Congenital Hypothyroidism*

Aetiological and Clinical Aspects

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Mäenpää, J. (1972). *Archives of Disease in Childhood*, 47, 914. **Congenital hypothyroidism: aetiological and clinical aspects.** In 67 patients with congenital hypothyroidism radioiodide tests, including thyroid scintigraphy, were used to study the aetiology. Athyrosis was found in 5 boys and 16 girls (31%), maldevelopment of thyroid gland in 1 boy and 2 girls (5%), ectopic gland in 4 boys and 20 girls (36%), and dyshormonogenesis in 7 boys and 12 girls (28%). In the last-mentioned group, organic binding of iodide was defective in 13; in the 9 families studied there was evidence of autosomal recessive inheritance. Duration of pregnancy had exceeded 42 weeks in 20 (32%) out of 63 pregnancies. Birthweights in 22 out of 64 patients and birth lengths in 21 out of 61 were over the 90th centile for the duration of gestation.

At the time of diagnosis a goitre was observed in only 3, and some thyroid tissue in 2 of the 19 patients with dyshormonogenesis, but a goitre frequently appeared later, particularly at puberty.

Neurological defects were found in 33%, and mental retardation in 44% of the patients. The prognosis was best in the children with a persisting ectopic thyroid gland and poorest in those with defective organic binding of iodide. The importance of early diagnosis of hypothyroidism is again emphasized.

Congenital hypothyroidism may be associated with athyrosis, maldevelopment, and maldescent of the thyroid gland, dyshormonogenesis, thyroiditis, endemic iodine deficiency, ingestion of goitrogens (Hutchison, 1969), and perhaps maternal auto-immunization (Blizzard *et al.*, 1960). The first four causes are the ones most commonly seen in Finland.

The purpose of this study is to emphasize the role of dyshormonogenesis in congenital hypothyroidism, and to draw attention to the features of the perinatal history which should arouse suspicion of hypothyroidism. The clinical picture of hypothyroidism is well described (Lowrey *et al.*, 1958; Andersen, 1961; König, 1968) and is therefore only briefly discussed here.

Abbreviations. BEI = butanol-extractable iodine, CF = complement fixation, NBERI = non-butanol-

extractable radioactive iodine, PBI = protein-bound iodine, PBRI = protein-bound radioactive iodine, TRC = tanned red cell agglutination, TSH = thyroid-stimulating hormone.

Patients and Methods

Patients. In the years 1950 to 1968, 103 children with congenital hypothyroidism were seen at this hospital. Those 67 who could be reached and whose parents were willing to co-operate were studied during 1967 to 1968 in order to define the aetiology in each case. The results are the subject of the present report. The initial diagnosis had been made in 63 patients at 1.0 to 15.8 years (mean 8.7 years) before, and in 4 was made during the period of the study. The diagnosis of hypothyroidism was based on the usual clinical findings (including retardation of bone age), serum PBI (below 4.0 µg/100 ml), and other laboratory data. One patient had a serum PBI of 5.8 µg/100 ml at the first determination but later values were subnormal. Two pairs of sibs had low PBI values at 1½ and 4 months respectively, and at the time of study 3 of these 4 children had normal values. In 42 cases the diagnosis was first made at this hospital; the other children had first been examined and treated elsewhere.

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Heredity. When possible, both parents were interviewed and clinically examined. Determinations of serum PBI, BEI, cholesterol, and thyroid antibodies were also made. In cases with evidence of thyroid dysmorphogenesis, genealogical data were obtained from church registers by a specially trained nurse to reveal possible consanguinity.

Methods. Careful clinical examination, including routine neurological examination, was performed in all cases.

Height growth was evaluated from the Finnish normal growth charts. Bone age was estimated from the charts of Greulich and Pyle (1966), when applicable. If the 2 epiphyseal ossification centres at the knee were not present, the bone age was judged not to have reached the birth level.

A clinical psychologist performed the intelligence tests, using the Wechsler Intelligence Scale for Children.

PBI, BEI, and cholesterol were determined as described in a previous paper (Mäenpää, 1972). Two types of thyroid antibodies were determined: * anti-thyroglobulin with a TRC test, and antimicrosomal antibody with a CF test.

