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Sex Steroid Treatment of Constitutionally Tall Stature*

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I. Introduction

WHILE as many children grow above the 97th percentile (corresponding to + 1.8 SDS) as below the 3rd percentile, tall stature is a far less common reason for seeking medical attention than short stature. Tall stature is more easily accepted in society and may even be an advantage. This holds specifically true for boys, and girls are more often referred.

Growth is a result of complex processes. Genetic constitution, nutrition, endocrine function, and psychosocial well being are all involved in the process of growth (1, 2). The genetic component of height has been estimated to be 0.5–0.9, *i.e.*, 50–90% of the height variation is accounted for by genetic factors. Assessment of the parental height as an indicator of the genetic component of growth and development of the child is therefore of critical importance (3). In addition, socioeconomic factors such as social class, family size, birth rank, housing, and crowding are associated with growth. Improved socioeconomic conditions and better health have led to the manifestation of a positive secular trend in growth and development over the last centuries. In 1865 the mean adult height among Dutch army recruits was 165 cm. One century later, in 1965, the mean adult height in boys was 178 cm. Fifteen years later, in 1980, the mean adult height had increased by another 4 cm to 182 cm. In the middle of the 19th century, age of menarche of European girls was about 16–17 yr. Nowadays, the mean age of menarche is 13 yr or even less.

Phenomena responsible for both positive and negative secular trends have affected height throughout our history. Studies of fossil remains of our hominid ancestors demonstrate that the stature of individuals living during the last hundred-thousands of years reached the range of heights seen today: the mean stature of early anatomically modern *Homo sapiens* in Europe was 184 cm in males and 167 cm in females (4, 5). Thus, stature is based on many factors, including heredity and environment.

In recent years, information concerning auxology and (neuro)endocrinology of tall stature has expanded. In addition, long-term results of height-reducing treatment modalities have become available. In this review we will give an update of the (neuro)endocrinology, the auxology, the differential diagnosis, and the therapeutic modalities available in the management of constitutionally tall stature (CTS).

II. Normal *vs.* Extremes of Growth

A. Defining CTS

A thorough understanding of the factors influencing the process of normal growth is essential to understanding the pathophysiology of the extremes of growth (6). It has been well established that populations of various ethnic origin differ considerably in growth and development. Therefore, reference growth curves have been obtained by measuring healthy individuals longitudinally or cross-sectionally (or both). Extremes of growth can be defined knowing the normal variance of growth of the reference population. Usually an individual whose height differs more than 2 SDS from the population mean, *i.e.*, a child with a height above the 97th percentile of the growth curve, is considered too tall just as a child growing below the 3rd percentile is considered too short. It should be emphasized, however, that most of the

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TABLE 1. Mean or median and + 1.8 SD height (p97) values (cm) in various countries

Country (year of ascertainment)	Height (boys)		Height (girls)		Reference
	Mean or median	(+ 1.8 SD/p97)	Mean or median	(+ 1.8 SD/p97)	
The Netherlands (1985)	182.0	194.5	168.3	179.8	7
Germany (1992)	179.9	192.5	167.0	179.0	8
Sweden (1976)	179.1	192.4	165.5	178.2	9
Czechia (1993)	178.3	191.7	165.0	176.8	10
Denmark (1982)	179.4	190.4	166.0	176.0	11
United Kingdom (1995)	176.4	190.5[a]	163.6	176.0[a]	12
USA (NHCS) (1977)	176.8	187.6[b]	163.7	173.6[b]	13
France (1979)	175.0	187.0	163.0	174.5	14
Mexico (1975)	172.8	186.3	160.6	174.5	15
Turkey (1978)	173.5	186.0	160.0	171.0	16
Argentina (1987)	172.8	185.6	160.7	172.2	17
Korea (1979)	170.2	180.0	157.6	166.5	18

[a] p98.
[b] p95.

children who grow beyond these percentiles are part of a continuum of a normal distribution curve, and only a minority will have a defined abnormality.

CTS is defined as a condition in which the height of an individual is 2 SDs above the corresponding mean height for a given age, sex, and population group. As shown in Table 1, height p97 values vary substantially among various populations. The Scandinavians and the Dutch are among the tallest people in the world.

In CTS, usually one or both parents are tall; thus, genetic and familial factors are most important etiologically. Mean birth length is in the 75th percentile, and tall stature becomes evident at the age of 3–4 yr. Growth velocity is accelerated in early childhood but slows down after 4–5 yr of age when the growth curve starts to parallel the normal curves (19).

The diagnosis is generally made from the family history of growth and from physical examination. No apparent abnormalities are present at physical examination, which permits distinction from excessive growth syndromes such as Marfan syndrome and Klinefelter syndrome (see Table 2).

TABLE 2. The differential diagnosis of tall stature

A. Variants of normal growth: constitutionally (familial) tall stature
B. Primary growth disorders
1. Sex-chromosome related disorders
Klinefelter syndrome and variants
XXY syndrome
XYY syndrome
2. Overgrowth syndromes with advanced bone maturation
Sotos syndrome
Weaver syndrome
Marshall-Smith syndrome
Beckwith Wiedemann syndrome
Hyperinsulinism
3. Syndromes with tall stature as outstanding feature
Marfan syndrome
Marfanoid phenotype
MEN IIB
Hemocysteinuria
Estrogen inactivity/resistance
C. Secondary growth disorders
GH excess
Precocious (pseudo) puberty

MEN IIB, Multiple endocrine neoplasia IIB.

B. Endocrinology of CTS

A significant positive correlation has been established between growth and GH secretion in studies of children with various heights (20–22). In a recent study, insulin-like growth factor (IGF-I) levels in prepubertal children correlated significantly with height velocity in the following year (23). In CTS children, relatively high levels of IGF-I were measured (24).

At the time of puberty GH secretion increases. Sex-specific changes regarding the timing of the pubertal increase of GH secretion during puberty have been found by analyzing 24-h GH profiles in healthy boys and girls (25). This increase, occurring about 1 yr earlier in girls than in boys, is correlated to estradiol levels in both boys and girls (26, 27). Similarly, serum levels of IGF-I rise at puberty (23). In boys with delayed puberty, testosterone (T) treatment caused increased GH pulse amplitude, thereby increasing the mean serum GH concentration. T exerts its effect on GH via an estrogen-dependent mechanism by increasing hypothalamic GHRH release (28). Paradoxical GH responses to glucose loading and to administration of TRH or GHRH, similar to those seen in acromegaly, have been observed in some CTS children (29–31). However, these observations have not been substantiated in studies properly controlled for age and stage of puberty. Tauber *et al.* (32) showed a clear heterogeneity of GH secretion in tall children, with some of them even having low GH secretion (32). Therefore, abnormal responses may be related more to the stage of puberty of the child than to abnormalities of GH secretion (33).

In conclusion, constitutionally tall children are healthy children without hard evidence of pathology of the GH-IGF-I axis.

III. Endocrinology of Bone Growth and Maturation

Given that stature of patients with CTS appears to have a genetic basis, it is worthwhile to review the biological factors known to regulate normal skeletal growth. This information is relevant in the context of the current treatment modalities of CTS, which are based on sex steroid action on bone growth and maturation (see below).

Longitudinal bone growth is the result of expansion of the growth plate cartilage. As puberty proceeds, a progressive decrease in cartilage expansion occurs. Because the vascular invasion and resorption of calcified cartilage by chondroclasts exceeds cartilage expansion, there is a progressive thinning of the growth plate. Ultimately, the growth plate becomes perforated and longitudinal bone growth ceases (34, 35).

