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Catch-up growth after prolonged hypothyroidism

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Abstract This report presents an analysis of four patients who suffered from longstanding untreated hypothyroidism, with special attention to the phase of catch-up growth after the start of L-thyroxine treatment. Although a permanent height loss could not be prevented, the capacity to establish a remarkable catch-up growth spurt proved to be still intact, even after a long period of thyroid dysfunction.

Conclusion Catch-up growth in hypothyroidism may be incomplete if treatment has been started shortly before or during puberty.

Key words Hypothyroidism · Growth · Catch-up growth

Abbreviation *FTI* free thyroxine index

Introduction

At delivery children with congenital hypothyroidism have a length similar to that of healthy children, but without replacement therapy with L-thyroxine (L-T₄) their growth rate diminishes shortly afterwards [2, 4, 7]. A continuing decrease or even complete arrest of statural growth is observed if congenital or acquired juvenile hypothyroidism remains untreated. It has been suggested that adequate treatment of hypothyroidism leads to complete catch-up growth and a normal adult stature [4, 12, 16]. It is now clear that short stature can indeed be prevented if L-T₄ substitution is started at an early age [1, 3], but if hypothyroidism remains untreated for a longer period a permanent height loss cannot always be avoided [2, 11, 13]. However, the number of reported clinical observations on long-term growth after prolonged untreated hypothyroidism is still relatively small [2, 4, 11, 13] and most of these studies did not involve the parental heights and the

pre-illness growth curve in the estimation of the loss in adult height.

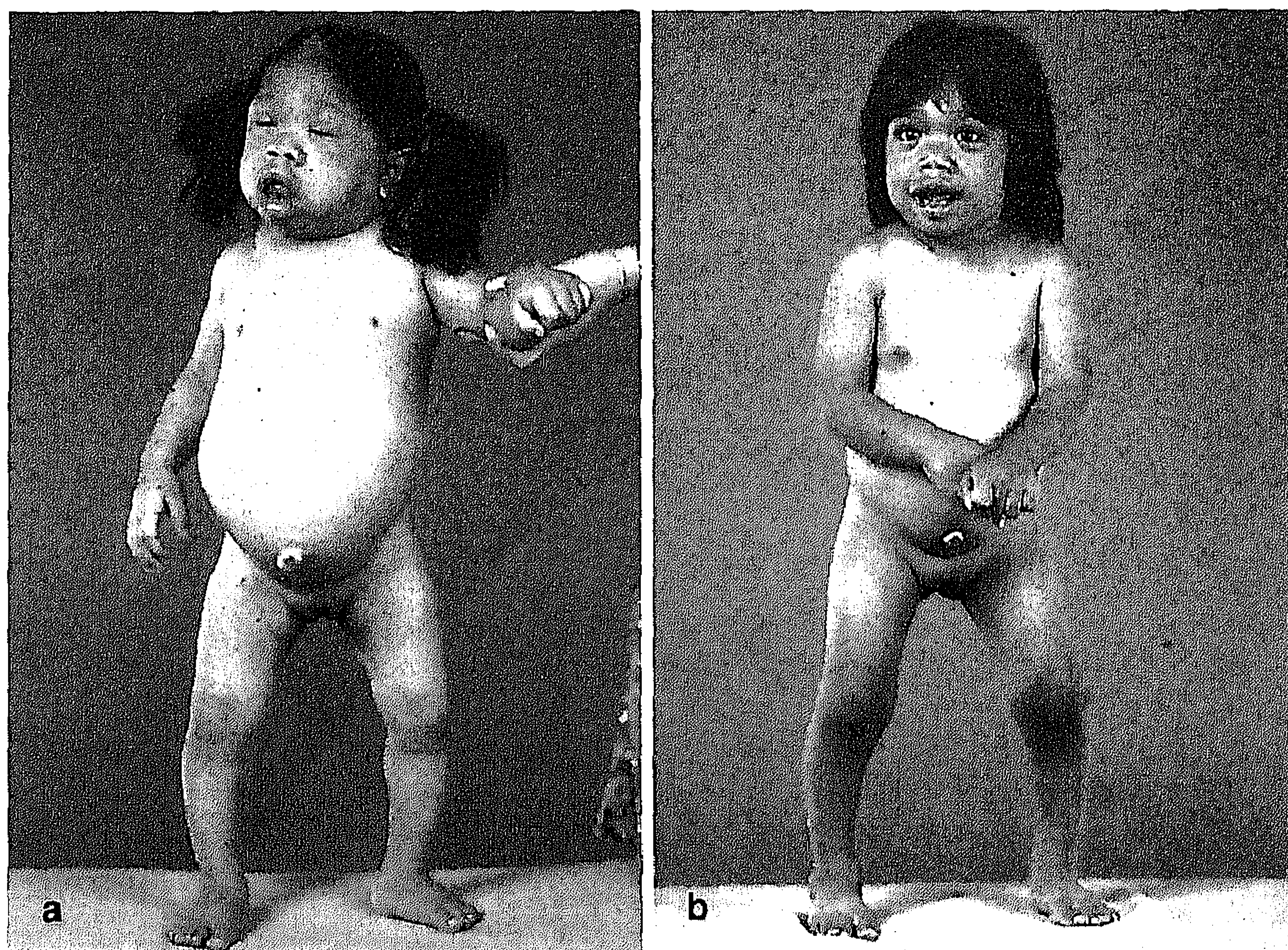
We present a description of four patients in whom hypothyroidism was left untreated for long period and discuss its consequences for catch-up growth.

