary CHT*

Primary hypothyroidism thought to be of a permanent nature was diagnosed in 21 infants. Since none of the patients had reached an age at which the diagnosis established in the first month of life could be evaluated without risk of damage to the central nervous system, the diagnosis "permanent" primary CHT was not always certain. A thyroid scan was performed in the majority of the cases; all - but one, an infant with a goiter - showed hypoplasia or absence of functional thyroid tissue. Of course, the diagnosis permanent CHT could be established in these cases. In cases in which no thyroid scan was performed, the diagnosis was based on evidently abnormal hormone levels.
The laboratory data, several general characteristics and the scanning results are summarized in Table 7.1.

Laboratory data
The TSH values found are characteristic for primary CHT. In all but three infants, the T4 levels were decreased. The screening T4 value

Table 7.1 Laboratory data, age at onset of therapy, general characteristics, and scanning results of 21 infants with permanent primary CHT

	heel puncture			serum measurements						
in-fant	age days	T4 nmol/l	s.d.	TSH mIU/l	age days	T4 nmol/l	TBG test(%)	FTI	T3 nmol/l	TSH mIU/l
1	*6*	109	-1.2	280	*16*	67	124	54	2.8	> 200
2	*7*	22	-3.5	150	*24*	65	113	58	2.6	240
3	*7*	29	-3.3	160	*24*	48	106	45	2.0	240
4	*7*	18	-4.4	400	*9*	12	119	10	1.1	245
5	*11*	17	-4.6	620	*6*	23	122	19	1.0	280
6	*12*	18	-4.1	480	*18*	6	136	4	-	950
7	*7*	37	-4.3	550	*18*	<10	117	< 8	1.3	2000
8	*6*	32	-4.4	280	*12*	14	113	12	-	660
9	*8*	66	-3.5	540	*13*	53	124	43	-	1200
10	*19*	15	-4.2	360	-	-	-	-	-	-
11	*10*	8	-4.5	500	*14*	<10	116	< 10	1.0	> 100
12	*9*	18	-4.3	380	*15*	10	127	< 10	1.1	350
13	*7*	52	-3.9	340	*16*	57	150	38	3.3	600
14	*9*	14	-5.3	400	*12*	17	112	15	1.5	500
15	*13*	15	-4.1	370	*16*	10	114	< 10	1.0	> 50
16	*11*	< 10	-4.7	440	*17*	<10	104	< 10	1.2	500
17	*8*	95	-2.1	70	*26*	81	106	76	3.9	140
18	*7*	58	-3.0	330	*11*	33	120	27	1.9	350
19	*1*	33	-2.9	450	*7*	15	101	15	1.1	450
20	*7*	61	-3.1	500	*9*	29	108	27	1.6	510
21	*14*	< 10	-3.3	475	*22*	<10	120	< 10	1.1	760

Skeletal age: skeletal age at the beginning of treatment.
G.a.: gestational age.
Clinical suspicion: (yes): suspected of CHT after referral because of an abnormal screening result; yes: suspected before screening result became known.
N.t.: no (functional) thyroid (tissue).

onset of therapy; age (days)	sex	length of gestation (weeks)	birth weight (g)	skeletal age	clinical suspicion	thyroid scanning
22	girl	41	3400	postnatal	no	-
45	girl	36	2065	postnatal	no	-
45	girl	36	1975	postnatal	no	-
11	girl	39	2800	postnatal	(yes)	-
11	boy	40	4000	postnatal	yes	n.t.
21	boy	41	3680	postnatal	no	-
18	boy	41	3890	32 weeks g.a.	yes	n.t.
13	boy	43	3180	34 weeks g.a.	(yes)	n.t.
23	girl	40	2840	postnatal	no	ectopia
-	boy	38	2880	-	no	-
21	girl	37	1695	37 weeks g.a.	no	n.t.
17	girl	42	3500	postnatal	yes	n.t.
18	girl	40	4500	prenatal	no	n.t.
13	boy	39	3560	38 weeks g.a.	(yes)	n.t.
17	girl	42	3255	36 weeks g.a.	(yes)	n.t.
24	boy	37	2770	prenatal	no	n.t.
37	boy	38	3050	postnatal	no	ectopia
17	boy	39	3060	postnatal	no	hypoplasia
8	girl	40	3140	prenatal	yes	enlarged
10	girl	41	3800	32 weeks g.a.	(yes)	ectopia
25	girl	40	3920	32 weeks g.a.	no	-

for one of the infants (infant 1) was within the normal range (T4 = $\bar{x}$ - 1.2 s.d.), and was, on that day, equal to the 10th percentile. This finding led to an increase in the percentage of blood samples in which TSH was assessed (from 10% to 20%). A T4 level in the low normal range was also found in follow-up: in infant 17, this corresponds with the finding of an ectopic thyroid; in infants 1 and 2, no scan was performed.
No follow-up data of patient 10 are available. This infant had a Down's syndrome complicated by a duodenal atresia; after surgical treatment, he died of septicaemia. In this infant, the diagnosis is based on the values found in screening.

Scanning
In 14 of the 21 infants, a 99m Tc pertechnetate scan of the thyroid was carried out. In 9 of them, no functional thyroid tissue could be demonstrated and athyroidism was likely to exist. In at least three infants no salivary glands could be demonstrated by scanning. It seems unlikely that this was due to a defective trapping mechanism for technetium (and thus for iodine as well) in all of them; rather, technical factors seem responsible.
An ectopia of the thyroid was found in three infants (patients 9, 17 and 20) and in one, a small active thyroid in the normal location (patient 18). An enlarged thyroid was demonstrated in one infant.
No scan could be performed in patient 21 because of iodine administration for the purpose of making an intravenous pyelogram several days before the diagnosis of CHT was established.

Urine analysis
In four patients (infants 1, 4, 12 and 20) the urine was analysed for presence of abnormal quantities of iodine and for iodohistidine and iodotyrosine (see Appendix II). Normal values were found. This is particularly interesting, because patient 12 was one of the infants in which no salivary glands were visible on the scan. Although no goiter was present, the possibility of a trapping defect had to be considered, but the normal analysis did not support this hypothesis.

Treatment
Thyroid hormone was administered to 20 of 21 patients. As mentioned, one infant died before treatment was started (infant 10). The median age at the beginning of treatment was 18 days, with a range of 8 to 45 days. Three infants were treated at an age above 1 month (infants 2, 3 and 17); all were initially suspected of transient hypothyroidism. In infants 2 and 3, the persisting abnormality in the hormone values eventually led to the diagnosis of permanent hypothyroidism; in infant 17, the scanning result - ectopia of the thyroid - gave reason to suspect a permanent thyroid hypofunction, but the initial normal T4 value and the only slightly elevated TSH were reasons to wait for the results of second measurements before beginning treatment.
Treatment consisted of levothyroxine (initially 25 to 50 µg/day) in infants 2, 3, 17, 18 and 19. The others, except for patient 10 (see above), were treated with liothyronine (3 x 2 µg/day), that was in-

creased to 3-4 µg/day within one to two weeks; from that time, the dose was gradually decreased and the administration eventually stopped. Liothyronine was replaced by levothyroxine from the time that liothyronine was decreased; the initial dose was about µg/day, which was increased to a daily dose of about 50 µg. With the availability of commercial preparations containing a constant quantity of L-T4, the eventual daily dose was about 5 µg/kg*.
Cardiac function and other clinical parameters were carefully monitored because of the hazards of overtreatment.

General characteristics of the patients
The clinical manifestations in CHT are the subject of the following chapter. Here, a few general characteristics will be described.
Sex. Permanent primary CHT was diagnosed in 9 males and 12 females.
Length of gestation. The median length of gestation was 40 weeks and one day, with a range of 36 to 43 weeks (the median of the sample of the total population was 39 weeks and 2 days).
Birth weight. The median birth weight was 3140 g, with a range of 1685 to 4500 g. The median in the sample of the total population (see Ch. 5) was 3370 g.
Skeletal maturation. In nine infants, the skeletal age conformed to the skeletal maturation normally seen in the prenatal period before a gestational age of 38 weeks; this corresponded with the actual length of gestation and age in two infants.
Clinical suspicion. Four infants were clinically suspected of CHT before the screening result became known. Three of them were examined for CHT by a pediatrician before the screening was performed; in one (infant 19) the reason for suspicion was a goiter.
Although, in several of the other infants, suspicion was aroused as soon as the screening result became known, in none of them had the clinical manifestations been reason for referral to a pediatrician.
Other diseases. Infant 10 suffered from Down's syndrome and had a duodenal atresia. The infant died of septicaemia. A renal cystic disease combined with several minor external malformations was found in patient 21.
Seasonal influence. In our group of infants, there was no seasonal influence on incidence of CHT patients.

Psychomotor development
The psychomotor development of the patients was regularly checked by the pediatrician in charge of the treatment of the infant. In addition, several infants were tested with the Baily mental, motor and behaviour scales for infant development at the termination of the trial period. The results are presented in Appendix IV.

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* Scheme for induction of treatment developed in the Department of Pediatrics, division of Pediatric Endocrinology, University Hospital Rotterdam / Sophia Children's Hospital.

7.2 *Transient primary CHT*

Transient primary CHT has been defined here as primary hypothyroidism occurring in the neonatal period, improving spontaneously to euthyroidism within several weeks. An infant was considered as hypothyroid if an elevated TSH level was found more than once, or, if an elevated TSH level found once was combined with a decreased T4 value. The laboratory data of the 6 infants are summarized in Table 7.2.

Table 7.2 Laboratory data in transient primary CHT

infant	age in days	heel puncture T4 nmol/l	s.d.	TSH mIU/l	serum T4 nmol/l	TBG test(%)	FTI	T3 nmol/l	TSH mIU/l
A	±10	114	-1.9	90					
	17				52	117	44	2.2	≥100
	23				131	113	116	3.2	4.7
B	12	40	-3.7	100					
	20				48	100	48	5.1	5.0
	31				88				
C	12	7	-5.4	170					
	20	46	-4.1	40					
	27	83	-3.3	< 5	39	70	56	1.0	3.0
	74				104	85	122	1.7	2.3
D	8	34	-3.6	70					
	13	138	-0.4	17.5	152	99	154	4.1	16
E	12	60	-3.2	45					
	20				134				85
F	11*	75	-3.0	40					
	20				38	112	112	4.2	23

* Values before treatment.