The regulation of longitudinal bone growth is very complex, and several factors, including nutritional, endocrine, paracrine, and autocrine, are necessary (36). For normal bone growth and maturation the gonadal steroids are essential in conjunction with several hormones and growth factors:

1. GH. GH has been shown to stimulate long bone growth in a dose-dependent fashion. At the cellular level GH interacts with the GH receptor. The expression of GH receptors is developmentally regulated in epiphyseal chondrocytes (37). There is ample evidence that GH interacts directly with cells of the growth plate and not only through IGF-I (*vide infra*). Green and associates (38) have proposed the dual effector theory based on *in vitro* observations (see also Ref. 39). This theory states that GH is a prerequisite of cartilage maturation. Priming of resting chondrocytes in the growthplate by GH is required for IGF-I to promote 'clonal expansion' of growth plate chondrocytes and to stimulate skeletal growth. More recently it has been suggested that this theory may not apply to the *in vivo* situation. The presence of GH receptors is not limited to resting chondrocytes. It was shown that both IGF-I and GH exerted their effect at each stage of differentiation rather than acting specifically upon particular subpopulations of cells at certain phases of chondrocyte differentiation (40). The observation that GH-overproducing transgenic mice have a significantly larger size than their controls, while IGF-I transgenic mice have a normal size, would support the theory of a differential effect of GH and IGF.

However, transgenic models are inadequate for studying the independent actions of IGF-I and GH as in IGF-overproducing transgenic mice GH production is not completely suppressed (41).

2. Thyroid hormone. Thyroid hormones are crucial for bone growth because of their direct effects on bone. In addition, there are indirect effects by stimulating pituitary GH release (42), thereby increasing serum IGF-I levels. Lastly, effects of thyroid hormone on IGF-I generation by chondrocytes have been demonstrated (43). The obvious experiment of nature is represented by the syndrome of resistance to thyroid hormone hallmarked by short stature and marked delayed bone maturation (44).

3. Vitamin D. In addition to the crucial role of vitamin D in bone mineralization, several observations point to a possible role in chondrocyte proliferation and bone growth. In rats, proliferation of growth plate chondrocytes is decreased by high doses and increased by low doses of 1,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$] (45). Moreover, short stature and delayed bone maturation may be present in the syndrome of vitamin D resistance (46).

4. Growth factors. As IGF-I and -II are among the most prevalent growth factors secreted by skeletal cells and have important actions on bone formation, it is reasonable to predict that they play a significant role in bone growth and maturation. In the circulation IGF-I and -II form a complex with IGF-binding proteins, and there is little, if any, free IGF-I or -II available in bone. Thus, locally secreted IGF-I and -II acting in a paracrine or autocrine manner might play an even more important role in the regulation of growth plate cell function. IGFs enhance the differentiated function of the osteoblast and increase collagen synthesis. Moreover, IGFs decrease collagen degradation and IGF-I (but not IGF-II) increases osteoclast recruitment (41).

The synthesis of IGF-I and -II takes place in cells of osteoblast lineage and is controlled by systemic hormones (stimulatory: PTH, GH, estrogens; inhibitory: cortisol, vitamin D) and local factors (stimulatory: bone morphogenetic proteins, PGE_2; inhibitory: fibroblast growth factor, transforming growth factor, platelet derived growth factor).

In addition, skeletal cells synthesize a variety of IGF-binding proteins (IGFBP). They act to regulate and modulate the local actions of IGFs. Most IGFBPs have been shown to have inhibitory effects on either IGF-I or -II. However, IGFBP-5 has been shown to potentiate IGF-II action on osteoblast- derived cell lines (47).

IV. Sex Steroid Action on Bone Growth and Maturation

The pubertal growth spurt has long been considered to be an androgen-dependent process. However, there is abundant clinical and experimental evidence showing that estrogens may be primarily responsible for accelerated growth during puberty (48). It is remarkable that peak height velocity occurs in girls and boys when estradiol levels are not only low but also quite similar (49, 50). Still, a direct relationship between levels of E_2, GH, and pubertal growth has not been established (51, 52).

Girls with Turner syndrome show a growth spurt during estrogen replacement therapy (53–55). Similarly, girls with central or pseudo-precocious puberty with clearly elevated estrogen levels show increased height velocity and premature epiphyseal closure (56). Whereas in patients with androgen insensitivity syndrome the growth spurt resembled that of women both in magnitude and timing, mean final adult height was taller than in normal women but shorter than in normal men (22, 48, 57). This would suggest that Y chromosome-related factors contribute to stature. Patients with familial male precocious puberty treated with antiandrogens alone did not revert to a normal prepubertal growth rate but only when an aromatase inhibitor was added (58).

Studies of acute infusion of gonadal steroids in peripubertal children have illustrated the complexity of the relationship between gonadal steroids and the GH/IGF axis (49, 59, 60). These studies suggest sex differences in the control of GH secretion in the response to E_2 during puberty. Moreover, acute and chronic E_2 exposure may have different effects: acute infusions decrease whereas prolonged exposure may increase GH bioactivity (60).

There is also evidence for a dose dependency as high doses of estrogens result in decreased growth velocity in both males and females (58, 61, 62). High-dose estrogen treatment decreased IGF-I levels in acromegalic patients as well as in tall girls (63, 64). Recently, a man was described with estrogen resistance. He had a normal prepubertal growth and normal timing of onset of secondary sex characteristics. Despite full masculinization he continued to grow. At 18 yr his height was 204 cm, and the growth velocity was 1 cm/yr. The bone maturation and mineralization were both markedly retarded (65). Moreover, a phenotypic female with aromatase deficiency was described showing markedly delayed bone maturation (66). It is well known that in boys with pseudo-precocious puberty as a result of congenital adrenal hyperplasia, height velocity is increased and epiphyseal maturation is advanced, resulting in stunted adult height. There is ample evidence that androgen-stimulated growth is largely based on influencing GH release and augmentation of IGF-I. However, it is not excluded that these effects are estrogen mediated. On the other hand, nonaromatizable androgens have growth-promoting effects not mediated via GH-IGF-I axis (67). Keenan *et al.* (68) reported that nonaromatizable DHT induced and maintained accelerated growth rate in short boys with delayed puberty in spite of a 50% decline in integrated GH concentration and no change of IGF-I level, suggesting that strictly androgen-mediated skeletal growth might be exerted locally in growing cartilage.

In vitro studies using rat- and human-derived cells have shown that there might be a sex-specific and age-dependent responsiveness of cartilage and bone cells to sex steroids. Cells and tissues derived from males respond primarily to T, whereas cells and tissues derived from females respond primarily to estrogen. The best response was obtained in tissue from children in early puberty (69–71). The mechanism of action of the gonadal steroids on growth plate cartilage is poorly understood. The effect of estrogens on proliferation of human chondrocytes *in vitro* was shown to be biphasic: at low concentration a stimulatory effect was observed, while at supraphysiological doses inhibition was observed.

High doses of estrogens stimulate the maturation of cartilage without increasing the growth rate: cell division by cartilage cells is inhibited in the proliferative zone of the growth plate, and the age-related decrease in size of the hypertrophic chondrocytes is accentuated by estrogens (72–76). The latter effects were not overcome by the addition of GH or IGF, suggesting that estrogens may act directly on chondrocytes or may influence the release of factors that inhibit cell proliferation locally (77). Using fetal rat osteoblasts in culture, McCarthy *et al.* (78) established that estrogens do not alter IGF-I promotor activity but inhibit the biological effects of all hormones that act through cAMP to regulate skeletal IGF-I expression and activity.

Collectively, bone growth and bone maturation are the result of a complex interplay of various hormones in which GH and the gonadal steroids have a pivotal role. Moreover, there might be a sex-specific and age-dependent responsiveness of cartilage and bone cells to sex steroids. At the level of the growth plate, estrogen receptor-mediated processes appear essential in expressing the effects of sex steroids.