Patients

Patient 1

A girl of Indonesian origin developed feeding difficulties shortly after birth requiring hospitalisation. Congenital hypothyroidism was diagnosed and L-T₄ replacement therapy was started. Therapy was discontinued after 4 months as a result of parental ignorance and the patient was lost to follow up. Finally, at the age of 13.9 years, she visited our clinic because she had become extremely slow. Physical examination showed a prepubertal, clearly apathetic, mentally retarded girl unable to speak and walk, with a height of 81 cm (3rd percentile = 151.2 cm) and a weight of 13.4 kg (3rd percentile = 37.3 kg). Her face showed coarse, puffy features with large lips and a big tongue, a flat nose and myxoedema

Fig. 1 a Patient 1 before the start of therapy at the age of 13.9 years. b Patient after 6 months of therapy



(Fig. 1a). She had brittle hair and a pale skin. The abdomen was distended and an umbilical hernia was present, while her arms showed slight contractures and her legs were strongly bowed. Her psychomotor development was equal to that of a child at the age of 13 months. Additional investigations showed a serum total T_4 < 13 nmol/l, free thyroxine index (FTI) < 13, TSH > 60 mU/l and cholesterol 11.0 mmol/l. X-ray investigations revealed stippled epiphyses of the femoral heads, immature vertebrae and bowed tibiae. L- T_4 substitution therapy was resumed and followed by a remarkable improvement of clinical symptoms (Fig. 1b). The first manifestations of pubertal development were noted within 8 months.

Patient 2

A 14-year-old boy was referred because of growth failure. At the age of 13 years he had undergone a surgical correction for epiphysiolysis of both femoral heads. Physical examination showed a boy with a pale, puffy face and skin depigmentation. Tanner stages were A1P1G1 but the testicular volume was 12 ml. His IQ was normal. Additional investigations showed a total T_4 of 10 nmol/l, free T_4 0.8 pmol/l and TSH 367 mU/l. Microsomal antibodies were positive and thyroglobulin antibodies negative. Plasma testosterone was 1.3 nmol/l. Cortisol secretion was normal. He was diagnosed as having primary hypothyroidism, probably due to Hashimoto thyroiditis and L- T_4 substitution therapy was started. Shortly thereafter a progression of genital development was noted and within 10 months he had reached genital stage 4.

Patient 3

A 13-year-old girl was referred because of growth failure and increased body weight. She also reported increased hair growth and a lowered voice. Physical examination showed an apathetic and

slightly obese girl with a pale coloured skin and a heart rate of 44 beats/min. She had hypertrichosis on the back, arms and legs, but no further signs of virilisation could be detected. Her psychological development was normal. Tanner stages were B3P3 and menarche had not occurred. Additional investigations showed a total T_4 of 5 nmol/l, FTI < 2 and TSH 580 mU/l and cholesterol 13.7 mmol/l. The presence of anticolloidal antibodies was dubious and antinuclear antibodies were weakly positive. The levels of circulating androgens were normal. Primary hypothyroidism was diagnosed, probably due to Hashimoto thyroiditis, and L- T_4 substitution therapy was started. The hypertrichosis was of familiar origin. Pubertal development progressed and menarche occurred at the age of 14.5 years.