Patient A was a healthy boy born after a length of gestation of 40 weeks and with a birth weight of about 4000 g. The history revealed no causes of hypothyroidism. The hypothyroidism improved spontaneously.
Patient B was a boy born after a length of gestation of 38 weeks with a birth weight of 3710 g. There were no clinical manifestations of hypothyroidism. At 35 weeks gestational age, an amniofetography as diagnostic examination in a hydramnios was performed; this probably induced the thyroid hypofunction. The elevated TSH level normalized spontaneously; the T4 remained low for several weeks, but also improved spontaneously. Thyroid scanning showed no uptake at the age of 24 days, but was normal at the age of 31 days.
Patient C was a preterm small-for-dates girl. No clinical information was received. The hypothyroidism improved spontaneously.

Patient D was a boy born after a length of gestation of 37 weeks with a birth weight of 2580 g. No clinical manifestations of CHT were present, nor did the history reveal a cause for hypothyroidism. The T4 level normalized within one week, while the TSH was slightly elevated at that time.
Patient E was a girl, one of twins, born after a length of gestation of 33 weeks with a birth weight of 1600 g. During the neonatal period, the infant suffered from gastroenteritis and showed no signs or symptoms of CHT. In the history, there was no reason for hypothyroidism. Serum measurements were not repeated. The infant was clinically euthyroid at the age of six months.
Patient F was a preterm boy in whom a ventricular septum defect was diagnosed. In this infant, the diagnosis transient hypothyroidism is not certain. The TSH level decreased but the T4 level was markedly reduced at the end of the third week. The levels of T4 and TSH found in serum were reason to start L-T4 therapy. Only reevaluation of the diagnosis after several years will reveal whether the hypothyroidism was transient or not. A thyroid scan was performed and was normal.

Apart from the abnormal values found in these infants, the TSH level was markedly increased at the time of screening in a preterm small-for-dates boy (the length of gestation was 30 weeks and the birth weight 900 g). The TSH value was 120 mIU/l, while the T4 value was normal ($\bar{x}$ - 1.3 s.d.). A second heel puncture revealed normal values for both T4 and TSH. In this case, a delayed TSH surge is more likely than a transient hypothyroidism.

7.2.1 *Amniofetography*

In the preceding section, a patient with transient CHT (infant B) in whom the CHT was probably connected with amniofetography was mentioned. During the trial period, it was remarkable to find that, in another two infants in which a follow-up examination was carried out because of an elevated TSH in screening and in which TSH values in the high normal range were found in follow-up, an amniofetography had been performed. In the period during which clinical information was obtained on infants who were referred to a pediatrician because of the screening result (infants born from May 1978 to February 1980, inclusive), in 10 of the 637 infants of whom a serum sampling was obtained (see Ch. 5), a slightly elevated TSH value was found (10 - 25 mIU/l). In two of them, an amniofetography had been carried out; the reason for this is not known.
Since it is known from experience that the pediatrician is not always informed about the fact that an amniofetography was performed and since we are not informed on the frequency in which amniofetography is still performed in the Netherlands in general, no definite conclusions can be drawn. Nevertheless, amniofetography is probably a cause of hypofunctioning of the thyroid (see Ch. 2).

7.3 *Tertiary hypothyroidism*

During the trial period tertiary hypothyroidism was diagnosed twice (Table 7.3).

Table 7.3 Laboratory data in tertiary CHT

in-fant	age in days	heel puncture T4 nmol/l	s.d.	TSH mIU/l	serum T4 nmol/l	TBG test(%)	FTI	T3 nmol/l	TSH mIU/l	TRH test (TSH in mIU/l)
G	12	99	-2.3	20-32						
	20	61	-3.6	50						
	25				50	98	56	2.4	2.2	
	34									0' 1.3
										30'17
										60'16
										90'20
										120'20
H	±12	78	-2.5	<5						
	26	49	-3.5	5						
	29				50	86	58	2.1	1.6	
	37				47	87	54	1.9	1.6	0'<1
										20'13.4
										60'11.2

Patient G was a girl born after a length of gestation of 41 weeks with a birth weight of 3385 g. Because of suspicion of maldevelopment of the fetus, estrogen excretion was measured during pregnancy, which proved to be very low. After the birth of an apparently normal infant, endocrinological examinations were done for possible adrenal cortical hypofunction which could explain the low estrogen excretion. The thyroid function at this time was normal. The screening result led to evaluation of the thyroid function. By this time, several clinical manifestations of CHT were present: large fontanels, icterus, a hoarse cry, a mottled skin and an umbilical hernia. The skeletal age conformed to the skeletal maturation of a full term infant in the neonatal period. Ophthalmological and neurological examinations revealed a septo-optic dysplasia. At the age of one year, an adrenocorticotropin deficiency was also discovered. The tertiary hypothyroidism was treated with levothyroxine from the age of 34 days.

Patient H was a boy born after an uncomplicated pregnancy of 38 weeks with a birth weight of 2460 g. During the neonatal period, the infant suffered from obstipation; except for large fontanels and a prenatal skeletal maturation, the infant showed no signs or symptoms of hypothyroidism. He had a club foot on the left side.

Ophthalmological examinations were normal and the computer tomography of the cerebrum was normal; at the time no other deficiencies

seemed to exist. The diagnosis tertiary hypothyroidism was based on the thyroid hormone levels, the TSH and prolactin response to TRH stimulation and the retarded skeletal maturation. Treatment, initially with liothyronine and later with levothyroxine, started at the age of 45 days.
Tertiary CHT was also suspected in a third infant; the infant was temporarily treated as suffering from tertiary CHT, because the distinction between TBG deficiency and TRH deficiency proved difficult to establish. This infant is further described in Section 7.4 (infant O in Table 7.4).

7.4 *TBG deficiency*

In 7 infants, the low T4 levels found by screening were ascribed to a hereditary deficiency of TBG (Table 7.4). This diagnosis should be based on the following findings: a low T4 level, a low TBG concentration (because a direct assay of TBG was not available, a TBG test was measured), normal FTI and TSH and the absence of signs and symptoms of hypothyroidism. Family data are needed to confirm the hereditary origin.
In all infants, the T4 levels found were considerably decreased. The TBG test varied from 25% to 79%, while there were also variations in results of repeated measurements in the same infant. In infant L, the values varied from 30% to 76%. Whether this was due to an accidental assay variation or to actual variation in TBG levels is not known. All FTI values found were either in the lower normal range or decreased.
Infant I was a healthy boy born after a length of gestation of 43 weeks with a birth weight of 3660 g. The pregnancy was complicated by hypertension. No problems were encountered during the neonatal period. Family data were not available.
Infant J was a boy born after a length of gestation of 42 weeks with a birth weight of 3540 g. Pregnancy and neonatal period were uncomplicated. The mother was TBG deficient as well.
Infant K was a healthy boy born after a length of gestation of 37 weeks with a birth weight of 2950 g. The neonatal period was complicated by a hyperbilirubinemia for which no cause was found. The mother had a normal T4 level and TBG test, which is an unexpected finding in an X-linked hereditary disorder. However, direct TBG measurement is necessary to confirm this probably normal TBG status of the mother.
Infant L was a boy. The birth weight was 3000 g; the length of gestation is not known. The pregnancy and the neonatal period were uncomplicated. Because of the initially low-normal TBG test and the very low T4 level, the infant was suspected of a pituitary-hypothalamic hypofunction. The TRH test excludes secondary CHT and does not support the diagnosis tertiary CHT*. The skeletal maturation was normal. At the age of one year no clinical manifestations of hypo-

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* TSH values in the TRH test: 0', 1.0; 20', 24.6; 60', 16.9; 90', 14.1; 120', 9.4 mIU/l.

thyroidism were present. No family data are available.
Infant M was a healthy boy born after a length of gestation of about 37 weeks with a birth weight of 3040 g. Apart from icterus, the neonatal period was uncomplicated. The skeletal maturation was normal. No family data are available.
Infant N was a healthy boy born after a length of gestation of 38 weeks with a birth weight of 2950 g. The twin sister is partial TBG deficient.
Infant O was treated as suffering from tertiary hypothyroidism for a while. The prolonged TSH response in the TRH test* aroused suspicion of tertiary CHT. Assessment of the TBG binding capacity in the parents revealed a TBG deficiency in the father; the diagnosis in this girl was changed to a partial deficiency.

Table 7.4 Infants suspected of hereditary TBG deficiency

			heel puncture			serum				
in-fant	sex	age in days	T4 nmol/l	s.d.	TSH mIU/l	T4 nmol/l	TBG test %	FTI	T3 nmol/l	TSH mIU/l
I	boy	±8	50	-3.6	-					
		17	43	-4.7	<5.0	22	38	58	1.0	<5
		18				24	36	67	0.7	<5
J	boy	7	29	-3.6	<5.0					
		13				48	65	75	2.5	<4.0
K	boy	8	44	-3.9	<5.0					
		12	33	-4.5	<5.0	29	37	78	1.7	1.3
L	boy	13	49	-4.3	7.5					
		26				21	76	28	2.4	3.2
		28				14	35	40	1.3	2.2
		46				26	53	49	1.4	2.2
		(1 year)				17	30	57		
M	boy	±12	40	-3.9	35					
		16				28	50	56	1.5	3.2
		23				39	50	78	1.9	2.2
N	boy	8	14	-4.6	<5.0					
		13				20	26	77	1.1	1.8
O	girl	10	44	-3.4	20					
		15	50	-3.6	5.0	44	59	75	2.0	2.7
		31				33	79	42	2.5	2.7

The first 6 infants mentioned are boys. Assuming a X-linked trait, males are generally affected by a more pronounced TBG deficiency

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* TSH values in the TRH test: 0',<1.0; 20', 18.8; 60', 11.6 mIU/l.

which is passed on by their "carrier" mother. In infant J, the mother was (partial?) TBG deficient indeed, in infant 6 the twin sister had a partial TBG deficiency. In infant K, the TBG status of the mother should be confirmed by a direct TBG measurement. On the other infants, no family data were available.

In one infant, not mentioned in Table 7.4, TBG deficiency was found to be secondary to liver dysfunction in galactosemia (galactose-1-phosphate uridyltransferase deficiency). The relevant laboratory data were as follows: T4, 31 nmol/l; TBG test, 43%; FTI, 72. The values normalized after a few weeks of dietary treatment.