V. Height Prediction

Height prediction plays a key role in the management of children with growth disorders and consequently in children with CTS. Therapeutic intervention is based on the estimated height prognosis: whenever the height prognosis exceeds a certain limit (usually 2 SDS above the mean of the population), treatment might be considered. Hence, accurate techniques for reliable height predictions are essential. The suitability and importance of skeletal maturity as a predictor variable for adult height have long been recognized (79–82). The techniques of Tanner-Whitehouse and Bayley-Pinneau both share the use of bone age (BA) as an indicator of skeletal maturity to estimate final adult height. The first prediction method uses the BA method developed by Tanner *et al*. (80), whereas the latter utilizes the BA method of Greulich and Pyle (83). Each BA determination is linked with potential problems as briefly summarized below (84).

A. Skeletal maturity or BA

A measure of skeletal maturity is generally obtained by assessing the appearance and shape of the bones of the hand and wrist on an x-ray. These appearances change with age, and their rate of change is a direct measurement of the rate of maturation. Various methods of evaluation of BA and maturity have been developed over the years. The methods most commonly used are the Greulich and Pyle Atlas (83) and the Tanner-Whitehouse (TW2) method (79, 80). In addition, other methods such as the FELS-method are also available (85).

The method of Greulich and Pyle for BA estimation is presented as an atlas of examples of radiographs of the left hand and wrist of healthy children at various ages (83). The children who form the standard group were drawn from the Brush Foundation Study, which selected children from the better socioeconomic strata in Cleveland, Ohio, from 1930 onward. All the children were white, had been born in the United States, and were of North European ancestry. Each of the standards of the atlas was selected from a large number of children of the same sex and age. All films were arranged in order of increasing maturity, and the film chosen as the standard is the one most representative of the central tendency or anatomical mode. The BA is determined by comparison with the standards.

The Tanner-Whitehouse technique describes maturity indicators for each bone of the hand and wrist (79, 80). Each bone progresses through a series of specific stages with assigned weighted scores. These scores are added to form a maturity score, which in turn can be converted to a corresponding BA. The source data for this method were obtained from large groups of British children of an average socioeconomic level in the 1950s.

The major problem in both techniques is that subjective processes and discontinuous scales are used that result in considerable inter- and intrarater variability in BA (84, 86–88). In a direct comparison, the BA as determined by the Greulich and Pyle method is generally about 1 'year' less than that as assessed by the Tanner-Whitehouse technique (86, 87, 89). One should realize, however, that BA determinations are

estimates of maturity and that, in fact, there is no objective quantification available. Recently, various authors have discussed the main problems of skeletal maturation assessment and the sources of possible bias (90–92). Therefore, it is mandatory that one is acquainted with the specific qualities of the BA determination method used.

B. Computed assisted skeletal age-scoring systems

As stated above, estimates of BA do not advance smoothly as the child matures but in a saltatory fashion. In the TW2 system, a difference of one stage in the rating of a particular bone may result in an increase of 0.3 'years' in BA. In actuality, skeletal maturity will advance gradually. To diminish the errors in the interpretation of maturity and to improve BA ratings, the TW2 system has been transformed recently by the original author into a computerized image analysis system using a continuous scale Computer-Assisted Skeletal Age System: CASAS (93, 94). So far, a limited number of studies have been performed on the reliability and validity of CASAS in healthy children and in children with tall stature (95–97). Results indicate that reliability of the CASAS ratings is extremely high, both within and across operators. Moreover, in longitudinal series, BA does advance far more smoothly compared with manual scores. With regard to children with tall stature, CASAS was found quite applicable. The CASAS method, however, is not without drawbacks and is still, to some extent, user dependent. Further developments are needed to improve these aspects.

C. Accuracy of height prediction

Prediction methods that have survived the tests of clinical usefulness are those that incorporate a multitude of variables relating to adult height and maturity and that are sensitive in their assessment of childhood maturity (82). Most prediction methods are based on growth data of unselected normally growing children. Therefore, when applied to children with tall stature, critical appraisal of their qualities is required. Knowledge concerning the specific advantages and disadvantages of the various methods is of utmost importance since it may influence possible therapeutic intervention.

Thus far, only a limited number of studies have been performed testing the reliability of height prediction methods in large groups of untreated children with tall stature. The accuracy of height prediction may be expressed mathematically as the difference between predicted adult height and actual adult height. In this way, positive values indicate overestimation, and negative values reflect underestimation of the final adult height. Absolute errors demonstrate the method's overall predictive error and is not influenced by over- or underestimation.

Table 3 summarizes the accuracy of various prediction methods in *boys* with tall stature (98–101). The systematic tendency of the prediction methods to over- or underestimate final adult height are not consistent. Variation in initial clinical data (CA and BA) and time definition of reaching adult height may account for this inconsistency. In general, however, the method of Bayley-Pinneau tends to overestimate final height, whereas the method of Tanner-Whitehouse slightly under- or overestimates final height. Joss *et al.* (102) described a systematic overprediction of the Bayley-Pinneau technique in a study of 32 tall boys. In addition, they reported a systematic overprediction using the Tanner-Whitehouse method, which was even more pronounced at an older BA. Some investigators have used repeated predictions in the same subject for accuracy assessment. This may have induced bias in reported means and/or standard deviations of the errors of prediction. When the group of patients was divided into age-specific subgroups it appeared that with increasing age both methods became more accurate in predicting adult height (100, 101). In our study the Index of Potential Height (IPH) based on the BA of Greulich and Pyle was found to be the most reliable method as it showed the lowest mean error and mean absolute error, −0.1 (2.9) cm and 2.3 (1.8) cm, respectively (101). The IPH is based on the assumption that the height SD scores for BA [rather than for chronological age (CA)] remains constant up to final height.

The accuracy of height prediction methods in *girls* with tall stature is given in Table 4 (64, 101, 103–109). Again, inconsistency is present in reported errors of prediction, probably due to differences in initial clinical data and timing of adult height assessment. Nevertheless, the mean errors are found to be rather small, indicating that height prediction in tall girls is quite accurate regardless of which method is used. As in boys, predicting adult height became more accurate with increasing age (101). The mean absolute errors were also small, a confirmation of their reliability. It seems that there is no 'best' prediction method in tall girls; the choice of method for use in daily practice may therefore depend on the preference and experience of the clinician.

TABLE 3. Mean error of prediction (cm) of the Bayley-Pinneau and Tanner-Whitehouse method in untreated constitutionally tall boys (prediction minus actual height)

Study	Number of patients	Prediction method (SD)		Reference
		Bayley-Pinneau	Tanner-Whitehouse	
Zachmann *et al.*	8	+2.3	+0.02 (3.7)	98
Brämswig *et al.*	9	+1.7 (4.5)	+1.1 (4.4)	99
Brämswig *et al.*	42	+2.1 (4.8) Absolute error 4.0 (3.3)	+0.6 (5.4) Absolute error 4.2 (3.3)	100
De Waal *et al.*	55	+2.8 (3.6) Absolute error 3.3 (3.1)	−0.9 (4.8) Absolute error 3.9 (2.9)	101

TABLE 4. Mean error of prediction (cm) of the Bayley-Pinneau and Tanner-Whitehouse method in untreated constitutionally tall girls (prediction minus actual height)

Study	Number of patients	Prediction method (SD)		Reference
		Bayley-Pinneau	Tanner-Whitehouse	
Zachmann *et al.*	9		+0.4 (3.8)	103
Reeser *et al.*	14	−0.8	+0.1	104
John and Schellong	18	+1.3 (2.5)	+0.7 (2.5)	105
Schambach and Nitschke	26	−0.5 (2.5)		106
Bartsch *et al.*	23	0.6 (2.2)		107
Svan *et al.*	12	+1.2 (1.5)		64
Ignatius *et al.*	28	−0.9		108
		−1.0		
		+0.8		
Joss *et al.*	21	+2.4 (2.9)	+1.3 (2.8)	109
De Waal *et al.*	88	+0.5 (2.7)	−0.8 (3.1)	101
		Absolute error	Absolute error	
		2.0 (1.9)	2.3 (2.2)	

TABLE 5. Regression equations based on samples of untreated constitutionally tall children

Boys (n = 71):
Final height = $213.66 + 0.62 \times H + 0.29 \times TH - 10.49 \times CA - 12.98 \times BA_{GP} + 0.72 \times (CA \times BA_{GP})$;
RSD = 2.6 cm.
Girls (n = 103):
Final height = $129.42 + 0.74 \times H + 0.17 \times TH - 7.70 \times BA_{GP} - 5.90 \times CA + 041\ (CA \times BA_{GP})$;
RSD = 2.7 cm

H, Height; TH, target height.