Patient 4

A nearly 6-year-old girl was referred because of abdominal pain, anorexia and fatigue. Physical examination showed a short, prepubertal girl with a puffy, broad and round face, macroglossia and a pale skin. Her psychological development was normal. Additional investigations: total T_4 22 nmol/l, FTI 19, TSH 60 mU/l, thyroglobulin antibodies and microsomal antibodies were absent. X-ray investigations revealed stippled epiphyses of the femoral heads. On scintigraphy no thyroid gland could be visualised, but ectopic thyroid tissue was detected at the base of the tongue, which was consistent with the findings of indirect laryngoscopy. Therefore she was diagnosed as having primary hypothyroidism probably resulting from decompensation of an ectopic dysgenetic thyroid gland and L- T_4 substitution therapy was started. Pubertal development started at the age of 10.7 years and menarche occurred at the age of 13.6 years.

Fig. 2a-d Growth charts of patients 1, 2, 3, 4. ● height; □ bone age according to Greulich and Pyle; *F* and *M* height of father and mother; *TH* target height

Results

In these patients the duration of hypothyroidism before onset of therapy, as measured by the duration of growth deceleration, varied from 5 to 13.5 years (Table 1). This period of untreated hypothyroidism had led to an extreme (patient 1) or marked (patients 2-4) growth retardation (Fig. 2 a-d). After the institution of L-T₄ treatment all patients exhibited a marked catch-up growth spurt, which is not distinguishable from the pubertal growth spurt in patients 1-3. This growth spurt enabled the patients to achieve an increase of height SDS for chronological age varying from 2.7 to 8.3. Patient 1 continued to grow until the age of 22 years but still ended up 15.5 cm below her target height. Patient 2 reached his target height but the first part of the growth curve suggests that his adult height was reduced in comparison to his original potential. Patient 3 did not return to her pre-illness percentile

position and reached a final corrected height SDS of -0.9, while patient 4 finally reached a height within the normal range for age but still slightly below her target height.

Discussion

All four patients show the impressive growth retarding influence of a prolonged period of untreated hypothyroidism. As neonatal screening procedures, routine measurements at child welfare centres and examinations by school doctors usually lead to early detection of hypothyroidism in children, these observations are nowadays relatively uncommon in western countries.

The marked acceleration of growth that occurred in all patients after the start of L-T₄ therapy shows that the capacity to establish a considerable catch-up growth spurt remains intact even after a long period of hypothyroidism. Although the catch-up spurt corrected an important part of the initial height deficit in all patients, three of them did not reach their target height and the adult height of the fourth patient was presumably also reduced.

Three possible explanations for this failure to reach complete catch-up growth after a longlasting period of hy-