7.5 *Patients missed by screening*

During the trial period, no patients with primary CHT were reported to the Rotterdam working party in which either no screening was performed or the screening result was false-negative.
A tertiary hypothyroidism was reported once in an infant screened but not recognized as suffering from CHT. The infant was referred to a pediatrician at the age of one year because of growth retardation. A low T4 level (58 nmol/l), as well as a delayed TSH response on TRH were found. At neonatal screening, the T4 value deviated minus 1.7 s.d. from the mean. In follow-up which was performed because the screening T4 value was among the lowest 3 percentiles, T4 was found to be 110 nmol/l. It was concluded that no hypothyroidism existed in this infant at the time of screening and follow-up. The underlying cause of the tertiary hypothyroidism described here has to be further investigated.

7.6 *Discussion*

Primary and tertiary hypothyroidism and TBG deficiency found in the screening program have been described in this chapter. Twenty-one infants proved to have primary hypothyroidism that was thought to be of a permanent nature; laboratory data which were evidently abnormal and scanning results led to this diagnosis. In several of these infants, however, a definite diagnosis has still to be established in the future.
Transient primary CHT was diagnosed in six infants; this concerned two full-term infants (in one case, the hypothyroidism was probably related to the performance of an amniofetography during pregnancy), and four preterm infants, a condition in which transient thyroid dysfunction is reported (Delange et al., 1980b). Tertiary hypothyroidism was found in two infants. In one - due to a congenital malformation (septo-optic dysplasia) - adreno-corticothropin appeared to be deficient as well. In the other - an idiopathic form - the TRH deficiency seemed to be isolated.
In some cases, it appeared to be difficult to distinguish between TBG

deficiency and tertiary hypothyroidism. In three of the 7 TBG deficient infants, tertiary hypothyroidism was considered because of low FTI values. These low values can be explained by the low free T4 levels in this condition (Hennemann et al., 1971). In one of them, thyroid hormone treatment was started, but terminated when it became known that the father was TBG deficient.

In evaluating the screening program, it is important to know to what extent the performance of adequate diagnostic investigations and rapid treatment appeared to be possible.
Especially at the beginning of the program, performance of a complete diagnostic regimen, including scanning, proved to be difficult. In only 14 of the 21 infants with primary CHT a thyroid scan was performed. Urine analysis, important in the diagnosis of dyshormonogenesis and in the differential diagnosis if the scan shows neither functional thyroid tissue nor uptake in the salivary glands (which can be seen in a trapping defect), was performed in four infants. This part of the diagnostic protocol was probably insufficiently explained in the information supplied to the participating pediatricians.
The delay between the first serum sampling and the beginning of therapy was in 8 of the 21 infants with primary CHT 6 days or more. All were infants in which clinical findings did not lead to suspicion of CHT, even when the screening result was known. In such cases the results of serum measurements were awaited before starting treatment. Three (patients 2, 3 and 17) were initially suspected of a transient form.
During the trial period, TSH only seldom exceeded 50 mIU/l ($\sim$0.20 µIU/punch) in normal infants. For this reason, it will emphasized in a future protocol for diagnosis and treatment, to start thyroid hormone therapy immediately after completion of the diagnostic procedures, without waiting for the result of the serum measurement, if the TSH level is higher than 50 mIU/l.

The following pediatricians kindly provided us with information on CHT patients and infants with TBG deficiency under their care:
E.R. Boersma, F. Bos, N. Ceelie, F.A.J. Enschede, C.J. de Groot, J. Haagendoorn, B.A. Lelieveld, J. van Loo, A.F.F. Manusama, P.E. Le-Maire, B.C. van Pelt, M. Reeser, E.J.C. Schipper, R. Schornagel, C. M.E. Smit, C.E. Vos and the Staff of the Division of Pediatric Endocrinology of the Department of Pediatrics of the University Hospital Rotterdam / Sophia Children's Hospital (G.J. Bruining, S. Drop and H.K.A. Visser).

8. CLINICAL MANIFESTATIONS IN PRIMARY CHT

Clinical manifestations of CHT are known to be nonspecific for the disease, especially during the neonatal period. For this reason, the screening procedure has to be independent of clinical parameters. Nevertheless, many CHT patients diagnosed by neonatal screening, show one or more symptoms belonging to the classical picture of severe symptomatic CHT. In only four, however, were they clear enough to arouse the suspicion of the pediatrician without knowledge of the screening results in the group of 21 infants suffering from permanent primary CHT. One of these four infants had a goiter.
In spite of neonatal screening, there is still need for rapid diagnosis. When an infant is referred to a pediatrician because of an abnormal screening result, he will generally not begin treatment based entirely on the screening results, except in cases in which the positive screening result is combined with severe clinical manifestations of CHT. With a combined T4 / TSH screening in which in practice the TSH result lags behind that for T4, the infant is often referred because of a low T4 value before the TSH result is known. Then, a decision has to be made as to whether to start extended thyroid investigations or merely to wait for the results of the serum measurements. This decision could probably be a more rational one if the absence or presence of clinical manifestations are also considered. The eventual aim is to compile a clinical score that gives a predictive value for CHT in the presence of certain clinical manifestations. For achieving this goal, our experience is too limited. The finding of 21 patients with primary CHT is, of course, insufficient for a more comprehensive statistical analysis. More can be said about the relative importance of each individual clinical manifestation. In addition, some insight is provided into the early clinical syndrome. We will confine ourselves here to the clinical syndrome in permanent primary CHT, the condition as defined in Ch. 7.

8.1 *Methods*

In order to investigate the relative importance of individual clinical signs and symptoms, the frequency within the patient population, the frequency within the normal population and the prevalence of CHT in the total population has to be known. Knowledge on these parameters allows the calculation of the conditional probability of CHT given the presence of certain clinical manifestations. The mutal relationship is again shown in a contingency table (Table 8.1); a predictive value of the presence of a clinical finding
$(P(CHT|F^+)= \frac{n(a)}{n(a+b)})$ can be computed as in the case of the predictive value of a postive screening test (Section 3.2.1)
The group selected by screening but proved to be euthyroid during

Table 8.1 Contingency table of the presence of a clinical finding in patients with primary CHT and a control group

		CHT	no CHT (controls)	total
clinical finding	+	a	b	a + b
	-	c	d	c + d
total		a + c	b + d	a + b + c + d

follow-up served as the control group. This means that a calculated predictive value can in principle apply only to infants having an abnormal screening result.
The group selected by screening consists largely of preterm infants. They were excluded from the control group, since some of the clinical manifestations in prematurity resemble the manifestations found in CHT. This limits the use of the calculated predictive value to infants born at term, here defined as infants born after a length of gestation of 37 weeks or more. In addition, the influence of age had to be excluded. The same age range at follow-up as was found in the patient group* (8 - 30 days) was chosen, although the median age differs between the groups; the median in the patient group is 16 days and in the control group 20 days.
The data were provided by the pediatricians who participated in the project. According to the protocol they noted data on the history and the clinical manifestations (see Appendix II). Since these data were (in principle) received only on *all* infants selected by the screening during period I (see Ch. 5), the control group was limited to infants screened during this first period.
Summarizing, the control group has the following characteristics:
a) an abnormal screening result ($T4 \leq \bar{x} - 1.8$ s.d. and/or TSH > 0.10 µIU/punch)
b) a length of gestation of 37 weeks or more
c) age of 8 to 30 days
d) screening during period I.
The control group consisted of 194 infants. No information was received on 27 infants; in these cases, a second heel puncture instead of a pediatric examination was performed. In several of the remaining 167 cases, the information on one or more items was lacking because of incomplete filling-in of the form.
The patient group consists of 16 infants. Five infants were excluded from the group of 21 infants with permanent primary CHT found by screening during the period of May 1978 up to August 1980, inclusive. Two infants (twins) were born after a gestational period of 36 weeks,

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* Age at which the inquiry on clinical findings was filled in by the pediatrician.

a gestational age which was also excluded from the control group (patients 2 and 3)*. Patients 10 and 21 were excluded because they additionally suffered from conditions other than CHT. Both conditions, a Down's syndrome and renal cystic disease, could considerably influence the clinical manifestations found. For patient 13, the inquiry form on history and clinical manifestations was not received.
In the remaining group of 16 infants, athyroidism was found in 8, ectopia of the thyroid in three, hypoplasia of the thyroid in a normal location in one and CHT combined with a goiter in one. In three infants without goiter, no scanning was performed.

The clinical findings will be indicated either as "absent" (-) or as "present" (+). Most of the findings could be described by the pediatricians in this manner. In several items, the definition of absent or present requires a further explanation which is given below.

Hypothermia: temperature below or equal to 36.5°C, measured more than once during the neonatal period or measured at time of the pediatric examination.
Constipation: defecation less than once per day.
Few child movements: few movements felt by the mother during pregnancy. The maternal perception of fetal movement seems a rather accurate indicator of the fetal motor activity (Hertogs et al., 1979).
Icterus: icterus during more than 10 days or icterus present at the pediactric examination.
Posterior fontanel: size of the posterior fontanel (measured according to the method of Popich and Smith (1972); size larger than 0.5 cm is indicated by (+). The size of the anterior fontanel was not included, since accurate measurement appeared to be difficult.

8.2 *Clinical manifestations in patients and controls*

The clinical manifestations found in the 16 infants who were included in the patient group are presented in Table 8.2 (the patient numbers correspond with the numbers in Table 7.1). In this group, the number of positive findings per infant varied from 1 to 9. In patients 2 and 3 (excluded from the patient group), no positive findings were reported.
The frequencies of the clinical findings in the patient group and in the control group are compared in Table 8.3. The predictive value of a positive finding has been calculated for separate findings, using a prevalence of primary CHT among infants with a gestational age of 37 weeks or more, selected by the screening, of 0.015.

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* The numbers correspond with the infant numbers in Table 7.1.