D. New prediction equations in constitutionally tall children

As stated above, for children growing at the upper extremes of normal, *i.e.*, beyond +2 SD above the mean of the normal population, it seems far better to use prediction models based on growth data derived from a sample of tall children. For this reason Tanner and co-workers revised their original equations (Mark 1) (79) by including numbers of very tall (and very short) children in the new source sample in the standardizing group (Mark 2) (80). Unfortunately, only tall girls had been included. This might explain the finding of Cameron *et al*. (110) that the accuracy of prediction in tall boys did not improve comparing the older TW Mark 1 method with the revised TW Mark 2 method.

To improve height prediction in children with constitutionally tall stature, we developed regression equations based on growth data derived from a sample of untreated tall children (55 boys/88 girls) (111). Since the quality of a regression model is reflected in its residual standard deviation (RSD), the smaller the RSD the better the model predicts the dependent variable (final height) by the combination of predictor variables. In our newly developed prediction equations the RSD was 2.5 cm for both boys and girls (see Table 5). This implies that about 95% of the predictions lie within approximately 5 cm of the real value (± 2 RSD). From a clinical point of view, this inaccuracy is quite acceptable. In comparison, Tanner *et al*. (79) reported RSD values up to 4.1 cm in boys and 3.6 cm in girls for the same age ranges. The prediction equations were tested on a separate sample of 32 tall children (16 boys/16 girls) and compared with other prediction techniques including the TW Mark 2 and Bayley-Pinneau method. The absolute errors of our prediction equations were smaller (though not reaching statistical significance) than the TW Mark 2 method and the Bayley-Pinneau technique, indicating less variability. These results give support to the idea that height prognosis in children with excessive growth is more accurate when based on growth data derived from tall children.

In conclusion, although prediction techniques may have small mean errors of prediction, it must be emphasized that considerable errors in height prognosis may be made in individual cases. This is reflected by the presence of the relatively large SDs of the mean errors of the prediction method applied. It is preferable, therefore, to give predicted adult height as a height with a confidence limit (using the residual SDs of the prediction technique for calculation).

VI. Treatment of CTS: General Concepts

Treatment of tall stature is generally based on psychological grounds. From a strict medical point of view, there is no reason for treatment. Therefore, the validity and necessity for treatment are questionable. Although psychosocial factors form the main reason for treatment, extensive psychological investigation before or during height reductive therapy has never been performed. Nevertheless, psychological problems in tall adolescent girls and boys have been recognized by pediatricians and endocrinologists (112–115). A commonly voiced concern is that these children feel different from their peers and that they are subject to hurtful remarks about their height. As a consequence, coping mechanisms such as kyphotic posture, social withdrawal, and even depression have been observed. Fear about future compatible partners (especially in girls) and career planning are also frequently reported problems (112–115). Practical problems for adolescents and adults alike might arise concerning clothing and shoes. Concurrent orthopedic problems, such as kyphosis or scoliosis, could make treatment desirable for purely mechanical reasons. A study of determinants of future trunk abnormalities in a cohort of 11-yr-old schoolchildren suggested that in addition to the onset of the adolescent growth spurt and the menarche, tall stature was positively associated with the incidence of adolescent idiopathic scoliosis and trunk abnormalities (116, 117).

Sex steroids have been used in the treatment of tall boys and girls since the late 1950s. The basis for the use of sex hormones to limit adult height came from observations in children with (pseudo-) precocious puberty. These children show early closure of the epiphyses due to premature production of gonadal steroids, which limits their eventual adult height (118, 119).

Studies mainly in children with gonadal dysgenesis have suggested a biphasic dose-dependent effect of estrogens on growth rate, low dose having a stimulatory and high dose an inhibitory effect (36, 120, 121). Furthermore, it has been demonstrated that the administration of high doses of gonadal steroids, specifically estrogens, accelerate bone maturation (98, 99, 103, 104, 112, 122–125). Since the first study in 1956, many reports have appeared describing the height-reducing effect of administration of high doses of sex hormones in girls (64, 103–109, 112, 122–131) and in boys (98, 99, 132).

VII. Treatment of Constitutionally Tall Boys

A. T treatment modalities

The effect of treatment with supraphysiological doses of T in reducing adult height in boys appears to be different from the effect of high doses of estrogens in girls. In T-treated tall boys, height velocity is not decreased and even increased in the early stages of puberty, whereas in estrogen-treated girls a decrease in growth velocity is observed (62).

It is generally agreed that the steroid hormone effects on bone maturation are due to an indirect action mediated by the GH/IGF-I axis combined with a direct effect at tissue level after metabolic conversion into estrogens (48).

The choice of the androgen preparation is unambiguous. 'Natural' compounds are preferred over 17-alkylated compounds as it has been observed that the latter may cause cholestasis and hepatic tumors and may negatively influence lipoprotein levels (115). The doses of the long-acting T esters (such as T propionate, enanthate, and decanuate) used in most studies are about 500 mg/m^2/month, which correspond to roughly 4 times the normal T production rate of adult men or to about 8–10 times that of early adolescence. In clinical practice, two weekly im injections of 500 mg or 250 mg once a week are used. Whether such high doses are really necessary to obtain a maximum effect on bone maturation is not known. However, treatment with T at a mean dosage of 265 mg/m^2/month resulted in a lower BA velocity and thereby less reduction of adult height in a small group of tall patients with hypogonadotropic hypogonadism (98). Theoretically, an alternative treatment modality is testosterone undecanoate. Testosterone undecanoate in oleic acid is administered orally and is absorbed preferentially through the lymphatics into the bloodstream bypassing first-phase degradation in the liver (133). However, dose frequency is 2–3 times a day, and circulating blood levels tend to vary substantially (134). Dose finding studies for CTS treatment have not been performed.

B. Height reduction

The 'uncorrected' effect of height reductive therapy, *i.e.*, height prediction minus achieved adult height, varies with the prediction method applied. Since every single prediction method has its own prediction error, the mean effect may be 'corrected' by subtraction of the corresponding mean prediction errors (98, 99, 132) (see Table 6). In our own studies the Bayley-Pinneau prediction showed the greatest mean 'corrected' effect of 2.0 cm, while the IPH, being the most accurate method, calculated a mean 'corrected' effect of only 0.6 cm (101). An important finding, however, was that at the time of referral the control groups (tall boys and girls) were significantly different from children who had received sex hormone therapy. The proper 'net' treatment effect on final height was calculated by multiple linear regression analysis adjusting for differences in age, BA, and height prediction between treated and untreated children. The mean adjusted effect for the various prediction methods varied from −1.7 to +0.7 cm in boys. There was, however, a marked variation in the individual height-reducing effect, ranging from −2.6 to +15.8 cm. Figure 1 shows the adjusted effect of therapy according to the IPH-Greulich-Pyle prediction and its 95% confidence interval.