¹³¹I tests. Thyroid substitution was discontinued at least 3 weeks before the patients were admitted for the study. Thyroidal uptake was measured with a scintillation detector 2½, 6, 24, 48, and 72 hours and scintigraphy (Four Dot II, 1748, Nuclear Chicago, U.S.A.) was performed 24 hours after administration of an oral dose of 20 to 40 µCi of the isotope. In patients with dysmorphogenesis a new test was performed and the early thyroid uptake was measured at 1 to 2 hourly intervals for the first 6 hours. The uptake values were corrected by subtracting the thigh counts from the neck counts. A well-type scintillation detector was used for measuring plasma concentration and cumulative urinary excretion of ¹³¹I at 24, 48, and 72 hours, and the concentration in saliva at 24 hours. The methods used for determining PBRI and NBERI (Mäenpää, 1972), the biological half-life of the thyroidal radioiodine (T½) (Lamberg and Mäenpää, 1970), the iodine content of thyroid tissue (Kivikangas, Lamberg, and Mäenpää, 1970), and the values given by chromatography for ¹³¹I compounds in plasma, urine, and thyroid tissue (Lamberg *et al.*, 1972) are described elsewhere. Thyrotropine stimulation and the carbimazole-perchlorate blocking tests have also been presented previously (Lamberg and Mäenpää, 1970). The perchlorate discharge test was carried out by giving 200 mg potassium perchlorate orally at about the time of the peak of thyroidal ¹³¹I. The thyroidal radioactivity was then measured at 30-minute intervals for 120 minutes. A decrease of more than 15% below the initial thyroidal ¹³¹I was considered significant (Trotter, 1962).

In patients in whom thyroidal tissue was detectable at the normal site, the presence of definable defects in thyroid hormone synthesis and secretion was sought

with the following methods and criteria (Stanbury, 1966)

(1) *Defective iodide trapping:* thyroidal uptake close to zero and the ratio of saliva to plasma ¹³¹I below 10 (normally above 10).

(2) *Defective organic binding of iodide:* abnormal perchlorate discharge test (see above).

(3) *Defective iodotyrosine coupling:* iodothyronines, if present at all, were found only in trace amounts on radiochromatography of thyroid tissue. This was considered when the urinary excretion of ¹³¹I remained at over 1% of the dose for 5 days and increased at least twofold during the carbimazole-perchlorate blocking test.

(4) *Dehalogenase defect:* radioactive iodotyrosines on chromatography of the 24-hour urine.

(5) *The production of abnormal iodoproteins in serum:* serum PBI-BEI difference more than 1.5 µg/100 ml or serum NBERI content above 25% of the PBRI when other possible reasons for this phenomenon were excluded.

Results

The patients were divided into 3 groups. *Group 1* comprised 24 patients, 6 boys and 18 girls, in whom no thyroid tissue was demonstrated either by palpation or by scintigraphy. In 1 boy and 2 girls, however, a significant serum concentration (>0.1%/l.) of PBRI was found. Presumably, they had a severely maldeveloped thyroid gland. Because clinically they did not differ significantly from athyrotic patients, they were included in this group. *Group 2* comprised 24 patients, 4 boys and 20 girls, in whom only ectopic thyroid tissue could be detected. *Group 3* comprised 19 patients, 7 boys and 12 girls, with thyroid tissue at the normal site. In 13 of these, defective organic binding of iodide was shown by the perchlorate test, and in the remaining 6 the results of the ¹³¹I tests gave evidence of other defects in the synthesis of thyroid hormones.

Heredity.

Group 1. In 22 of the 24 families reliable data were obtained on the occurrence of thyroid disease. 22 of the mothers and 12 of the fathers were interviewed and examined.

A history of thyroid disease in the immediate family was given by 5 parents. 3 of the mothers had undergone thyroidectomy for nontoxic goitre, and in one the operation had been performed 2 weeks before the time of conception. One of the mothers had been treated for thyrotoxicosis with antithyroid drugs and in another hypothyroidism had been suspected 4 months after delivery. At the time of study all parents were clinically euthyroid and healthy. Antithyroglobulin antibodies (TRC titres 1 : 25–1 : 250) were found in 2 of the

*The determinations were made at the Department of Serology and Bacteriology, University of Helsinki.