Table 8.2 Clinical findings in patients with permanent primary CHT (the number corresponds with the numbers in Table 7.1)

clinical findings	1	4	5	6	7	8	9	11	12	14	15	16	17	18	19	20
pregnancy																
few child movements	+	-	-	-	-	-	-	+	+	-	-	-	-	-	-	-
neonatal period																
respiratory distress	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
feeding problems	-	+	-	-	+	+	-	+	-	-	+	-	+	-	-	-
lethargy	-	-	-	-	+	+	-	-	-	+	+	+	+	-	-	+
grimaces without crying	-	-	-	-	-	-	-	-	-	+	-	-	+	-	-	+
hypothermia	-	-	+	-	+	-	+	+	+	+	-	-	-	+	+	-
constipation	-	-	-	-	+	-	-	-	-	-	+	-	-	-	-	-
icterus	-	+	+	+	+	+	-	-	-	+	+	+	-	-	-	+
physical examination																
heart rate <100/min.	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
hypotonia	+	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-
hypoactivity	+	+	-	-	-	+	-	-	-	-	+	-	-	-	+	+
facial edema	-	+	-	-	-	-	-	-	-	-	-	-	-	-	+	+
general edema	-	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-
epicanthus	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+
low nasal bridge	-	-	-	-	+	+	-	+	-	-	-	-	-	-	-	+
protruding tongue	-	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-
hoarse cry	+	+	-	-	+	+	-	-	-	+	-	-	-	-	-	-
size post. fontanel	-	+	-	-	+	+	-	+	+	+	?	+	-	+	-	+
abdominal distension	-	-	-	-	+	+	-	-	+	+	+	-	+	+	-	+
umbilical hernia	-	-	-	-	+	+	-	+	-	-	-	-	+	+	-	-
goiter	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-

The percentage of positive screening values is 3% of the total number of screened infants. Screening of 100,000 infants will select 3,000 infants. Seventy-one (71) percent of the selected group is born after a pregnancy of 37 weeks or more, or 2,130 of 3,000 infants.
Among 100,000 screened infants, 33 patients will be found (prevalence 1/3,000). About 95% of the total number of patients was born after a pregnancy of 37 weeks or more, or 32 infants.
The prevalence of primary CHT in infants selected by screening, born after a pregnancy of 37 weeks or more, is 32 patients in 2,130 selected infants (0.015).

Comparison of the frequencies reveals that the 11 of the 20 items differ significantly between the two groups. Only for these findings were predictive values calculated.
Abdominal distension appeared to be the parameter with the highest predictive weight, followed by hypotonia and hypothermia, with respective values of 0.56, 0.24 and 0.20. Seven items had a predictive value of less than 10%.
The prevalence of combinations of various signs and symptoms is summarized in Table 8.4, considering only the findings that differed significantly in both groups. Patients 2 and 3 were also included

Table 8.3 Frequency of clinical findings in the patient group and in the control group; significance of difference between the frequencies*; predictive value of a positive finding in infants selected by screening (gestational age 37 weeks or more)

clinical finding	frequency patient group	frequency control group	significance of difference	predictive value
abdominal distension	8/16(0.50)	1/167(0.01)	< 0.001	0.56
hypotonia	3/16(0.19)	2/167(0.01)	< 0.01	0.24
hypothermia	8/16(0.50)	5/159(0.03)	< 0.001	0.20
icterus	9/16(0.56)	12/163(0.07)	< 0.001	0.10
hoarse cry	5/16(0.31)	7/167(0.04)	< 0.01	0.10
lethargy / inactivity	10/16(0.63)	15/166(0.09)	< 0.001	0.10
few child movements	3/16(0.19)	4/146(0.03)	< 0.05	0.09
low nasal bridge	4/16(0.25)	9/166(0.05)	< 0.05	0.07
umbilical hernia	5/16(0.31)	13/167(0.08)	< 0.05	0.06
feeding problems	6/16(0.38)	16/167(0.10)	< 0.001	0.06
large post. fontanel	9/15(0.60)	29/129(0.22)	< 0.01	0.04
grimaces without crying	3/16(0.19)	10/153(0.07)	> 0.05	
facial edema	3/16(0.19)	11/166(0.07)	> 0.05	
protruding tongue	2/16(0.13)	3/167(0.02)	> 0.05	
constipation	2/16(0.13)	6/153(0.04)	> 0.05	
general edema	1/16(0.06)	0/165(0.0)	> 0.05	
epicanthus	1/16(0.06)	3/167(0.02)	> 0.05	
goiter	1/16(0.06)	0/165(0.0)	> 0.05	
heart rate (<100/min.)	1/16(0.06)	5/116(0.04)	> 0.05	
respiratory distress	0/16(0.0)	6/166(0.04)	> 0.05	

* Fisher's exact test.

(neither of them showed clinical manifestations) to illustrate that the presence of signs and symptoms is not conditional for CHT. A combination of more than three positive parameters did not occur in the control group, compared to a prevalence of 61% in the patient group.

Table 8.4 Prevalence of combinations of signs and symptoms differing significantly in the patient group and the control group*

number of positive findings	patient group n	patient group cum.%	control group n	control group cum.%
11	-		-	
10	-		-	
9	1	6	-	
8	1	11	-	
7	-	11	-	
6	3	28	-	
5	2	39	-	
4	4	61	-	
3	1	67	4	4
2	2	78	9	13
1	2	89	40	51
0	2	100	52	100

* In the control group, infants were included only if the presence or absence was known for every item. In the patient group one unknown item was assumed to be negative; patients 2 and 3 were included (see text).

8.3 *Discussion*

The clinical picture of neonatal primary hypothyroidism, such as found in infants diagnosed by screening deviated clearly from the clinical picture in a control group - selected by the screening program but proved to be normal in folluw-up -, despite the nonspecificity of the signs and symptoms. This finding is in agreement with experience in other neonatal CHT screening programs. Several authors have published on the clinical manifestations of patients found by screening (Walfish et al., 1979; LaFranchi et al., 1979; Illig, 1979). The results indicated that a symptomatic stage of the disease had developed in many patients by the age of screening.
To assess the significance of this clinical picture for early diagnosis, comparison with a normal control group of the same age is necessary. As far as we know, the only results published in this area come from the Québec program (Letarte et al., 1980a) using the same method of investigation as reported in this study. Although the frequencies of the clinical parameters differed between the two studies (in the Québec study, a higher prevalence of individual signs and symptoms was found) the difference with the control group is clear. Such comparisons show that the detection of a combination of a certain number of clinical parameters has to be acted upon by immediate

follow-up investigations and therapy.
Several restrictions for implementation has to be made. The first concerns the fact that the above mentioned applies only for infants with an abnormal screening result. The control group cannot be supposed to be representative for the normal neonatal population, although, rather less than more clinical manifestations are expected in the normal population than in the control group as defined by an abnormal screening result.
A second fact is the reliability of the results. Probably, the distribution in the *control group* has a longer "tail" towards combinations of more than three parameters. A larger control group would be needed to give evidence to support this hypothesis. The distribution in the *patient group* could be influenced by the fact that, in some patients, the result of the serum measurements were known before the inquiry was filled in. This could influence the objectivity in the examination of the child.
The reliability is also influenced by the fact that the patient group is small. For example, hypothermia was found in 8 of 16 patients; in a binominal distribution, the 95% confidence limits of the percentage of 50 are 24.6% - 75.4% or a number of infants with positive finding between 3.9 and 12.1. The frequency of 5/159 within the normal population could vary within 95% confidence limits of 3.3 tot 15.4 positive findings in 159 infants.
A third restriction concerns the fact that it was not possible to calculate the predictive value of different combinations of positive findings. The combination of hypotonia and lethargy / hypoactivity certainly has another meaning than the combination of hypothermia and few child movements during pregnancy, although both combinations consist of an approximately equal sum of predictive values for the individual parameters. The contribution of each parameter to the diagnosis should be weighed in a discriminant analysis, but requires larger samples. A sample of the total population is needed for assessment of predictive values, regardless of the screening results.

Despite these uncertaincies, the results of these clinical studies stress the need for careful observation of infants referred because of the screening result. In the screening program as performed in the trial area, follow-up is asked for in most cases because of a low T4 at that time without knowledge of the TSH. The finding of a combination of four or more of the 11 items mentioned in an infant with an abnormal screening result and a gestational age of 37 weeks or more should at least be reason to shorten the time period in which follow-up investigations are initiated and treatment is started.

9. THE SCOPE OF SCREENING FOR CHT: DISCUSSION

Screening for congenital hypothyroidism was performed in a trial area (a part of the province of Zuid-Holland). From the first of May 1978 to August 1980, inclusive, 59.455 infants were screened for CHT in combination with the existing screening for phenylketonuria. Duplicate radioimmunoassay for thyroxine (T4) in all samples (blood spotted on filter paper) and for thyroid stimulating hormone (TSH) in the same samples if the T4 was among the lowest 20% of values for the day, was used as screening method. In the beginning of the trial period, TSH was assessed in 10% of the samples; the findings in the first patient (a T4 value equal to the 10th percentile of that day) led to an increase in the number of TSH measurements to 20%. The cut-off points for T4 and TSH were changed during the trial period; eventually T4 values above $\bar{x}$ - 1.8 s.d. and TSH values below or equal to 0.10 µIU/punch (∿25 mIU/l) were considered to be normal.
Since the first of January 1981, screening for CHT has been performed on nation-wide scale in five screening laboratories. The national Steering Committee decided to use the following screening method: T4 measurement in all samples; TSH measurement of the T4 belongs to the lowest 20th percentiles. The T4 cut-off point is $\bar{x}$ - 2.1 s.d. and the TSH cut-off point is 25 mIU/l. Different criteria will be used for referral and a second heel puncture.
The main aim of this study was focused on the feasibility for nation-wide institution. In this chapter, the trial project will be judged on the results of the screening, the organization of the program, the screening test and the validity of the method.

9.1 *Results*

Primary CHT presumed to be permanent was diagnosed in 21 infants, transient primary CHT in six infants and tertiary CHT in two infants. In addition, a deficiency of thyroxine binding globulin (TBG) probably of hereditary origin was found in seven infants.
The prevalence of primary CHT found by screening (1/2800) is significantly higher than the incidence estimated in previous epidemiological studies (De Jonge, 1977; Alm et al., 1978; Jacobsen and Brandt, 1980). Moreover, the screening prevalence found is higher than the mean screening prevalence found world-wide (1/4400). Future screening will show whether this is a persistent difference.
The result of two screening programs suggested seasonal differences in the incidence of primary CHT: in Australia, a higher incidence was found during winter (Connelly et al., 1980); Miyai et al. (1979b) found a higher incidence in Japan during summer. No difference in seasonal occurrence could be demonstrated in our study.