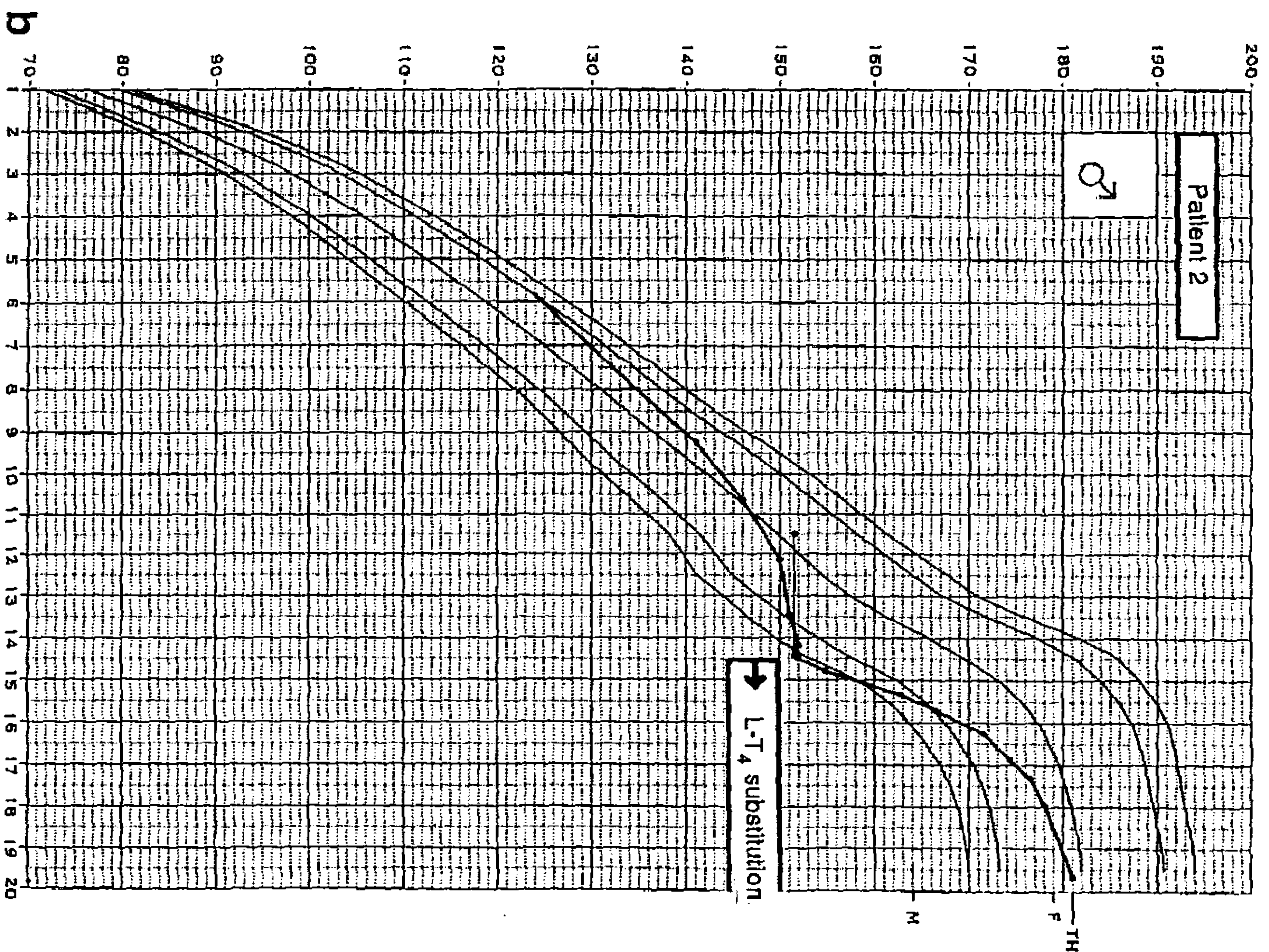
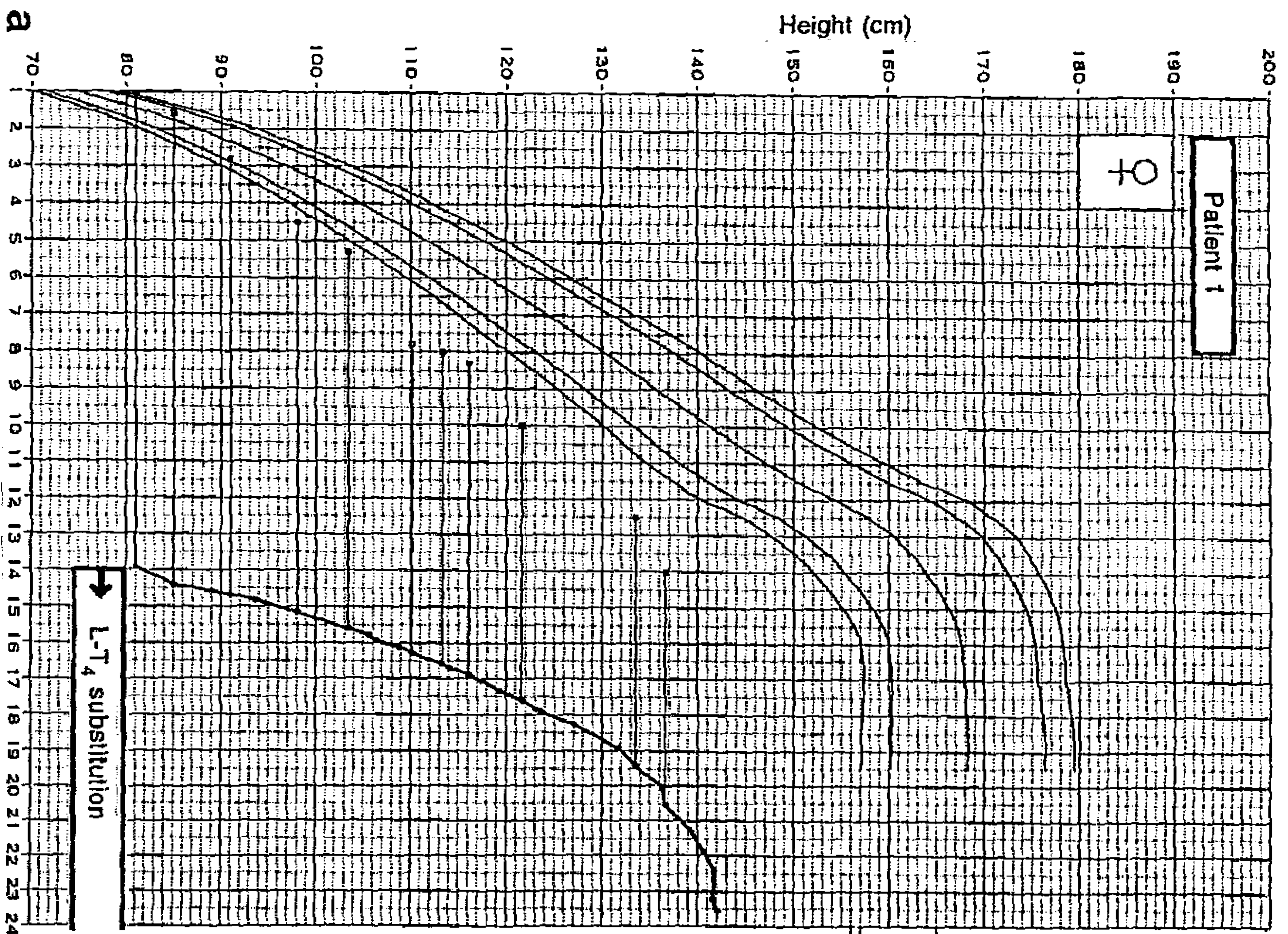