FIG. 1.—The pedigrees of consanguineous families with defective organic binding of iodide.

mothers and in one of the fathers. In another family the mother and father had TRC titres of 1 : 2500 and 1 : 250, respectively.

Group 2. A family history was available in 23 of the 24 families. 14 of the mothers and 12 of the fathers were interviewed and examined. 4 of the mothers had had clinical thyroid disease; 3 had been operated on because of thyrotoxicosis and in one spontaneous hypothyroidism had developed and she was on thyroxine treatment. At the time of study all were clinically euthyroid and the serum PBI, BEI, and cholesterol were normal. None of these 4 had circulating thyroid antibodies, but 3 of the other mothers and one of the fathers had TRC titres from 1 : 25 to 1 : 250.

Group 3. The 19 patients belonged to 13 families. 10 of the mothers and 7 of the fathers were interviewed and examined. One of the mothers had nodular goitre; the others were clinically normal. One of the mothers had a CF titre of 1 : 32 and 2 others TRC titres of 1 : 250 and 1 : 25.

The 13 patients with a defect in organification belonged to 9 families comprising altogether 29 children. Parental consanguinity was proved in 4 families and, in addition, 2 fathers were related to each other (Fig. 1). The administration of perchlorate did not lead to a fall in thyroïdal ^{131}I in any of the 4 mothers, 3 fathers, or one sister studied.

Perinatal history. During the third trimester 2 of the mothers had toxæmia of pregnancy. There was a tendency to prolonged gestation, as

shown in Fig. 2. The duration of pregnancy was known with certainty in 64 instances; in 20 (32%) it was over 42 weeks. In contrast, this was so in only 6.6% of 24,565 normal hospital deliveries in Finland (Timonen *et al.*, 1969). In 12 cases delivery was induced with an oxytocin preparation, and in 5 cases caesarean section was done because of prolonged pregnancy and overdue labour.

FIG. 2.—The duration of pregnancies of 63 mothers of congenitally hypothyroid children. Zero indicates term. □ = athyrosis and maldevelopment of thyroid gland; ▨ = ectopic thyroid gland; ■ = dysrhormonogenesis.

FIG. 3.—Birth lengths and weights of congenitally hypothyroid children according to centiles of distribution of normal newborn infants, taking into account the sex, duration of gestation, and parity. Symbols as in Fig. 2.

There was one set of binovular twins, one of whom had maldevelopment of the thyroid, the other being normal.

Birthweights and lengths. The median birth-weight was 3795 g (range 2500–5480). In a Finnish normal series of 29,515 pregnancies

FIG. 4.—Birth lengths of congenitally hypothyroid children. Symbols as in Fig. 2.

(Bäckström and Kauppinen, 1968) it was 3480 g at 40 weeks and 3640 g at 43 weeks of pregnancy. When the birthweights were compared with the normal series of Timonen *et al.* (1969), and length of gestation, parity, and sex were taken into account, 22 of the 64 patients (34%) were above the 90th centile (Fig. 3). When the birth lengths (Fig. 4) were similarly compared with the normal distribution, 21 of the 61 patients were over the 90th centile (Timonen *et al.*, 1969).

Onset and symptoms. The age of the patients when the diagnosis was made is presented in Fig. 5. It is evident that athyrosis (or completely defective synthesis of thyroid hormones) led to a more severe clinical picture of the disease and to an earlier diagnosis. According to the history and growth curve, 89% of the whole series had some symptoms or signs of hypothyroidism before the age of 1 year.

Clinical signs.

Growth and skeletal development. All growth curves showed stagnation. In 25% of the 42 patients studied, however, the height was still within the normal range. These were 6 athyrotic patients and 2 with dysmorphogenesis in whom the diagnosis was made before the age of 3 months, and 2 patients with ectopic thyroids diagnosed at the age of 1.0 year. In 4 patients aged 2 to 4 months the bone age had not reached the birth level, and in 21 other patients aged 1 month to 1.5 years it remained at the birth level.

FIG. 5.—Age at the time of diagnosis in congenitally hypothyroid children. Symbols as in Fig. 2.