The prevalence of transient hypothyroidism found in the Netherlands (1/19,900) is certainly not as high as that of 1/700 reported in Belgium (Delange et al., 1980b), a country bordering on ours. The marginal iodine supply in Belgium is supposed to be an etiological factor in transient CHT (Delange et al., 1979; Ermans et al., 1980). Probably, a better iodine supply in the Netherlands prevents a wide occurrence of transient CHT. An additional explanation for the difference could be that the Dutch program screens at a later age than the Belgium one (6 to 13 days of age compared to the age of 5 days); the subtle changes in thyroid function could have been missed in this way. This hypothesis, however, is not supported by data from other screening programs performed also as early 5 days.
Secondary and tertiary hypothyroidism occurring in the neonatal period are infrequent disorders. It is not possible to give a reliable estimate of the frequency for our country based on the finding of two patients. Prevalences reported recently in the literature approximate 1/100,000 (Delange et al., 1980a; Dussault et al., 1980d). As applies for primary CHT, also applies here that the prevalence found is related to the cut-off points chosen. TRH or TSH deficiency does not always result in a complete deficiency in thyroid hormones, which means that the T4 values will not be very low in these disorders; a higher T4 cut-off point would probably lead to the finding of a higher frequency. Knowledge of the frequency of secondary and tertiary CHT which can be expected in screening using a certain cut-off point and knowledge of the prognosis to be expected in these infants is of crucial importance for the eventual choice of the screening method: knowledge which can be only derived by prolonged screening.
It proved to be difficult to distinguish between tertiary hypothyroidism and TBG deficiency on several occasions, because of the low normal FTI values in TBG deficiency and the fact that the TSH response to TRH in tertiary CHT can be the same as in normal infants. Apart from this, TBG deficiency is of minor clinical importance and will not be further discussed.
We have little experience with long term follow-up of infants with CHT in our program. The preliminary results of examination for mental and motor development are presented and discussed in Appendix IV. Results reported from other programs are reassuring (Dussault et al., 1980a; Reed and LaVecchio, 1980; Rochiccioli, 1980b), although definite conclusions cannot be drawn.

9.2 *Organization of the program*

The screening for CHT was combined with the existing screening procedure for PKU. As far as the organization was concerned, only minor modifications of the program were possible and the question remains of whether this PKU program as performed in the Netherlands is suitable for CHT screening. The organization has to cope with a far higher recall rate than is necessary in the PKU program; in addition, CHT screening makes probably higher demands on the time period during which screening and follow-up has to be performed.

It is difficult to relate these organizational aspects with findings in other countries. Each organization is typical for the Health Care system in which the program operates. Moreover, comparison is complicated by the fact that our organization has to be suitable for screening at home, since many infants are born at home and even 60% is screened at home, a situation that distinguishes the Netherlands from many other countries.

Heel puncture. In the evaluation of the performance of the heel puncture three important aspects have to be considered. The first is the participation in the screening program. In 1979, 99.3% of the newborns in the province of Zuid-Holland were screened. The main reasons for nonparticipation were refusal by the parents and neonatal death. The obligatory birth registration in the Netherlands and the check system for participation in the screening operated by the Vaccination Administration Bodies guarantee a high compliance. Of course, the nonparticipation results in a chance of occasionally missing a patient, but to achieve greater compliance seems hardly possible.
The second aspect is the age at which the heel puncture is performed. It was advised that the heel puncture be done preferably at the age of 6 to 8 days or in any case before the end of the second week of life, a goal reached in, respectively, 60% and 97% of the cases. A further advance of the time to the beginning of the second week of life is desirable.
Thirdly, the filling of the circles of the filter paper has to be considered. In insufficient filling, the infant is retested, which occurred in approximately 0.3% of the cases during the PKU screening. This percentage increased to about 1% after the institution of the combined screening, when four circles were actually needed instead of the previous two. This increased the recall rate considerably. Furthermore, it meant the possible age at which the diagnosis could be made was later.
In the province of Zuid-Holland, many different persons are involved in the performance of the heel puncture, each of whom does only a few per year. In a nation-wide screening program, it will have to be evaluated whether the insufficient filling is less of a problem in provinces where the heel puncture is performed by selected persons.

Follow-up. At the beginning of the program, it was stated that, if pediatric examination was necessary, this should take place preferably within 24 hours after the screening result was known. Given the median age at which the screening was performed (about 7 days) and the median time lapse between screening and T4 measurement (3 days), the median age at which pediatric examination could take place could be 11 days. In actuality, this was delayed by more than one week and the median age at which pediatric examination took place was about 23 days.
Fortunately, this figure is not representative for the age at which the first pediatric examination was carried out and treatment started in the patient group. In the group of patients with primary CHT, the median age of the first pediatric examination was 16 days and the

median age at which treatment was started was 18 days. If the screening result was seriously suspect for CHT, personal involvement by the the head of the CHT laboratory and the head of the Vaccination Administration Bodies (under responsibility of the Provincial Pediatrician or the physician of the Municipal Health Service in Rotterdam) appeared to hasten the follow-up. The median of 18 days is quite comparable to data mentioned in various screening programs: the Australian program reports a range of 8 to 56 days (Connelly et al., 1980), the Québec program an average of 21 days and both the New England and the Northwest American program an average of 27 days (Dussault et al., 1980d). In the Swiss program, an early median age of 10 days could be achieved (Illig, 1980).
In a nation-wide program, the general practitioners and the pediatricians should be urged to hasten the day of referral and follow-up. In the decision to start extensive diagnostic examinations and treatment as soon as possible (Landelijke Begeleidingscommissie CHT, 1980), the presence of clinical manifestations should be taken into account. In Chapter 8, the results of the clinical investigations were presented. A group of 11 clinical findings appeared to be significantly more frequent in the patient population than in a control group; if a low T4 level is found and the TSH level not yet known, a combination of several positive clinical findings is highly suspect for CHT.
During the second period of the trial, the possibility to do a second heel puncture, depending on the screening result, instead of a referral was introduced into the trial area. In about 30% of the second heel punctures, a third examination was necessary. Although the second heel puncture (mostly performed at home) considerably reduced the number of referrals and, because of that, the anxiety of the parents and the costs of the program, it delayed the age of a possible diagnosis. This seems to be acceptable, since in cases in which a second heel puncture was thought to be sufficient the values found in screening were near the normal limits. This suggests that, if present at all, hypothyroidism is of a less severe degree at that time.
Another important aspect of the performance of the follow-up is the nonparticipation. From the first of May 1978 up to the first of March 1980, 1420 infants were selected by the screening. In 94 of these (7%) either no follow-up was done or the follow-up was not completed. In only 24 cases was the exact reason for nonparticipation known: death of the infant, move of the family, out of the area, refusal by general practitioner or parents or administrative error. In addition, the number of foreign infants among the group not complying with follow-up appeared to be relatively high. This is an aspect of screening which requires special attention.

Administration. Apart from the statistical analysis of the T4 measurement in screening, the administration work for both the PKU and the CHT screening was done completely by hand. Each screening result is - for the time being, for an infinite period - filed by name and birth date at the Vaccination Administration Bodies. The administration involves many steps, all of which include the possi-

bility of making mistakes. The system, however, functions well and accurately. During the trial period, an administrative error occured twice and a necessary second heel puncture was omitted (2% of the cases of nonparticipation). Automation as carried out in the Québec screening program (Morisette and Dussault, 1979) should decrease the number of such mistakes, although it is doubtful whether human error can be totally avoided.

9.3 *The screening test*

The reliability of the T4 measurement is influenced by several factors. Firstly, the within-assay variation coefficient was about 5% and the between-assay variation coefficient was about 10%. In addition, the level measured is influenced by the amount of serum that is collected on the filter paper and the apparently different amounts of serum at different sites of the filter paper (Schopman, 1979).
To minimize the influence of the assay variation, the T4 values were expressed as the number of standard deviations from the daily mean. This standardization has disadvantages. The T4 distribution can be changed by a large number of blood samples being stored for a long period, by a large number of blood samples collected relatively late in the neonatal period and by a large number of samples from preterm and small-for-dates infants. The first two factors seem to play a part in individual cases only (Ch. 5.3). The number of samples of preterm and small-for-dates infants (with lower T4 values than found in full term infants with a birth weight appropriate for gestational age) could have influence on the total distribution and, by this, on the cut-off point. In an early phase of the screening, date were collected on screening T4 values in preterm and small-for-dates infants (unpublished data). Although the data provided insufficient information to exactly determine the consequences, it could be estimated that an incidental doubling of the number of preterm infants screened on one day would result in an increase in the standard deviation from 20 pg/punch to 22 pg/punch. The daily calculated mean would decrease from 110 pg/punch to 108 pg/punch. A T4 cut-off point of $\bar{x} - 2.0$ s.d. (on the average, equal to 70 pg/punch) would then select at a level of 64 pg/punch.
These disadvantages do not outweight the advantages. The correlation between T4 measured in heel puncture blood and T4 measured in serum (collected simultaneously) was better in the standardized values, even in the beginning of the program when the daily series were small (number of samples about 60 per day) and the distribution was considerably influenced by the number of samples. In addition, the variation coefficient in the standardized values is lower than in the nonstandardized values (Schopman, unpublished data).
Apart from the fact that the T4 levels in preterm and small-for-dates infants influence the T4 distribution, the lower levels in these infants result in a high percentage of preterm and small-for-dates infants among the false-positives. To reduce this effect, Dussault et al. (1976b) apply a correction factor for the T4 level using birth

weight. It is preferable to correct for both birth weight and gestational age, but it is doubtful whether such a correction would be feasible in the situation in the Netherlands. A large percentage of the infants is born at home, where precise assessing of gestational age and even accurate weighing is difficult.

The assay variation coefficient of the within-assay variation of the TSH is about 11% and that of the between-assay variation is about 18%. Since the TSH distribution is very skewed (to the right), conversion of the distribution to a standard normal distribution is not possible. A cut-off point based on a percentile value would be appropriate in such a situation, but would considerably increase the number of false-positives due to an elevated TSH level. In many series, all values found were far below the cut-off point chosen and the highest value did not necessitate a recall, even considering the assay variation. For this reason, the cut-off point for TSH had to be based on a fixed value.

9.4 *Validity of the screening method*

The discussion on the validity of different screening methods is found in Chapter 6. A model in which the validity of the screening method used in the trial area can be estimated for different combinations of T4 and TSH measurement was described.
A screening method such as used in the trial area, with the difference that the T4 cut-off point is arbitrarily decreased from $\bar{x}$ - 1.8 s.d. to $\bar{x}$ - 2.0 s.d., can be estimated to have a sensitivity of 0.97, a specificity of 0.98 and a predictive value of a positive test of 0.015. (The predictive value is comparable to the predictive value of an abnormal PKU test. During two and a half year screening, suspect values requiring a second heel puncture were found in 1230 cases and positive values requiring a referral in 27 cases; PKU was found in 25 cases, which means a predictive value of 0.02. (Landelijke Begeleidingscommissie Phenylketonurie, 1978). Although the specificity in the PKU screening is higher, the lower prevalence of PKU implies a low predictive value).
It was estimated that the use of this method could mean missing 3% of the patients with primary CHT, because of T4 levels above the 20th percentile in these infants. Although such high T4 levels probably indicate only a minor hypofunction of the thyroid without severe clinical consequences, aiming for a higher percentage of TSH measurements should be considered. An increase to 50% means an increase in the sensitivity to virtually 1; the specificity is decreased to 0.976 and the predictive value to 0.014.