Fig. 2 c, d

pothyroidism have been proposed [13]. Firstly, hypothyroidism may directly diminish the potential for catch-up growth. Secondly, overtreatment with L-T₄ may stimulate skeletal maturation too much and finally, pubertal development during the catch-up phase may limit the chance to achieve full catch-up growth.

The way in which hypothyroidism may diminish the potential for catch-up growth has not been described but the most likely mechanism seems through irreversible damage to the cartilage growth plates. The influence of hypothyroidism on osseous development is well known [18] and illustrated by the signs of epiphyseal dysgenesis

Table 1 Clinical characteristics at diagnosis and results of therapy

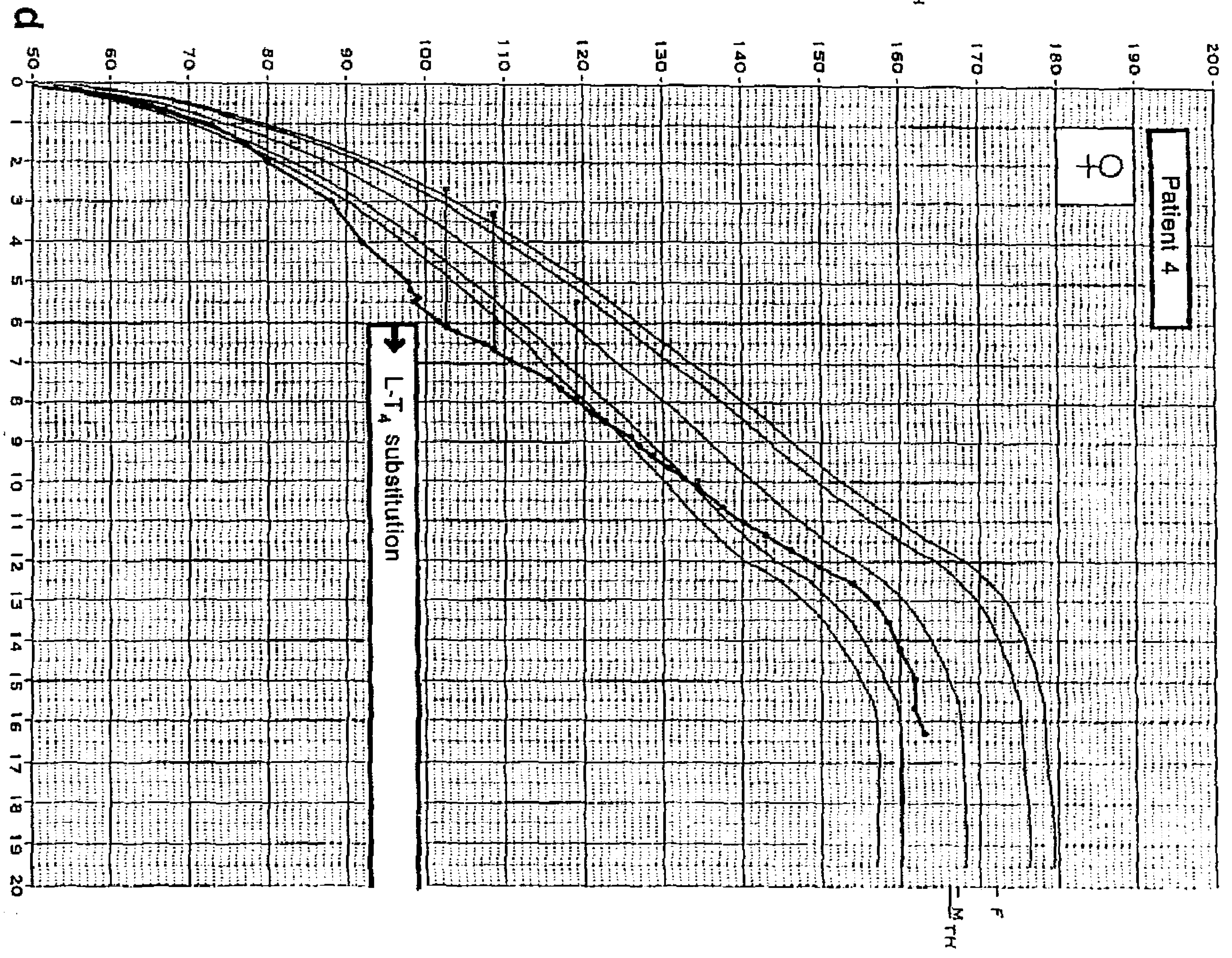
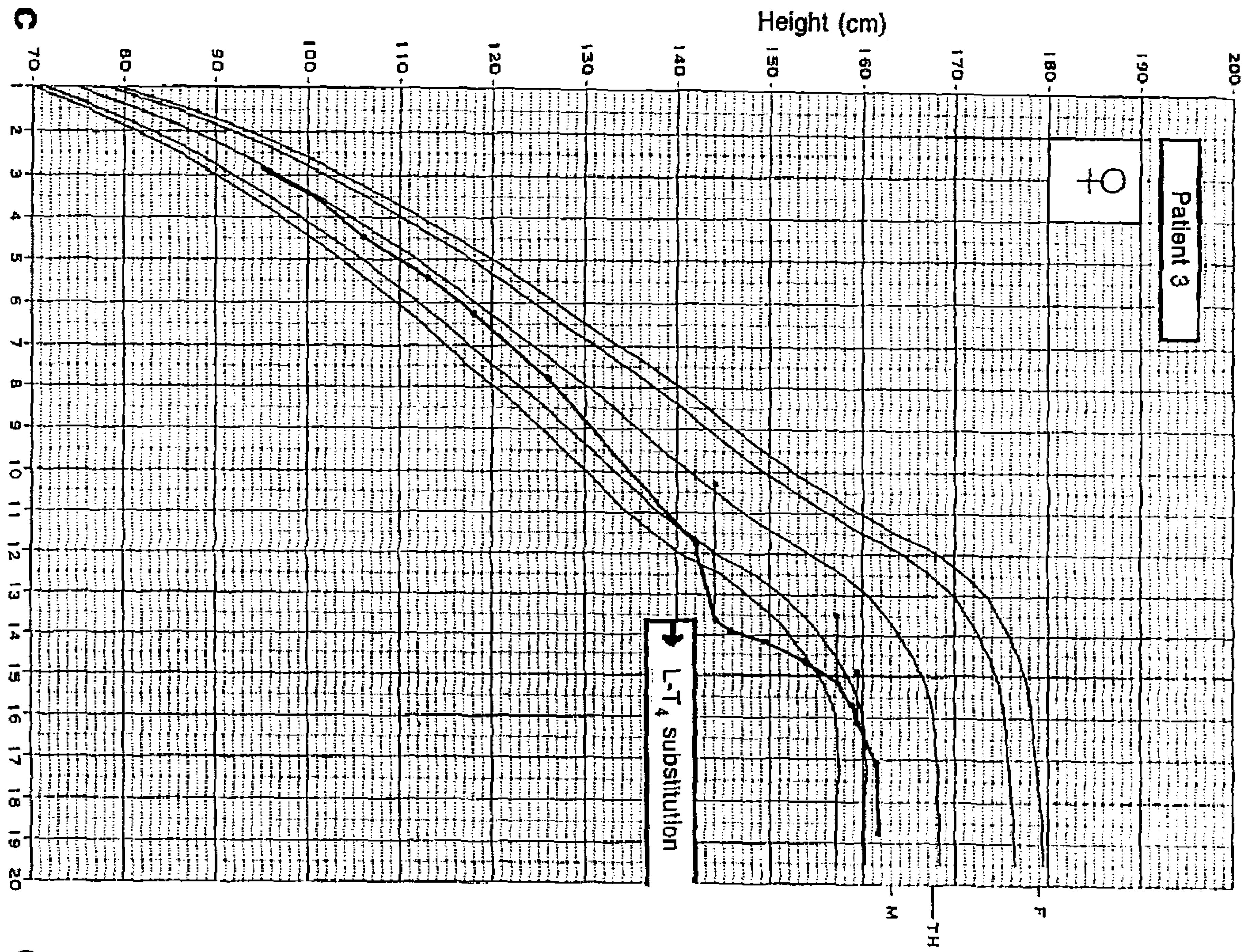
Patient	1	2	3	4
Age at diagnosis (years)	13.9	14.3	13.6	6.0
Bone age at diagnosis (years) ^a	1.0	11.5	10.3	2.7
Duration of decreased growth before start of therapy (years) ^b	13.5 ^c	8.4	7.4	5.0
Height loss before start of therapy (SDS)	Unknown	3.1	2.4	2.6
Height SDS for chronological age at diagnosis ^d	-10.7	-1.7	-2.6	-3.2
Height SDS for bone age at diagnosis	2.4	0.3	0.2	2.3
Height increment during therapy (SDS)	8.3	1.7	1.7	2.7
Final height (cm)	142.0	181.0	161.7	163.1
Final height (SDS) ^d	-2.4	0.0	-0.9	-0.5
Final height - target height (cm)	-15.5	0.5	-6.3	-3.4