Thyroid. By definition *Group 1* consisted of patients in whom thyroid tissue was not detected by palpation or by scintigraphy. *Group 2* contained only one patient in whom thyroid tissue could be palpated as a mass in the right submandibular region. Unexpectedly, in *Group 3* only 3 patients out of 19 had a goitre and in 2 others some thyroid tissue was found at the time of diagnosis of hypothyroidism. The remaining 14 were originally considered athyrotic but in 4 a goitre appeared at the time of the pubertal growth spurt, when the thyroid substitution dose had become insufficient.

At the time of the present study the thyroid was enlarged in 15 and of normal size in 3 patients. In 1 patient thyroid tissue could be shown with certainty at the normal site only by scintigraphy. The thyroid enlargement was diffuse in 11 and nodular in 4 patients.

Neurological signs. *Group 1.* Neurological defects, spastic diplegia, ataxia, or muscular hypotonia were detected in 13 and a squint in 9 patients. Patients in whom hypothyroidism had been detected at the age of 2 months or earlier had no neurological defects. *Group 2:* Neurological defects were found in 2 patients and a squint in 1 patient. These 2 patients had very early onset of symptoms and their hypothyroidism had been detected at 1 year of age. *Group 3:* 7 of the 13 patients with defective organification had spastic diplegia, ataxia, or hypotonia. None was deaf. Audiometry was done in only 5 patients, as it was not possible in all patients with severe mental retardation. A mentally retarded girl with neurological defects had a perceptive high tone hearing loss of 30 db, a finding which is compatible with Pendred's syndrome (Fraser, Morgans, and Trotter, 1960; Nilsson *et al.*, 1964). A retarded boy with poor muscular co-ordination had a perceptive hearing loss of 40 db at all tone

frequencies. On the basis of psychological tests, auditive agnosia was suspected in him.

Mental development. The results of intelligence tests are summarized in Table IV. The patients with normal school achievement were not tested. Of the 63 patients treated for 1 year or longer after the initial diagnosis, 56% were considered normal ($IQ \geq 85$), and of the 45 patients tested 49% were normal. Mental development was normal in *Group 1* in 41%, in *Group 2* in 78%, and in *Group 3* in 44%. The mental prognosis was poorest in the patients with defective organic binding of iodide, only 2 of these 12 being normal. These were patients whose treatment had been started at the ages of 2 and 4 months.

Laboratory data.

Thyroid antibodies. *Group 1:* 3 patients had TRC titres of 1/25; none of their mothers had thyroid antibodies. *Group 2:* 3 patients had TRC titres of 1/5 to 1/25 and 2 CF titres of 1/4 to 1/8; the patient with a CF titre of 1/4 had a mother with a TRC titre of 1/250 and the patient with CF titre of 1/8 had a father with a TRC titre of 1/25; one boy and his mother had TRC titres of 1/25. *Group 3:* no patient had any circulating thyroid antibodies.

¹³¹I studies. The ratio of salivary to plasma ¹³¹I was over 10 in all patients. Data of *Groups 1* and *2* are summarized in Table I. *Group 1:* one patient had a thyroidal uptake of 14 and 7% at 2½ and 6 hours, respectively, and PBRI of 0.17%/l. at 72 hours. In 2 other patients the uptake values were 8 and 1.2% at 2½ hours and 1.7 and 0% at 24 hours with PBRI values of 0.11 and 0.22%/l., respectively. *Group 2:* the 24-hour thyroidal uptake varied from 1 to 10%, the accumulation of

TABLE I

Neck Uptake of Radioactive Iodine, Serum Protein-bound Radioactive Iodine (PBRI), and Non-butanol-extractable Radioactive Iodine (NBRI) in 48 Patients with Congenital Hypothyroidism

		Athyrosis and Maldevelopment of Thyroid Gland	Ectopic Thyroid Gland
Uptake 2½ hr	<5%	20/24	23/24
	5-10%	3/24	1/24
	10-15%	1/24	
Uptake (24 hr)	<5%	20/24	14/24
	5-10%	4/24	10/24
	<0.1%/l.	20/23	13/24
PBRI (72 hr)	0.1-0.2%/l.	2/23	4/24
	0.2-0.3%/l.	1/23	3/24
	>0.3%/l.		4/24
	>30		4/6
NBRI (% of PBRI)			