9.5 *Conclusions*

What conclusion can be drawn from the results in the trial area, also

taking into account more theoretical considerations, on screening for CHT? The screening in the trial area has proved to be effective as far as case finding is concerned. The prevalence found by screening was much higher than was expected from several epidemiological studies carried out previously. This means that a percentage of the group of patients found by screening consisted of infants who would have formerly escaped clinical attention. Whether this percentage eventually proves to have a transient hypothyroidism remains a matter for constant attention and stresses the need for a careful diagnosis in the neonatal period, a centralized evaluation of the screening and follow-up and the participation of every pediatrician in such an evaluation. Another reason for this is the need for increasing knowledge on the clinical picture of secondary and tertiary hypothyroidism in the neonatal period.

The organization also proved to be effective. A 99% coverage in screening and a 93% coverage in follow-up were achieved. In the future, more attention will have to be paid to the filling of the circles with blood and the time period during which the screening is performed.

At present, it is preferable to screen for all forms of CHT which occur in the neonatal period: primary, secondary and tertiary CHT. There is no reason to suppose that infants with secondary and tertiary hypothyroidism occurring in the neonatal period should not have the benefit from early detection and treatment. For this purpose, a combined T4 / TSH method is necessary, in which the number of TSH measurements should preferably be as high as 50% of the total measurements.

This is a far-reaching aim of screening and such a program should be carried out only if adequate diagnostic examination of possible patients and adequate follow-up and evaluation of the results are guaranteed. Furthermore, it should be a conditional choice. The national organization will have to prove to be sufficiently competent to perform this exacting program; it will also have to be proved that the national program is accepted by the population and prolonged screening here and elsewhere will have to assure that, in screening for primary CHT as well as for secondary and tertiary CHT, the benifits outweigh the disadvantages.

Congenital hypothyroidism (CHT) is an important health problem which can result in permanent mental retardation. Detection of the disorder and initiation of treatment in the first weeks of life can partly or even completely prevent these serious consequences. Laboratory tests are required for early detection, since clinical manifestations are seldom obvious during the neonatal period.
As has been done in many other countries, a screening program was also started in the Netherlands. The project was begun in a defined trial area (the southern part of the province of Zuid-Holland). Screening was combined with the existing phenylketonuria (PKU) screening which was instituted nation-wide in 1974. Thyroxine (T4) and thyroid stimulating hormone (TSH) were measured by microradioimmunoassay in blood spotted on filter paper. Nation-wide screening for CHT began in the first week of January 1981.

The main aim of this study was the evaluation of the screening in the trial area; emphasis was placed on the question of whether the screening procedure and method chosen was the optimal one for permanent and nation-wide use. A second aim was to investigate the contribution of early clinical manifestations to early detection of CHT (Ch. 1).

Literature data are presented in Chapter 2. They were confined to those aspects of the function and dysfunction of the thyroid which were thought to be important for purposes of screening for CHT. Damage to the central nervous system caused by CHT results in mental retardation and other neuropsychological sequelae. Two reasons for these serious consequences are: the rapid development of the central nervous system during the fetal period and the first years of life and the fact that fetal thyroid hypofunction cannot be corrected by the maternal thyroid.
The causes of CHT, clinical manifestations, prognosis, screening prevalence and clinical incidence, diagnosis and treatment are discussed. Aspects relating to primary CHT and secondary and tertiary CHT are considered separately.

Concepts and background information on screening as such are presented in Chapter 3. It was determined whether the CHT screening procedure was in compliance with the principles for screening of Wilson and Jungner. The procedure did fulfil these criteria, although several questions remain to be answered. These concern mainly the natural history of cases detected by screening and the problem of whether screening detects every case of hypothyroidism of congenital origin.

The design of the study in the trial area is presented in Chapter 4. The screening procedure is described within the framework of the

existing screening for PKU and the system of health care in the Netherlands. The screening method consisted of a T4 measurement and, if the T4 was among the 20% of the lowest T4 values for the given day (in the beginning of the program, among 10%), a TSH measurement. Follow-up was requested in case of a low T4 value whether or not combined with an elevated TSH value. During the first period, every follow-up examination was done by a pediatrician; during the second period, the possibility to do a second heel puncture instead of a referral in case of slightly abnormal values was introduced.

Chapter 5 presents some of the screening results. The screening process is described using data collected on infants born in the trial area during the months of May 1978 to February 1980, inclusive. During this period, 43,554 infants were screened.
The first part of the chapter includes the results of the T4 and TSH measurements. The T4 values were influenced by assay variation, variation in quantity of serum on the filter paper punch and the biological variation dependent on length of gestation and birth weight. In addition, it was assumed that there was a negative association between the T4 value determined and the time lapse between the heel puncture and the T4 measurement.
The second part contains data on follow-up examinations, the time lapse between the different steps in the screening procedure and the participation of the subjects in screening and follow-up examinations. Follow-up was requested in about 3% of the infants screened. Dependent on the screening values, either a referral or a second heel puncture was recommended. In addition, a second heel puncture was performed in one percent of the infants screened because of insufficient filling of the blood circles on the filter paper.
The median age at which the screening took place was 8 days, the median time lapse between screening and T4 measurement 3 days, and that between T4 measurement and follow-up 7 days. The median age at which follow-up was done in infants selected by screening was 23 days (in the patients group, 16 days); in the group in which a third examination was necessary, it was 34 days.
The laboratory results and some general information on infants selected by screening are discussed. As expected from T4 screening, the number of preterm infants was relatively high in the selected group. More than 99% of the newborns were screened. Follow-up was not done or completed in 7% of the group in which it was necessary. Reasons for nonparticipation in follow-up were, as far as known, the death of the child, family leaving the area, or refusal by parents or general practitioner. Foreign infants appeared relatively more often not to participate in follow-up.
It was left to the pediatricians to decide whether or not the screening was a cause of anxiety for the parents. Most often anxiety was due to insufficient information on screening and follow-up.

Different methods for early detection of CHT are compared in Chapter 6. The results derived during the total trial period (May 1978 to August 1980, inclusive) are compared with a Dutch epidemiological study on the incidence of clinically diagnosed CHT. The prevalence

found by screening was considerably higher than the clinical incidence. The median age of initiation of treatment was 18 days as compared to 60 days following clinical diagnosis. The validity of different screening methods are compared. A model for calculating the predictive value of a positive screening test (as conditional probability dependent on the sensitivity, the specificity of the test and the prevalence of the disease) was constructed using our results and those reported in the literature. The highest predictive value is found when the test includes a T4 determination plus a TSH measurement (in case of a low T4), in which follow-up is requested only if the TSH value is elevated. Optimal sensitivity can be achieved by employing a T4/TSH test in all samples in which follow-up is indicated on the basis of a low T4 and/or elevated TSH value, but with a loss of specificity and predictive value. The advantages and disadvantages of the different methods are discussed.

The findings in 21 infants with permanent primary CHT, six with transient primary CHT, two with tertiary CHT and seven with a probable hereditary deficiency of thyroxine binding globulin (TBG) are reported in Chapter 7. These cases were detected during the total trial period in which 59,455 infants were screened. Laboratory measurements, scanning results and several clinical characteristics are described. In some cases, it appeared to be difficult to distinguish between TBG deficiency and tertiary hypothyroidism.

A second aim of this study was to investigate whether clinical findings which were nonspecific for the disease contributed to early diagnosis (Ch. 8). For this purpose, the patients with permanent primary CHT were compared with a control group consisting of infants selected by the screening but proved to be normal in follow-up examination. The way in which the control group was chosen limits the conclusions in this chapter to infants selected by screening.
Eleven clinical manifestations were more often found in the patient group. In addition, 60% of the patients showed four or more positive clinical signs or symptoms, while not more than three such findings were ever evident in the control group.
These data on 21 patients are, of course, insufficient for extensive statistical analysis. However, it was concluded that careful examination is necessary when the child if referred to a pediatrician and that several clinical manifestations should at least result in a shortening of the time period between the diagnostic examination and the initiation of treatment.

It was concluded that screening for CHT in the trial area was effective (Ch. 9). Several aspects concerning the heel puncture, the time period during which screening and follow-up is performed and the participation in screening and follow-up require constant attention. At present, it seems to be preferable to screen for all forms of CHT, primary as well as secondary and tertiary. The screening method used in the trial area, with several restrictions, is suitable for this purpose. Some of these restrictions are: (1) the T4 cut-off point can be decreased; (2) to ensure optimal sensitivity, the T4 cut-off

point for TSH should be elevated to about the 50th percentile. Such a far reaching aim of screening can be achieved only if adequate diagnostic examinations and treatment and evaluation of screening results are guaranteed.

SAMENVATTING

Congenitale hypothyreoïdie (CHT) is een ernstige aandoening die onder meer kan leiden tot blijvende achterstand van de mentale ontwikkeling. Vroege herkenning en behandeling, dat wil zeggen behandeling vanaf de eerste levensweken, kan deze ernstige gevolgen grotendeels en mogelijk geheel voorkomen. Aangezien de lichamelijke verschijnselen van CHT in de neonatale periode zelden zodanig zijn dat op grond daarvan de diagnose kan worden gesteld, is voor vroege opsporing een laboratorium onderzoek noodzakelijk.
In navolging van vele andere landen werd ook in ons land een screening op CHT ingevoerd, waarbij gebruik wordt gemaakt van micro-radioimmunologische bepalingen van het thyroxine (T4)-gehalte en het thyreoïd stimulerend hormoon (TSH)-gehalte. Het onderzoek is als proef begonnen in het zuidelijk gedeelte van Zuid-Holland, in combinatie met de reeds in 1974 ingevoerde screening op phenylketonurie (PKU). Daartoe wordt in de tweede levensweek door middel van een hielprik bloed afgenomen dat op filtreerpapier wordt verzameld.