These outcomes are clearly less than the 'corrected' reductions of 4.7–7.5 cm previously reported (98–100, 132). In addition to the variability in adult height prediction methods as discussed above, these conflicting results may be due to differences in study design, comparability of the control group, inclusion criteria (such as age and BA at start of therapy), and therapeutic regimen. Furthermore, differences in CA at the time of final adult height was measured, and differences in BA at the time of cessation of therapy are important contributing factors.

It has been clearly shown that height reduction was dependent on the BA at start of therapy: height reduction was more pronounced when treatment was started at a younger BA (100, 101, 132). However, an important issue that caused a significant reduction in the height-limiting effect was the observation of a marked additional posttreatment growth after cessation of therapy. This posttreatment growth might partly be explained by late-pubertal completion of spinal growth. On the other hand, the additional growth could result from the fact that treatment had been stopped before complete closure of the epiphyses. A significant negative relationship between posttreatment growth and BA at the time of stopping therapy ($r = -0.53$; $P < 0.001$) was observed (101). The latter contrasts with the opinion of Brämswig and co-workers (132), who advocated short-term therapy and reported significant height reduction (uncorrected: 7.6 cm) with a mean BA (SD) of 15.3(0.8) yr at the time of stopping therapy. However, these results seem too optimistic, since final height assessment was performed at a relatively young mean (bone) age. Moreover, others failed to show any height reducing effect using the same therapeutic strategy, but with assessment of final height at a definite later point in time (135).

As illustrated in Fig. 1, when therapy was started at a BA of 14 yr or older, adult final height significantly exceeded height prognosis at the time of start of treatment. This suggests that treatment had resulted in induction rather than reduction of growth.

TABLE 6. Effect of hormonal treatment in boys with CTS

Study (Ref.)	n	Therapy	CA	G-P BA	B-P Pred HT, uncorrected	Final HT corrected	TW BA	TW Pred HT, uncorrected	Final HT corrected[a]
Whitelaw (1967) (187)	5	TE 200 mg/2 wk im	10.5 (1.1)	10.3 (0.8)	12.7 (−)				
Zachmann *et al.* (1976) (98)	29	TE 500 mg/2 wk im	13.9 (1.7)	14.6 (0.8)	5.4 (4.8)	5.4			
	8	Controls	13.6 (2.6)	NR	0.0 (3.7)				
Brämswig *et al.* (1981) (99)	25	TE 500 mg/2 wk im	14.2 (1.3)	14.0 (0.7)	7.2 (4.0)	5.5	14.4 (1.0)	6.4 (4.8)	5.3
	9	Controls	12.1 (2.1)	12.3 (2.1)	1.7 (4.5)		12.5 (2.4)	1.1 (4.4)	
De Waal *et al.* (1996) (101)	60	TE 250–500 mg/week–2 wk im	14.2 (1.3)	14.0 (0.9)	4.8 (4.9)	2.0	14.8 (0.9)	0.5 (5.3)	1.4
	55	Controls	13.9 (1.5)	14.2 (1.5)	2.8 (3.6)		15.2 (1.5)	−0.9 (4.8)	
Binder *et al.* (1997) (181)	33	TE 500 mg/2 wk im	14.1 (1.7)	13.6 (1.0)[b]	6.3 (4.6)	4.4			
	52	Controls	13.3 (1.9)	13.7 (1.0)	1.9 (4.4)				

Data are expressed in cm as mean (SD). n, number; CA, chronological age at start of treatment; G-P BA, bone age according to Greulich-Pyle (83); TW BA, bone age according to Tanner-Whitehouse (80); B-P Pred HT, prediction of final height according to Bayley-Pinneau (81); FH, final height; TW Pred HT, prediction of final height according to Tanner-Whitehouse (80); TE, testosterone esters; NR, not reported; BP, Bayley-Pinneau (81); TW 2, Tanner-Whitehouse Mark 2 (80).

[a] Correction by subtraction of the mean prediction error of the control group.

[b] BA at start of study; BA at start of treatment not given.

C. Effects on gonadal function

High doses of T induce suppression of the hypothalamo-pituitary-gonadal axis (113, 136). Contraceptive studies in adult men have shown that androgen-induced suppression of gonadotropins and of spermatogenesis is reversible (137, 138). However, extrapolation of these data to the management of tall stature in pubertal boys must be viewed with caution since factors that regulate spermatogenesis in normally functioning adult testes may not be the same as during puberty (139). Androgen therapy in tall boys is usually initiated at the first signs of puberty, and it is in this peripubertal period that important maturational changes take place in the testis (139–144). Influenced by complex hormonal actions, these maturational processes eventually lead to initiation of spermatogenesis. Onset of spermatogenesis (spermarche) as detected by urine analysis (spermuria) appears to be an early pubertal event: the median age of spermarche has been estimated to be 13–14 yr (145–148). In addition, it is noteworthy that administration of T esters at high doses may cause morphological and cytological changes, as shown in rat and human adult testes (149–151).

1. Plasma hormone levels. High T levels are obtained during treatment with supraphysiological doses of androgens suppressing the hypothalamo-pituitary-gonadal axis (152).

Zachmann, Prader, and co-workers (98, 113) reported a slow recovery of pituitary gonadotropins during LHRH-stimulation tests after discontinuation of T therapy. Brämswig *et al*. (136) demonstrated normalization of gonadotropin levels in 100 tall boys after discontinuation of treatment with follow-up periods up to 48 months, although transient hypergonadotropic LH- and FSH- secretory patterns were observed. In a recently published study by the same group (153), hormonal levels and testicular function were evaluated after a follow-up period of approximately 10 yr and compared with normal volunteers. Mean values of LH, FSH, PRL, T, estradiol, and sex hormone-binding globulin were in the normal range in both groups. T was lower and FSH was higher in treated tall men compared with volunteers, but the only statistically significant difference was for T. We observed different levels of gonadotropins in previously treated tall men compared with controls (tall and 'normal' men) (154). Androgen-treated tall men had significantly higher FSH levels compared with controls. Levels of plasma hormones were not significantly correlated with parameters of sperm quality; however, we observed significant negative correlations between plasma FSH levels and sperm concentration as well as the age at start of therapy in the androgen-treated men. We speculate that the higher levels of FSH may reflect intratesticular changes due to androgen treatment received during a period of testicular maturation especially during the earlier pubertal stages (155). These increased FSH levels may compensate for partially disturbed germinal function to maintain normal sperm quality (156). In a subgroup of previously treated and untreated men, we also measured inhibin B, which probably is a more direct marker of spermatogenesis than FSH (157). We found similar levels, well within the normal range (F. H. De Jong and W. J. De Waal, unpublished results). On the other hand, the difference in

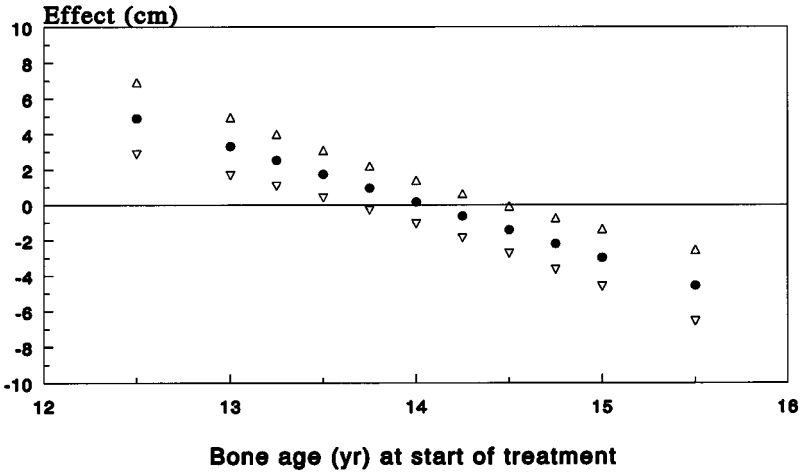

FIG. 1. Adjusted effect of androgen therapy. The effect of therapy was calculated by multiple regression analysis using final height as dependent variable and treatment, and CA, BA, and height prediction (and their interactions) as independent variables. Using the height prediction according to the index of potential height for bone age, the estimated treatment effect was a linear function related to BA (Greulich and Pyle) in the form: Effect (cm) = 44.19–3.15 × BA (yr). The *solid dots* (●) represent all patients with a given bone age, and the *open triangles* (△) represent the 95% confidence interval of the calculated adjusted effect. [Reproduced with permission from W. J. de Waal *et al.*: *J Clin Endocrinol Metab* 81:1206–1216, 1996 (101). © The Endocrine Society.]

gonadotropin levels may also reflect a change in responsiveness at the hypothalamo-pituitary level (136).