TABLE II

Biological Half-life of Thyroid Iodine ($T_{\frac{1}{2}}$), Serum Protein-bound Radioactive Iodine (PBRI), Non-butanol-extractable Radioactive Iodine (NBERI), and Results of Perchlorate Test in Patients with Defective Organic Binding of Iodide

		No. of Patients
$T_{\frac{1}{2}}$	9-18 hr	11
PBRI	78-85 hr	2
	<0.1%/l.	6
	0.1-0.3%/l.	6
	>0.3%/l.	1
NBERI at 72 hr (% of the PBRI)	>25%	6
	<25%	1
KClO ₄ test, decrease of thyroidal radioactivity as % of initial level	80-95%	12
	58%	1

^{131}I reached a peak at 24 or 48 hours; half the patients had a 72-hour PBRI above 0.1%/l., the highest value being 0.71%/l., and in most patients PBRI was higher at 72 hours than at 24 or 48 hours.

Scintigraphy was performed only in the frontal plane. Thus the exact site of the ectopic thyroid could not be determined. In 21 patients it was located in the midline at the base of the tongue and in 3 on the right side of the midline.

The serum ^{131}I was in most cases too low for chromatography. In 2 instances trace amounts of iodide and thyroxine were detected.

Group 3: data on 13 patients with defective organic binding of iodide are given in Table II, and the thyroidal uptake in Fig. 6. The accumulation of ^{131}I reached a peak between 1 and 4 hours in 12 patients and at 24 hours in one patient. In 9 the maximal uptake ranged from 13% to 53% and in 4 was below 10%. 2 patients with low uptake values had small goitres and 2 had normal sized glands. Therefore the TSH stimulation test was performed in 7 patients, and this increased the uptake in one patient from 4.4 to 9.1 and in another from 7.4 to 12.0%. In 5 others there was no response to TSH. In 11 patients the urinary and plasma ^{131}I decreased exponentially, paralleling the thyroidal radioactivity.

The remaining 6 patients belonged to 4 sibships. One of the patients (Case 1) has been reported earlier by Lamberg, Jussila, and Hintze (1960). Relevant data of the present investigation are summarized in Table III. The 24-hour urinary excretion of ^{131}I remained for 5 days at about 1.5% of the dose, and rose during the carbimazole-perchlorate block to 3.0 and 7.5% in Cases 1 and 2, respectively. Thus, a coupling defect was suspected, but could not be shown. The other 4 patients had some unidentified partial defect in the synthesis of thyroid hormones.

FIG. 6.—Thyroidal uptake curves of patients with defective organic binding of iodide.

Discussion

Athyrosis was found in 31%, maldevelopment in 5%, ectopic thyroid gland in 36%, and dysmorphogenesis in 28% of the patients studied. Most of the patients were examined after several years' thyroid substitution therapy. The 3 weeks' interruption of therapy may not have been enough for full recovery of the pituitary

TABLE III
Results of Laboratory Tests of Patients with

Case No.	PBI ($\mu\text{g}/100\text{ ml}$) (4-8)	BEI ($\mu\text{g}/100\text{ ml}$) (3.5-7.5)	Uptake Max. % Dose	PBRI 72 hr % Dose/l. (<0.3)	NBERI % of PBI (<20)	$T_{\frac{1}{2}}$ dy (>35 dy)
1	4.3	3.3	86	0.41	38	8.0 (8.0-8.5)
2	2.0	1.6	90	0.32	20	29 (4.6-10.1)
3	5.8-6.0	5.1-5.0	32	0.1	6	15.7
4	7.5	6.8	24	0.45	10	10.5
5	2.4	1.6	56	0.08	0	2.6 (2.2-2.8)
6	6.0	3.9	41	0.54	0	5.5 (5.0-6.0)

*Iodine content 51 $\mu\text{g}/\text{g}$ tissue.

†Iodine content 400 $\mu\text{g}/\text{g}$ tissue.

‡During the perchlorate-carbimazole blocking test.

and thyroid glands from the long suppression of all patients. Because of this possibility, the TSH stimulation test was performed in 7 patients. In 2 patients the thyroïdal uptake rose from 4.4% to 9.1% and from 7.4% to 12%, respectively. 5 other patients showed no response. However, involution of a hypoplastic gland in the normal site may occur after as little as 2 years therapy (Neel *et al.*, 1961; Job, Canlorbe, and Tutina, 1965). A significant amount of PBRI was found in 3 patients in whom no iodide concentrating tissue was seen in scintigrams. A higher dose of the isotope might have revealed thyroid tissue in these patients.