^a According to Greulich and Pyle

^b According to growth curve

^c Previous growth data not available; estimation based on patient history

^d SDS corrected for parental height by substracing mid parental height SDS from the patient's height SDS



in patients 1 and 4 and by the history of epiphysealysis in patient 2. However, although it has been reported that hypothyroidism indeed causes damage to the epiphyseal growth plate cartilage, this proved to be fully reversible during L-T₄ treatment [8]. Therefore it is questionable whether this explains incomplete catch-up growth in our patients.

Although thyroid hormones are indeed important stimulators of skeletal maturation, it is also unlikely that overtreatment with L-T₄ has caused incomplete catch-up growth in these patients. They all received the recommended daily dosage of 100 µg/m² L-T₄ and none of them showed clinical or biochemical evidence of excess of thyroid hormones.

The third explanation seems to correspond best with the observations in our patients. Patient 1 entered puberty shortly after the start of treatment and failed to reach her target height. Patients 2 and 3 already showed signs of pubertal development at the start of treatment and failed to return to the pre-illness percentile position or to reach target height. Patient 4 entered into puberty more than 4 years after the start of treatment and she was the only patient who reached nearly complete catch-up growth. These observations seem to confirm that if L-T₄ substitution is initiated at the moment that the patient has already

entered puberty or if pubertal onset occurs shortly thereafter, catch-up growth is incomplete. Sex steroids probably induce a disproportional acceleration of bone maturation in relation to linear growth, which finally results in epiphyseal fusion before complete catch-up growth has been reached.

A recent case report showed that suppression of pubertal development by administration of synthetic gonadotropin releasing hormone plus growth hormone improved height gain in a patient with juvenile hypothyroidism [9]. This approach of gonadal suppression in combination with growth hormone therapy in order to improve final height is sometimes also applied in conditions such as idiopathic short stature [6, 14], idiopathic growth hormone deficiency [5, 17] and precocious puberty [10, 15]. It is tempting to speculate that the outcome of catch-up growth in the first three of the herein described patients might have been better if they had been treated according to this new therapeutic strategy.