2. Testicular volume. Treatment with high doses of androgens induces reduction in testicular volume in adult men (158) as well as in tall adolescent boys (98, 99, 113). This implies major intratesticular changes during therapy such as a decrease in seminiferous tubule size (149, 150). These processes are likely to be reversible since testicular volume normalizes after discontinuation of therapy as shown in several studies (98, 99, 113, 158). This is in contrast to the observations of Willig *et al*. (159, 160), who reported significantly smaller testicular sizes in previously treated men. In contrast, in our studies at a mean follow-up period of 8 yr after cessation of treatment, there was no difference in mean testicular volume between treated and untreated tall men (154).

3. Sperm quality. When sperm quality is evaluated, one must be aware of the normal distribution in the population as well as of confounding factors interfering with parameters of sperm quality. It is well established that varicocele (161–164), smoking (165), sexually transmitted disease (166), and cryptorchidism (167) are likely to affect sperm quality and/or plasma hormone levels. Semen analysis in our study of previously androgen-treated men showed that sperm quality was comparable with a control group of untreated tall men, even after correction for the above mentioned possible interfering conditions, after a mean follow-up period of 8 yr. These findings are in agreement with the experiences reported by Zachmann and Prader and co-workers (98, 113). In contrast, Willig and co-workers (159, 160) found significantly reduced sperm concentrations in previously treated tall men compared with controls. Their control group, however, showed a relative high mean value of sperm concentration of 120.2 × 10′6/ml, almost twice as high as values found in the normal population at present (168, 169). Their treated group showed a mean sperm concentration of 63.4 × 10′6/ml, which is comparable with values found in our study (154). It is possible that differences in patient selection, semen analysis methodology, and treatment regimens may account for the observed differences. In addition, the extent to which interfering conditions are present may cause important bias as well. In a recent report Lemcke and co-workers (153) showed that 10 yr after T treatment, none of the tall men had azoospermia, and the mean ejaculate parameters were in the normal range or only slightly subnormal. Overall, seminal parameters of T-treated tall men were slightly, but not significantly, lower compared with normal statured volunteers. Interestingly, they found a significantly higher prevalence of varicocele and maldescended testes in the tall men compared with their control group of normal volunteers (153). They surmised that varicocele and maldescended testes, rather than T treatment, caused the somewhat lower semen quality in the tall men. In our studies in treated and untreated tall men, we observed an overall prevalence of varicocele of 42% (12% subclinical and 30% clinical) (154). This would suggest that varicocele occurs more often than reported in the normal population (12.4–25.8%) (170–172). A relationship to androgen treatment is unlikely since no difference in the prevalence of varicocele was observed between androgen-treated men and controls. One could speculate on the impact of stature on the pathogenesis of varicocele (153, 154).

4. Pregnancy/paternity. Thus far, only casuistic and exclusive female data have been available on successful pregnancies after height-reductive therapy. At the time of our follow-up studies five of the 43 androgen-treated men and six of the 30 untreated tall men had fathered one or more children (154). All 11 men reported that pregnancy had occurred in their partners after less than 1 yr of unprotected coitus. Two other pregnancies, fathered by a previously treated man and a control, respectively, ended in spontaneous abortion. These very limited numbers do not allow any further conclusions.

D. Other clinical effects

Many patients experience side effects during therapy (98, 99, 113, 132, 173, 174). Most of these, however, are mild and transient (see Table 7). In some patients, slight to moderate edema, notably in the pretibial or malleolar area, was associated with marked weight gain during the first 6 months of treatment. This indicates that the early gain in weight is not only due to protein anabolism but also to water retention (98). Acne was by far the most reported side effect (98, 99, 175). Occasionally acne fulminans has been reported and necessitated discontinuation of therapy (173, 176). A causal relationship with androgen therapy is likely as shown by Fyrand *et al*. (177). Hinkel *et al*. (178) investigated the effects of high doses of androgens on lipoproteins during and after the cessation of therapy. Although during treatment a significant fall of triglycerides and HDL was observed, all values normalized after the end of treatment (178). In our studies, gynecomastia occurred in 13% of the cases. Since gynecomastia is rather prevalent in population studies in pubertal boys (179), it is difficult to say whether the condition had increased. One would expect that treatment would have effects on sexuality (sex interest, masturbation). Although in one study a marked increase of sexuality in younger, but not in older patients, was noted, it never exceeded the normal range seen in adolescence (98). Treatment with supraphysiological doses of T were not shown to provoke aggressive behavior in adolescents or young adults (180, 181).

VIII. Estrogen Treatment in Tall Girls

A. Estrogen treatment modalities

In 1956 Goldzieher introduced estrogen as a treatment of excessive growth in adolescent girls (182). Since then, many reports have appeared describing the height-reducing effect of high-dose estrogen therapy in tall girls (64, 101, 103–109, 112, 122–131). Many investigators, mainly in the United States, treated excessively tall girls with conjugated estrogens (114). In Western Europe, others used ethinyl estradiol (EE) in varying dosages usually combined with a progestogen 7–10 days each month to induce cyclic bleeding and to avoid overstimulation of the endometrium (103, 107, 131). Norethisterone, medroxyprogesterone, and dydrogesterone have been used as progestagen, 5–10 mg/day. The two last preparations, in particular, show low to absent androgenic effects (183). In the past, estrogens have been administered in the form of stilbestrol, 1–5 mg per day (112, 113, 182, 184). However, since it has been reported to cause vaginal cancer in the female offspring of women treated during pregnancy (185, 186), stilbestrol is not a suitable treatment modality. It has the additional disadvantage of inducing marked pigmentation and hyperkeratosis of the nipple. Estradiol esters, such as estradiol-valerate and -benzoate, have been used since they were considered to be more 'physiological' than oral ethinyl estradiol (EE) or conjugated estrogens (113, 187). A disadvantage is that three injections per cycle are required. Considering all advantages and disadvantages, it appears that EE is the preparation of choice, since the dose is standardized, administration is easy, and side effects are not more marked or frequent than with any other preparation (103). Whether the estrogens are given continuously or cyclically seems to be of minor importance for the effect on height or for the resumption of regular menstrual cycles after discontinuation of treatment (103). It seems that the pituitary-gonadal axis tolerates continuous therapy for a period of 1–2 yr very well. In the 1960s most practitioners used 500 μg EE; in the 1970s 200–300 μg were used, and in the 1980–1990s a dosage of 100 μg/day was claimed to be sufficient (101, 106, 107, 109, 113, 114, 125, 130, 131, 183, 188–191). Whether even lower dosages (*e.g.*, 35 μg daily) are equally effective remains to be assessed in a prospective clinical trial (131).