Of 501 published cases of congenital hypothyroidism reviewed by König (1968), 21% had proven and 5% suspected ectopic glands, 41% were athyrotic, and 33% had a thyroid gland at the normal site. The highest incidence of ectopic thyroids, 68%, has been reported by Sapelier (1965), with 7% of athyrosis and 25% of a thyroid gland at the normal site in a series of 131 congenitally hypothyroid patients.

There was no great difference in the thyroïdal uptake between Group 1 (athyrosis and maldevelopment) and Group 2 (ectopic gland). Half the patients of Group 2 had PBRI values of over 0.1%/l. of the dose, and in 6 of them these were high enough for determination of NBERI. In 4 the NBERI was over 30% of the PBRI. This phenomenon has been described earlier in patients with an ectopic gland (Little *et al.*, 1965).

Defective organic binding of iodide was found in 13 of the 19 patients with dysmorphogenesis.

Surprisingly, a goitre had earlier been found in only 2 of them, though the degree of hypothyroidism was severe enough to cause poor mental development. The palpation of the thyroid is difficult in a hypothyroid infant, and it is possible that a goitre had not been searched for carefully enough in every case. After discontinuing substitution therapy for 3 weeks a goitre was seen in 9 patients. Of a pair of sibs, the sister had a small goitre and her brother some thyroid tissue demonstrable by scintigraphy only. In 7 out of 43 cases recently reviewed by Marie *et al.* (1969), there was no goitre. The possibility of dysmorphogenesis must thus be taken into account in every patient with congenital hypothyroidism regardless of whether a goitre is demonstrable or not.

In the remaining 6 patients, defects in iodide trapping, organic binding of iodide, and deiodination of iodotyrosines were excluded. In Case 2 (Table III) a defect in the coupling of iodotyrosines was excluded by radiochromatography of thyroid tissue. In Case 1 only a determination of the iodine content of the thyroid tissue was obtained. This was very low (51 $\mu\text{g}/\text{g}$ tissue wet weight). The butanol-insoluble fraction of serum PBRI was 38%, serum PBI 4.3 $\mu\text{g}/100\text{ ml}$, and BEI 3.3 $\text{mg}/100\text{ ml}$. This patient may have one of the plasma iodoprotein defects.

Two pairs of sibs, Cases 3, 4, 5, and 6, had serum PBI values below 1.7 $\mu\text{g}/100\text{ ml}$ and severe hypothyroidism already apparent between 1½ and 4 months of age. The treatment of Cases 5 and 6 was very irregular and Case 5 was without any thyroid substitution therapy from 4 to 8 years

II

Unidentified Defects in Synthesis of Thyroid Hormones

TSH Test	Perchlorate Test Decrease (%)	Radiochromatography of Thyroid Tissue	Radiochromatography of Urine	Radiochromatography of Serum	Ratio of Salivary to Plasma Radioactivity (> 10)
No response	No	*	I—	MIT + DIT 22% I— 30% T ₃ + T ₄ 48%	+
	No	†MIT + DIT 19% I— 41% T ₃ + T ₄ 9% NBEI 31%	I—	0	+
	No		I—	0	+
	No		I—	Traces of T ₄ , T ₃ and DIT	+
	No		I—	Traces of DIT	+
	No		I—	MIT + DIT 33% I— 6% T ₃ + T ₄ 30% UK§ 31%	+

§UK: Unknown compound.

Normal values in brackets.

of age. Nevertheless, her height growth was normal, she was only mildly hypothyroid, and her serum PBI was 2.4 µg/100 ml. A patient studied by Lamberg *et al.* (1960) also had normal growth, bone age, and mental development at the age of 12 years, despite a very low serum PBI (1.4–1.7 µg/100 ml); she had been thyroidectomized for nontoxic goitre at the age of 2 years. The explanation for the discrepancy between the normal development and the low serum PBI might be found in a normal production of tri-iodothyronine (Sterling *et al.*, 1969; Hackenberg, Reinwein, and Horster, 1970). Cases 3 and 4 had normal PBI values and were euthyroid 5 weeks after discontinuation of thyroxine therapy. The 4 patients of this series had some partial defect in the synthesis of thyroid hormones. After receiving thyroxine therapy they had remissions which lasted from 6 weeks to 4

years. This resembles the iodine effect on thyroid function in the sporadic goitrous cretinism described by Zondek and Leszynsky (1965).