In summary, hypothyroidism exerts profound effects on human growth. Nevertheless, even after an extremely long period of thyroid dysfunction the capacity to establish a striking catch-up growth spurt remains intact. However, catch-up may be incomplete in patients in whom therapy is started shortly before or during puberty.

References

1. Aronson R, Ehrlich RM, Bailey JD, Rovet JF (1990) Growth in children with congenital hypothyroidism detected by neonatal screening. *J Pediatrics* 116:33-37
2. Bucher H, Prader A, Illig R (1985) Head circumference, height, bone age and weight in 103 children with congenital hypothyroidism before and during thyroid hormone replacement. *Helv Paediatr Acta* 40:305-316
3. Grant DB (1994) Growth in early treated congenital hypothyroidism. *Arch Dis Child* 70:464-468
4. Harnack GA, Tanner JM, Whitehouse RH, Rodriguez CA (1972) Catch-up in height and skeletal maturity in children on long-term treatment for hypothyroidism. *Z Kinderheilkd* 112:1-17
5. Hibi I, Tanaka T, Tanae A, et al (1989) The influence of gonadal function and the effect of gonadal suppression treatment on final height in growth hormone (GH)-treated GH-deficient children. *J Clin Endocrinol Metab* 69:221-226
6. Job J-C, Toublanc JE, Landier F (1994) Growth of short normal children in puberty treated for 3 years with growth hormone alone or in association with gonadotropin releasing hormone agonist. *Horm Res* 41:177-184
7. Letarte J, LaFranchi S (1983) Congenital hypothyroidism. In: Dussault JH, Walker P (eds) *Basic and clinical endocrinology*, 2nd edn. Butterworths, New York, pp 351-383
8. Lewinson D, Harel Z, Shenzer P, Silbermann M, Hochberg Z (1989) Effect of thyroid hormone and growth hormone on recovery from hypothyroidism of epiphyseal growth plate cartilage and its adjacent bone. *Endocrinology* 124:937-945
9. Minamitani K, Murata A, Ohnishi H, Wataki K, Yasuda T, Niimi H (1994) Attainment of normal height in severe juvenile hypothyroidism. *Arch Dis Child* 70:429-431
10. Oostdijk W, Drop SL, Odink RJ, Hummelink R, Partsch CJ, Sippell WG (1991) Long-term results with a slow-release gonadotrophin-releasing hormone agonist in central precocious puberty. Dutch-German Precocious Puberty Study Group. *Acta Paediatr Scand [Suppl]* 372:39-45
11. Pantiotou S, Stanhope R, Uruena M, Preece MA, Grant DB (1991) Growth prognosis and growth after menarche in primary hypothyroidism. *Arch Dis Child* 66:838-840
12. Prader A, Tanner JM, Von Harnack GA (1963) Catch-up growth following illness or starvation. An example of developmental canalization in man. *J Pediatr* 62:646-659
13. Rivkees SA, Bode HH, Crawford JD (1988) Long-term growth in juvenile acquired hypothyroidism: the failure to achieve normal adult stature. *N Engl J Med* 318:599-602
14. Saggese G, Cesaretti G, Barsanti S, Rossi A (1995) Combined therapy with GnRH agonists (GnRHa) and GH in short subjects without a GH deficiency and with a normal onset of puberty. *Horm Res* 41:97 (Abstract)

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15. Saggese G, Pasquino AM, Bertelloni S, et al (1995) Effect of combined treatment with gonadotropin releasing hormone analogue and growth hormone in patients with central precocious puberty who had subnormal growth velocity and impaired height prognosis. *Acta Paediatr* 84: 299-304
 16. Tanner JM (1981) Catch-up growth in man. *Br Med Bull* 37: 233-238
 17. Toublanc JE, Couprie C, Garnier P, Job JC (1989) The effects of treatment combining an agonist of gonadotropin-releasing hormone with growth hormone deficiency. *Acta Endocrinol* 120: 795-799
 18. Wilkins L (1965) Thyroid disorders: I. Hypothyroidism. In: Wilkins L, Blizzard RM, Migeon CJ (eds) *The diagnosis and treatment of endocrine disorders in childhood and adolescence*, 3rd edn. Thomas CC, Springfield, pp 92-114