Het hoofddoel van deze studie is de evaluatie van de in de Zuid-Hollandse proefregio gekozen screeningsmethode, met als vraagstelling of deze methode als optimaal kan worden beschouwd voor een landelijke invoering (hoofdstuk 1). Het onderzoek naar de bijdrage die vroege klinische kenmerken en verschijnselen zouden kunnen leveren aan de herkenning van CHT is een nevendoel van deze studie.

Hoofdstuk 2 is een literatuuroverzicht van die aspecten van de schildklierfunctie die in het kader van de vroege opsporing van CHT van belang worden geacht. Aan de mentale retardatie en aan andere neurologische stoornissen, die het gevolg kunnen zijn van een CHT, liggen afwijkingen in het centrale zenuwstelsel ten grondslag. Deze kunnen bij een onvoldoende schildklierfunctie ontstaan in de periode van snelle groei en ontwikkeling van het centrale zenuwstelsel (de foetale periode en de eerste levensjaren). Een foetaal tekort aan schildklierhormonen kan niet door de moederlijke schildklierfunctie worden gecompenseerd.
Vervolgens worden besproken: de oorzaken van CHT, de klinische verschijnselen, de prognose ten aanzien van mentale ontwikkeling en neurologische verschijnselen, de frequentie van CHT, de diagnostiek en de behandeling. De verschillende aspecten van de primaire CHT enerzijds en de secundaire en tertiaire CHT anderzijds komen afzonderlijk aan de orde.

Hoofdstuk 3 geeft enkele begrippen en achtergronden over screening in het algemeen. De CHT-screening wordt getoetst aan de door Wilson en Jungner geformuleerde principes voor screening. Hoewel op grond hiervan kan worden geconcludeerd dat de CHT-screening aan deze principes voldoet, blijven enkele problemen onopgelost. Deze hebben vooral betrekking op het natuurlijke verloop van de bij screening

opgespoorde gevallen en op de vraag of alle vormen van CHT in de neonatale periode reeds zijn aan te tonen. De mogelijke screeningsmethoden voor CHT worden besproken.

De organisatie van de CHT-screening in de proefregio wordt in hoofdstuk 4 besproken. Aangezien deze vrijwel parallel verloopt aan de reeds bestaande PKU-screening, wordt ook de gang van zaken bij de PKU-screening beschreven. Tevens wordt de plaats van de screening binnen het kader van de Nederlandse gezondheidszorg geschetst. De gekozen screeningsmethode behelst een T4-bepaling in alle bloedmonsters en een TSH-bepaling indien de T4-waarde behoort bij de 20% (aanvankelijk 10%) laagste waarden.
Vervolgonderzoek is geïndiceerd bij een lage T4-waarde en/of een hoge TSH-waarde. In de beginperiode van de screening werden alle vervolgonderzoeken door een kinderarts verricht, later werd de mogelijkheid ingevoerd om bij licht-afwijkende waarden een tweede hielprik te doen.

In hoofdstuk 5 wordt een deel van de resultaten van de screening gepresenteerd. Het verloop van het screeningsproces wordt nagegaan aan de hand van gegevens die werden verzameld gedurende de geboortemaanden mei 1978 tot en met februari 1979; in deze periode werden 43.554 kinderen gescreend.
Het eerste gedeelte van het hoofdstuk betreft de resultaten van de T4- en TSH-bepalingen. Behalve door bepalingsvariaties wordt het T4-gehalte beïnvloed door variaties in hoeveelheid serum per monster en door biologische variaties, afhankelijk van zwangerschapsduur en geboortegewicht van het kind. Bovendien wordt een relatie vermoed tussen de gemeten T4-waarde en de tijd die verstrijkt tussen de hielprik en de T4-bepaling.
Het tweede deel van het hoofdstuk bevat gegevens over het vervolgonderzoek, het tijdsverloop tussen verschillende stappen van de screening en de deelname aan screening en vervolgonderzoek.
Op grond van de gestelde indicaties was bij ruim 3% van de gescreende kinderen een vervolgonderzoek noodzakelijk, hetzij door een kinderarts, hetzij in de vorm van een tweede hielprik. Bovendien was bij 1% van de kinderen een tweede hielprik noodzakelijk in verband met onvoldoende vulling van het filtreerpapier.
Het tijdsverloop was als volgt: de mediane leeftijd waarop werd gescreend was 8 dagen, de mediane duur tussen screening en vervolgonderzoek was 3 dagen, het mediane tijdsverloop tussen T4-bepaling en het vervolgonderzoek 7 dagen. De mediane leeftijd waarop een vervolgonderzoek werd verricht was 23 dagen (16 dagen bij de patientengroep) en 34 dagen bij de kinderen bij wie een derde onderzoek werd verricht.
De laboratorium-resultaten van het vervolgonderzoek en enkele klinische kenmerken van de kinderen die bij de screening werden geselecteerd zijn in het kort beschreven. Het percentage vroeg geborenen en kinderen met een laag geboortegewicht was relatief hoog.

De screening werd uitgevoerd bij ruim 99% van de pasgeborenen. Bij 7% van de kinderen bij wie vervolgonderzoek noodzakelijk werd geacht

werd dit niet uitgevoerd dan wel niet volledig afgerond. Redenen om niet deel te nemen aan screening of vervolgonderzoek waren overlijden van het kind, verhuizing en weigering door huisarts of ouders. Bij het vervolgonderzoek blijken buitenlandse kinderen relatief vaak niet te worden onderzocht.
Bij de ongerustheid van de ouders over een vervolgonderzoek bleek vooral een onvoldoende geïnformeerdheid een rol te spelen.

In hoofdstuk 6 worden verschillende methoden van vroege opsporing van CHT onderling vergeleken. Allereerst worden de resultaten, verkregen in de totale proefperiode (van 1 mei 1978 to en met 31 augustus 1980), vergeleken met de resultaten van een Nederlandse epidemiologische studie naar CHT-patienten bij wie de diagnose op klinische gronden was gesteld. De screeningsprevalentie bleek aanmerkelijk hoger te zijn dan de incidentie die op grond van de epidemiologische studie werd berekend. Het tijdstip waarop de diagnose werd gesteld lag bij de klinisch gediagnostiseerde patienten op een mediane leeftijd van circa 60 dagen (screening: 18 dagen).
Vervolgens wordt ingegaan op de geschatte validiteit van de diverse screeningsmethoden. Daartoe wordt aan de hand van eigen resultaten en resultaten die zijn vermeld in de literatuur, een model opgesteld waarmee de voorspellende waarde van een positieve screeningstest - als voorwaardelijke kans afhankelijk van de sensitiviteit en specificiteit van de betrokken methode en van de prevalentie van CHT - kan worden berekend. Ook zijn de consequenties van vier verschillende screeningsmethoden voor één jaar screening in het gehele land berekend. De hoogste voorspellende waarde wordt bereikt in een T4-methode met additionele TSH-bepalingen, waarbij vervolgonderzoek slechts geïndiceerd is op grond van een verhoogde TSH-waarde. Een optimale sensitiviteit wordt bereikt met een methode waarbij zowel T4 als TSH wordt bepaald in alle bloedmonsters en vervolgonderzoek wordt ingesteld op grond van een lage T4- en/of een hoge TSH-waarde. Dit gaat echter ten koste van de voorspellende waarde en de specificiteit van de test. De voor- en nadelen van de verschillende methoden en de keuze van de indicaties van vervolgonderzoek worden besproken.

Hoofdstuk 7 beschrijft de resultaten van het vervolgonderzoek bij de CHT-patienten en bij de kinderen met een deficiëntie van het thyroxine-bindend globuline (TBG), die bij de screening in de totale proefperiode werden gevonden. In deze periode zijn 59.455 kinderen gescreend. De laboratorium-gegevens, de resultaten van de schildklier-scan, de gegevens over de behandeling en enkele klinische kenmerken worden besproken. De gegevens betreffen 21 kinderen met een vermoedelijke permanente primaire CHT, vijf kinderen met een passagère primaire CHT en twee kinderen met een tertiaire CHT. Een onderscheid tussen tertiaire CHT en TBG deficiëntie bleek niet altijd eenvoudig te maken.

Het was een tweede doel van deze studie na te gaan of klinische verschijnselen een bijdrage tot vroege diagnostiek zouden kunnen leveren. Daartoe werden de verschijnselen van de patienten vergeleken

met verschijnselen gevonden in een controle-groep. De laatste groep bestond uit kinderen die door de screening werden geselecteerd, maar gezond bleken te zijn. De wijze waarop de controle-groep werd samengesteld beperkt de conclusies tot kinderen met een afwijkende screeningsuitslag.
Elf klinische verschijnselen werden significant vaker in de patientengroep gevonden. In 60% van de patientengroep werden vier of meer verschijnselen opgemerkt, terwijl in de controle-groep geen van de kinderen meer dan drie verschijnselen had.
De patientengroep is uiteraard te klein voor verdere statistische analyse. Er werd slechts geconcludeerd dat zorgvuldig klinisch onderzoek noodzakelijk is en dat de aanwezigheid van meerdere klinische verschijnselen in ieder geval spoedig dient te leiden tot verdere diagnostiek en eventueel begin van de behandeling.

In hoofdstuk 9 wordt geconcludeerd dat de screening in de proefperiode effectief is gebleken. Diverse aspecten betreffende de uitvoering van de hielprik, het tijdsverloop en de deelname aan het vervolgonderzoek verdienen echter blijvende aandacht.
Op grond van ervaringen die elders èn in dit onderzoek zijn opgedaan en op grond van theoretische overwegingen dient de screening zich vooralsnog niet alleen te richten op de vroege opsporing van primaire CHT maar tevens op de vroege opsporing van secundaire en tertiaire CHT. De screeningsmethode, die in de proefregio werd gebruikt, zou op enkele punten dienen te worden gewijzigd. De T4-grenswaarde die als normaal wordt beschouwd, zou kunnen worden verlaagd. Voor een optimale opsporing van primaire CHT zou het percentage TSH-bepalingen tot circa 50% moeten worden verhoogd. Een dergelijk programma kan slechts worden uitgevoerd indien begeleiding bij diagnostiek en behandeling en evaluatie van de resultaten gewaarborgd zijn.