TABLE 7. Reported percentages of side effects during hormonal therapy in boys with CTS

Side effect	Reported percentage in study		
	Brämswig *et al.* (99)	De Waal *et al.* (101)	Binder *et al.* (181)
Aggravation of acne	64	39	28
Painfulness of injection	8	16	
Weight gain		14	
Gynecomastia		13	
Muscle ache		13	
Edema		9	
Change in psychological/sexual behavior	0	5	7
Hypertrichosis			13
Decreased performance after treatment	20		

B. Height reduction

Studies on the effect of height reduction in tall girls have shown various results using different prediction models within the same study population (104, 105, 107–109, 124, 127, 129). The mean calculated effect of therapy is 'corrected' by subtracting the systematic prediction error, as has been commonly reported in the literature. The mean reported height reduction ('corrected' and uncorrected) in girls with CTS ranged from 2.1 to 10 cm (64, 101, 103–109, 112, 122–131) (see Table 8). A clear comparison, however, is hampered by differences in initial clinical data (especially CA and BA), duration of treatment, therapeutic regimen (different doses and estrogen preparations), and the point in time of final height assessment. Concerning the latter, De Waal *et al*. (101) observed a mean (SD) additional growth of 2.7 (1.1) cm after cessation of therapy, which is of the same order of magnitude as in boys (107, 123, 127). The cause of the observed additional growth is not quite clear. It could be explained by cessation of therapy before complete closure of the epiphyses. In addition, it is plausible that part of the remaining posttreatment growth reflects additional spinal growth.

As discussed earlier, evaluating the effect of sex steroid treatment after 'correction' for the mean errors of the separate prediction methods might induce bias. To calculate the 'net' treatment effect, multiple regression analysis has been used while adjusting for differences in age, BA, and height prediction between treated and untreated children. The mean adjusted effect for the various prediction methods varied from 1.1 to 2.4 cm and ranged from −2.6 to 6.2 cm in girls (101). These mean results are less than previously claimed

TABLE 8. Effect of hormonal treatment in girls with CTS

Study (Ref.)	n	Therapy	CA	G-P BA	B-P Pred HT, uncorrected	Final HT corrected[a]	TW BA	TW Pred HT, uncorrected	Final HT corrected[a]
Zachmann *et al.* (1975) (103)	40	EE, 0.3 mg/day	12.9 (1.2)				13.4 (0.5)	4.6 (2.4)	4.2
	9	Controls	14.1 (0.9)				NR	0.4 (−)	
Wettenhall *et al.* (1975) (112)	87	Stilbestrol 3 mg/day	13.0 (1.1)	13.2 (0.8)	3.5 (2.2)				
Von Puttkamer *et al.* (1977) (122)	41	Conjugated estrogens, 7.5 mg/day	13.0 (1.4)	12.4 (0.8)	7.3 (2.0)				
Kuhn *et al.* (1977) (123)	17	EE, 0.5 mg/day	12.7 (1.2)	12.6 (0.6)	6.2 (2.8)				
Reeser *et al.* (1979) (104)	14	EE, 0.2 mg/day	10.6 (0.4)	10.4 (0.5)	9.3 (1.1)	10.2	NR	7.1 (1.4)	7.0
	14	Controls	10.7 (0.3)	11.2 (0.4)	−0.8 (0.8)		NR	0.1 (−)	
John and Schellong (1980) (105)	71	EE, 0.3 mg/day	12.5 (1.1)	12.7 (0.8)	5.2 (2.8)	3.9	13.3 (0.8)	5.7 (2.9)	5.0
	18	Controls	12.3 (1.3)	12.5 (1.3)	1.3 (2.5)		13.4 (1.3)	0.7 (2.5)	
Andersen *et al.* (1980) (127)	40	Estradiovalerate, 30 mg month im	12.6 (1.4)	11.8 (1.0)	5.0 (3.7)		NR	2.9 (3.4)	
Stöver and Kollmann (1982) (128)	46	Conjugated estrogens, 7.5 mg/day	12.7 (1.2)	NR	5.8 (3.2)		13.0 (0.6)	4.1 (2.4)	
Sorgo *et al.* (1984) (129)	14	EE, 0.3 mg/day or conjugated estrogens, 7.5 mg/day	12.0 (1.4)	11.8 (1.4)	6.5 (5.5)	4.2	12.7 (1.0)	5.5 (5.5)	2.1
	7	Controls	13.5 (1.5)	13.1 (1.1)	2.3 (3.6)		13.6 (1.1)	3.4 (3.7)	
Schambach and Nitschke (1985) (106)	20	Mestrenol 3×/month 80 μg/day	9.8 (0.7)	9.3 (0.4)	7.6 (1.7)	8.1			
	20	Idem	10.1 (1.0)	10.4 (0.4)	5.5 (2.0)				
	16	Idem	11.7 (0.9)	11.5 (0.4)	3.0 (1.3)				
	30	Idem	12.3 (0.9)	12.6 (0.4)	2.2 (0.6)				
	26	Controls	9.2 (0.7)	9.4 (0.4)	−0.5 (2.5)				
Bartsch *et al.* (1988) (107)	35	EE, 0.1 mg/day	12.3 (−)	12.5 (−)	4.2 (2.3)	3.9	13.1 (−)	4.0 (−)	3.6
	23	Controls	12.5 (−)	12.5 (−)	0.6 (2.2)		NR	0.4 (−)	
Grüters *et al.* (1989) (130)	38	EE, 0.5–0.3 mg/day	12.5 (1.6)	12.4 (0.8)	4.9 (2.6)				
	44	EE, 0.1 mg/day	12.4 (1.4)	12.4 (0.8)	5.1 (2.4)				
Svan *et al.* (1991) (64)	21	EE, 1.0 mg/day	13.4 (1.5)	12.9 (0.8)	5.5 (2.7)	4.3			
	20	EE, 0.5 mg/day	13.3 (1.0)	12.8 (0.7)	5.9 (3.3)	4.7			
	15	EE, 0.25 mg/day	13.5 (1.1)	12.6 (0.9)	5.6 (2.7)	4.4			
	12	Controls	NR	NR	1.2 (−)				
Normann *et al.* (1991) (131)	263	EE, 0.5 mg/day	13.2 (−)	12.6 (−)	5.9 (−)				
	178	EE, 0.25 mg/day	13.1 (−)	12.6 (−)	5.3 (−)				
	98	EE, 0.1 mg/day	13.8 (−)	12.7 (−)	4.4 (−)				
Joss *et al.* (1994) (109)	16	EE, 0.5 mg/day	12.8 (0.9)	NR	6.9 (1.6)	4.5	12.5 (0.3)	5.1 (2.7)	3.8
	25	EE, 0.3 mg/day	12.8 (0.9)	NR	6.6 (2.4)	4.2	12.5 (0.4)	4.3 (2.4)	3.0
	11	EE, 0.1 mg/day	13.5 (0.9)	NR	6.5 (2.1)	4.1	12.5 (0.3)	3.6 (2.1)	2.6
	21	Controls	13.0 (1.1)	NR	2.4 (−)		12.6 (1.1)	1.3 (2.8)	
De Waal *et al.* (1996) (101)	159	EE, 0.2 mg/day	12.7 (1.2)	12.4 (1.0)	4.1 (3.0)	3.6	13.3 (1.1)	1.4 (3.3)	2.2
	88	Controls	12.8 (1.5)	12.9 (1.4)	0.5 (2.7)		13.8 (1.3)	−0.8 (3.1)	
Binder *et al.* (1997) (181)	56	Conjugated estrogens 7.5 mg/day	12.9 (1.2)	12.5 (0.6)[b]	3.7 (3.6)	3.6			
	79	Controls	11.8 (1.5)	12.3 (1.4)	0.1 (3.6)				

Data are expressed in centimeters as mean (SD). N, number; CA, chronological age at start of treatment; BA, bone age at start of treatment; EE, ethinyl estradiol; BP, Bayley-Pinneau (ref); TW1, Tanner-Whitehouse Mark 1 (80); TW2, Tanner-Whitehouse Mark 2 (80); TW-RUS, bone age RUS score according to method of Tanner-Whitehouse (80); BA-GP, bone age according to method of Greulich and Pyle (83); NR, not reported.