A history of thyroid disease in the immediate family was obtained in 5 of the 22 families of *Group 1* and in 4 of the 23 families of *Group 2*. One of the mothers of *Group 1* and 3 of *Group 2* had been treated for thyrotoxicosis. The significance of this finding is difficult to evaluate, because an appropriate control series is lacking. However, a high incidence of thyroid diseases, especially hyperthyroidism, is a fairly common finding in relatives of patients with congenital hypothyroidism (Childs and Gardner, 1954; von Harnack, 1957).

One of the mothers of *Group 2* had binocular twins, one of whom had ectopic thyroid while the other was normal. König (1968) found 12 twin pairs with hypothyroidism in the literature. In only

TABLE IV

Mental Development in 63 Patients with Congenital Hypothyroidism, Studied 1.0 to 15.8 Years (mean 8.7 years) after Primary Diagnosis

	Intelligence Quotients						N
	40–54	55–69	70–84	R	85–100	101–116	
Athyrosis and maldevelopment of thyroid gland	2	4	3	4	5	2	2
Ectopic gland		1	3	1	6	4	8
Dyshormonogenesis*	2 (2)	5 (5)	3 (2)		4 (2)	1	3 (1)
Total	4	10	9	5	15	7	13

R = retarded
N = normal } on clinical evaluation

*The number of patients with defective organic binding of iodide is given in the brackets.

one case were both twins hypothyroid; they were goitrous, probably with some defect in the synthesis of thyroid hormones. Of these 12 pairs of twins, 9 pairs were uniovular and 2 binovular, and in 2 cases the ovularity was not known. These observations are difficult to explain and are compatible neither with exogenous damage *in utero* nor with simple recessive inheritance.

The data on patients with defective organic binding of iodide are consistent with simple recessive inheritance.

The male : female ratio of *Groups 1* and *2* was 10 : 38, while in *Group 3* it was 7 : 12. The preponderance of females among cases of nongoitrous congenital hypothyroidism has been reported in many other series. Andersen (1961), on reviewing the published cases of nongoitrous hypothyroidism, found an even sex distribution among those diagnosed within the first 6 months, but a remarkable preponderance of females within the group diagnosed later. On the same division of the present series, the ratio was 6 : 12 in the early diagnosed and 4 : 26 in the later diagnosed group.

A clear tendency to prolonged pregnancy was seen since 32% of the pregnancies continued for more than 2 weeks beyond term. This phenomenon has also been mentioned by others (Childs and Gardner, 1954; Andersen, 1961). In many cases delivery was induced. This long duration of pregnancy supports the theory that the fetus determines the initiation of labour and that fetal lack of thyroid hormones in some way prevents the onset of uterine contractions.

Not only the birthweights but also the birth lengths were greater than in the normal population. This has already been observed by Andersen (1961.) The prolonged gestation is one reason for this phenomenon but not the only one, as is evident when the birth length is compared with that of healthy infants born after gestation of the same duration (Fig. 3). In this series 4 patients were in a prenatal stage of bone development at the time of diagnosis and their birth lengths varied from 49 to 55 cm.

Mental development was normal in 56%. There was a striking difference between patients diagnosed before 3 months of age and those diagnosed later, 81% of the former group and 47% of the latter being normal. This is in conformity with the results of Raiti and Newns (1971). The prognosis was best in patients with a persistent ectopic thyroid gland and poorest in those with defective organic binding of iodide. Presumably, this is due to the fact that the synthesis of thyroid hormones had been defective already *in utero*.

Probably the athyrotic patients had had some functioning thyroid tissue during fetal life, which later involuted.

In conclusion, the prognosis of mental development was influenced by the type of thyroid disturbance, by the patients' age at the onset of hypothyroidism, and by the severity and duration of the thyroid hormone deficiency before the initiation of therapy. Early diagnosis of hypothyroidism ensures that at least some of the permanent damage can be prevented.

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