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APPENDIX I

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Dr. H.W.A. Voorhoeve, pediatrician, representative of the Provincial Pediatricians
Dr. S.K. Wadman, chemist, Dutch Association for clinical Chemistry

APPENDIX II

Protocol for follow-up and therapy

The protocol for follow-up was drawn up by members of the National Steering Committee and the Rotterdam Working Party. The protocol for the combined L-T3 and L-T4 therapy was developed by the Staff of the Division of Pediatric Endocrinology of the Department of Pediatrics of the University Hospital / Sophia Children's Hospital, Rotterdam.

Serum measurements
T4, TBG test, FTI, T3, TSH.
Indications for repeat measurements:
T4 $\leq$ 60 nmol/l (60-70 dubious)
TBG test $\leq$ 80%
FTI $\leq$ 60 (60-70 dubious)
T3 $\leq$ 1.0 nmol/l
TSH $\leq$ 20 mIU/l (10-20 dubious)

Additional investigations (in case of CHT)
- thyroid scan with 99m Tc pertechnetate
- protein bound iodine in serum
- iodohistidine, iodotyrosine and iodine in urine
- radiological examination of the left foot and knee
- TRH test (serum measurement of TSH at 0, 20 and 60 min. after injection of 40 µg TRH), if there is suspicion for secondary or tertiary CHT

Therapy
1. Combined T3 and T4.
   Initiation with 3 µg L-T3/day. Increase by 3 µg every two days up to a dose of 15 µg/day. When this dose is reached, T3 is gradually decreased by 3 µg every week and eventually stopped.
   L-T4 treatment is started when a T3 dose of 15 µg/day is reached. The initial dose is 15 µg/day which is increased by 15 µg every week up to a dose of 75 µg/day (with the availability of commercial L-T4 with a constant concentration to a dose of 5 µg/kg/day). In the beginning of this form of therapy, careful monitoring of the cardiac function and other clinical manifestations is required.
2. T4.
   L-T4 is started in a daily dose of 25 µg, after 4 days increased to 30 µg and after 4 days to an eventual dose of 75 µg/kg/day (with the availability of commercial preparation to a dose of 5 µg/kg/day).

*Questionnaire for history and clinical examination**

General data:
name and surname :
sex :
date of birth :
residence : general practitioner:
pediatric examination: date:
inpatient / outpatient
pediatrician : name: hospital:

Family history:
thyroid disorders : no / yes
if present, specify :
consanguinity : no / yes

Pregnancy:
disturbances : no / yes . . . . . .
medication : no / yes . . . . . .
expectorant : no / yes . . . . . .
antithyroid drugs : no / yes . . . . . .
smoking : . . number of cigarettes/day
radiological examination : no / yes . . . . . .
multiple pregnancy : no / yes . . . . . .
child movements : many / normal / few
other relevant information: . . . . . .

Gestational age / birth weight:
length of amenorrhoea : . . weeks, . . days
Dubowitz score : . . weeks
birth weight : . . . . g

Delivery:
undertaken by : G.P. / midwife / consultant obstetrician
where : hospital / outpatient department / at home
spontaneous delivery : no / yes: cephalic / breech
operative delivery : no / yes:
forceps / vacuum / caesarean section
medication during labour : no / yes . . . . . .
resuscitation : no / yes . . . . . .
apgar score : after 1 min. ; after 5 min.
other relevant information: . . . . . .

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* Translation of the Dutch text.

Neonatal period:
respiratory distress : no / yes . . . . . .
feeding problems : no / yes . . . . . .
feed : . . . . . .
lethargy : no / yes . . . . . .
grimaces without crying : no / yes . . . . . .
hypothermia : . . °C
occurring at the age of . . days
first defecation : age . . days
frequency of defecation : . . . . . .
icterus : no / yes, during . . days
maximum bilirubin level: . . .
other relevant information: . . . . . .

Physical examination:
weight : . . . . g; length: . . cm
head circumference : . . . cm; heart rate: . . ./min.
temperature : . . °C
anterior fontanel : length: . . cm; width: . . cm
posterior fontanel : length: . . cm; width: . . cm
underline if present:
hypotonia / inactivity / icterus / facial edema / general edema / epicanthus / low nasal bridge / protruding tongue / hoarse cry / thyroid visible sideways / goiter / trachea palpable better than usual / abdominal distension / umbilical hernia
other relevant information: . . . . . .

Conclusion:
healthy / suspicious for CHT /
other disease: . . . . . .

Parents:
anxiety more than can be reasonably expected: no / yes . . . . .

Venepuncture:
performance: easy / difficult / not successful
site: . . . . . .

APPENDIX III

Participating hospitals in the trial area and bordering areas

The following hospitals in the trial area and bordering areas have a pediatric inpatient and outpatient department. The pediatricians attached to one or more of these hospitals participated in the project.

Rijnoord Hospital, Alphen aan den Rijn
Bethel Hospital, Delft
St. Hippolytus Hospital, Delft
Oude en Nieuwe Gasthuis, Delft
Van Weel-Bethesda Hospital, Dirksland
Municipal Hospital, Dordrecht
Deaconesses' Hospital Refaja, Dordrecht
Roman Catholic Hospital, Dordrecht
Prinses Beatrix Hospital, Gorinchem
Bleuland Hospital, Gouda
St. Jozef Hospital, Gouda
Juliana Children's Hospital, The Hague
Roman Catholic Hospital Betlehem, The Hague
Deaconesses' Hospital Bronovo, The Hague
Leyenburg Hospital, The Hague
Westeinde Hospital, The Hague
Pediatric Department of the University Hospital, Leiden
St. Antoniushove, Leidschendam
St. Franciscus Gasthuis, Rotterdam
St. Clara Hospital, Rotterdam
Zuider Hospital, Rotterdam
Eudokia Hospital, Rotterdam
Van Dam Hospital, Rotterdam
Ikazia Hospital, Rotterdam
Pediatric Department of the University Hospital / Sophia Children's Hospital, Rotterdam
Nolet Hospital, Schiedam
Municipal Hospital, Schiedam
Municipal Hospital, Sliedrecht
Holy Hospital, Vlaardingen
Deaconesses' Hospital, Voorburg
Hofpoort Hospital, Woerden

APPENDIX IV

Psychomotor and mental development of infants with primary CHT

The mental and psychomotor development of infants with permanent primary CHT was investigated at the end of the trial period. For this purpose, the mental and motor scale of the Bayley Scales of Infant Development (BSID) were administered (Bayley, N. Manual for the Bayley Scales of Infant Development. The Psychological Corporation. New York, 1969). The Mental Scale measures sensory-perceptual acuities, discriminations and the ability to respond to these; the Motor Scale measures the gross motor ability and finer manipulatory skills of hands and fingers.
The study was aimed at infants which had reached an age of 9 months or older (infants 1 to 16, inclusive, Table 7.1). The examinations were performed by M. Uleman-Vleeschdrager (psychologist) and in one infant, one of a twin simultaneously examined, by I. Skoda (psychologist), in the outpatient Department of Child Psychiatry of the University Hospital Rotterdam/Sophia's Childrens Hospital (Prof.Dr. J.A.R. Sanders-Woudstra). Two infants were not investigated. Infant 10 died in the first month of life. Infant 13 did not participate in the study.

Results
In Table 1, the results of the test are summarized in relation to the age at the onset of the thyroid hormone supplementation, the skeletal age at that time and the results of the thyroid scan. The results of the Bayley test are expressed in a Mental Developmental Index (MDI) and a Psychomotor Developmental Index (PDI) (in the normal population, both the MDI and the PDI have a mean of 100, and a standard deviation of 16). The numbers of the infants correspond with the numbers in Table 7.1.

Discussion
Although most of the infants investigated seem to develop within the normal range, the group functions, on the average, at a lower level than expected of a group with normal mental and motor development. The mean (Mental Developmental Index) MDI was 87.2. A MDI below the mean minus one standard deviation (84) was found in five infants and below the mean minus two standard deviations (68) in one infant (infant 8). The mean (Psychomotor Developmental Index) PDI was 80.6. In eight infants, a value below the mean minus one standard deviation was found. The impression, obtained during the observation of the test, that several infants seemed to have minor fine motor coordination disabilities apart from a retardation of motor development, will have to be supported by more thorough investigations in this area.
No difference in developmental index was found between infants with

Table 1 Results of the Bayley Scales of Infant Development (see also Table 7.1)*

infant	age (months)	MDI	PDI	scan	onset of therapy; age (days)	skeletal age
12	15	112	99	n.t.	17	postnatal
15	9	111	80	n.t.	17	36 weeks g.a.
11	14	103	97	n.t.	21	37 weeks g.a.
7	16	102	81	n.t.	18	32 weeks g.a.
16	9	89	77	n.t.	24	prenatal
9	16	86	80	ectopia	23	postnatal
2	21	85	100	-	45	postnatal
3	21	85	92	-	45	postnatal
4	22	85	84	-	11	postnatal
14	9	83	80	n.t.	13	38 weeks g.a.
5	21	77	62	n.t.	11	postnatal
6	18	73	62	-	21	postnatal
1	27	68	73	-	22	postnatal
8	15	62	65	n.t.	13	34 weeks g.a.

* n.t.: no thyroid; g.a.: gestational age.

athyroidism and an early onset of hypothyroidism - as indicated by the retardation of the skeletal maturation - and infants with milder hypothyroidism.
These results are slightly less reassuring than those reported in other screening programs (Dussault et al., 1980a; Reed and LaVecchio, 1980; Bucher and Illig, 1980; Rochicciolo, 1980b). Future studies will have to reveal whether developmental scores in the lower range are incidental findings or not. A developmental index provides a basis for establishing the current status, but has limited value as predictor of later abilities (Bayley, 1969; see above). For this reason, the assessment of the ultimate level of intelligence and motor skills require long term follow-up.

CURRICULUM VITAE

De schrijfster van dit proefschrift werd in 1951 te Amsterdam geboren. In 1969 behaalde zij het Gymnasium-β diploma aan het Montessori Lyceum te Amsterdam. De medicijnenstudie welke in Groningen werd gevolgd, werd in 1975 met het behalen van het artsdiploma afgerond. Na enige tijd in het Rooms Katholiek Ziekenhuis te Groningen werkzaam te zijn geweest en later als consultatiebureau-arts voor zuigelingen en kleuters, is zij sinds 1978 verbonden aan het Nederlands Instituut voor Praeventieve Gezondheidszorg / TNO te Leiden. Haar werkzaamheden daar verrichtte zij binnen het kader van het project "Begeleiding van Screening op Congenitale Hypothyreoïdie in Nederland" (projectleider: Dr. G.A. de Jonge).