[a] Correction by subtraction of the mean prediction error of the control group.

[b] Bone age at start of study; bone age at start of treatment not given.

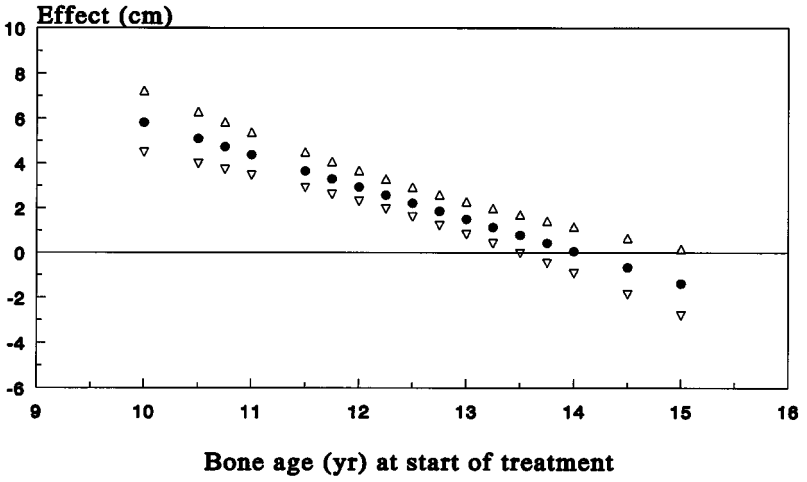

FIG. 2. Adjusted effect of estrogen therapy. The effect of therapy was calculated by multiple regression analysis using final height as dependent variable and treatment, and CA, BA, height prediction, and menarche (0 − no; 1 − yes) (and their interactions) as independent variables. Using the Bayley-Pinneau prediction method, the estimated treatment effect was a linear function related to BA (Greulich and Pyle) in the form: effect (cm = 20.22 × 1.44 × BA (yr.). The *solid dots* (●) represent all patients with a given bone age and the *open triangles* (△) represent the 95% confidence interval of the calculated adjusted effect. [Reproduced with permission from W. J. de Waal *et al.*: *J Clin Endocrinol Metab* 81:1206–1216, 1996 (101). © The Endocrine Society.]

(64, 103–109, 112, 122–131), probably due to differences in statistical approach and study design, as explained above. Various studies show (as illustrated in Fig. 2) that the effect of treatment was more pronounced when treatment had been started at a younger BA (105, 108, 112, 123, 130, 131). However, others did not find such a relationship (103).

Results are inconsistent concerning whether or not premenarcheal girls may experience more height reduction compared with postmenarcheal girls. Some reports are in favor of this finding (109, 122, 123, 125) while others observed no difference (103, 107, 128, 130). In our study (101), premenarcheal girls seem to benefit more from therapy than postmenarcheal girls. However, this was likely to be due to the differences in CA between the groups since we found no additional effect of menarche on CA explaining the variability in the effect of treatment. This may, at least in part, explain the conflicting results.

C. Effects on gonadal function

1. The hypothalamo-pituitary-gonadal axis and menstrual cycles. Suppression of the hypothalamo-pituitary-gonadal axis induced by pharmacological doses of estrogens via a negative feedback mechanism was found to be reversible (136, 192). Hanker *et al*. (192) assessed the functional state of the hypothalamo-pituitary axis by standardized LHRH testing in 16 tall girls treated with 300 μg EE daily for 7–26 months. While absent LH responses were observed in all girls immediately after therapy was stopped, 4 to 8 weeks later the LH responses had normalized in 13 girls and 12 weeks after therapy in 14 girls. All girls experienced spontaneous menstrual bleeding within 3 to 22 weeks after termination of therapy. The same was observed in most later follow-up studies in which first menstruation was reported within 1–6 months after cessation of treatment, in most cases even after the first month (103, 114, 127, 130). Amenorrhea of longer than 6 months after cessation of height-reductive therapy was reported in about 5% of the cases (175). The incidence of prolonged amenorrhea after cessation of oral anticonceptive therapy is about 0.5% (193). In addition, the overall prevalence of secondary amenorrhea of more than 6 months in women aged 15–34 yr is about 1.3% (194). This may suggest an increase of amenorrhea after height-reductive therapy. It should be noted, however, that there are no convincing data that use of oral contraceptives (OCs) is causally related to amenorrhea and that other risk factors for amenorrhea, such as smoking, nutrition, and exercise, were not adequately investigated (193, 195). No differences were found in menstrual cycle characteristics between previously treated and untreated tall women after a mean follow-up period of almost 11 yr (175).

2. Pregnancy. In girls, pregnancy, which is the ultimate 'proof' of complete reversibility of hypothalamo-gonadal suppression, has been reported in various single cases (112, 113, 127, 128, 130, 131, 189). In our own study, information on a total of 63 pregnancies was obtained from 40 previously treated tall women. No distinct differences in details and outcome of pregnancies between treated and untreated tall women were found (175). These results indicate that long-term effects of high doses of estrogens on fertility are unlikely.

Although a mean follow-up period of 10 yr is still too short to draw definite conclusions, there is no clear evidence that treatment with high doses of sex steroids does induce harmful effects on reproductive function in tall girls.

D. Other adverse effects

In most studies, unwanted side effects have been reported only during treatment or shortly after discontinuation of therapy (109, 112, 113, 127, 128, 130, 131, 183, 189, 196, 197). Most side effects were found to be mild and reversible (see Table 9). In a large retrospective study short-term and long-term effects of high doses of estrogens in the management of CTS were evaluated at a mean follow-up period of 10 yr after discontinuation of height-reductive therapy. OCs were used by a high proportion of previously estrogen-treated girls as well as controls. An impressive bulk of data on the association between long-term OC use and possible health risks (reviewed in Refs. 198 and 199) form an excellent reflection of the prospective risk in estrogen-treated girls. The proportion of OC's use and reported side effects were not significantly different between estrogen-treated and nontreated women. More than 70% of the estrogen-treated women had experienced one or more side effects during therapy, such as weight gain, headache, nausea, leg cramps at night, in-

TABLE 9. Reported percentages of side effects during hormonal therapy in girls with CTS

Side effect	Reported percentage in study			
	John and Schellong (105)	Trygstad (183)	De Waal *et al.* (101)	Binder *et al.* (181)
Headache/migraine	14	2	13	
Nausea/vomitus	27	66	14	
Fluor vaginalis	10	2	13	
Pigmentation of areola and nipples	38	23	27	
Weight gain	44	90	41	13
Calf cramp		<1	20	17
Change in psychological/sexual behavior		<1	3	
Galactorrhea		2	4	
Hypertrichosis		<1	3	
Thrombosis			—	
Hypertension			2	
Bleeding disturbances	11	2	9	
Cysts or tumors in mammae/uterus or ovariae		<1	2	
Polyphagia		<1	4	
Striae	44		3	
Dizziness/orthostatic problems			1	7

creased pigmentation of areola and nipples, and vaginal discharge. Although most of them were mild and transient, the adverse effects of estrogens occurred more frequently during therapy than during OC use (175). This would suggest a dose-dependent effect of estrogens on the incidence of adverse events (107, 130).

Although hemostatic changes have been reported (196, 200, 201), thrombosis is found to be a very uncommon side effect of height-reductive therapy (112, 132, 196). Whenever thrombosis occurred it usually coincided with other risk factors for thromboembolism such as immobilization (202). Galactorrhea is an infrequent side effect of estrogen therapy in tall girls (113, 123, 183). Hyperprolactinemia may be more frequent but is reversible in most cases (Ref. 192 and M. C. A. M. Houdijk and H. A. Delemarre-Van de Waal, submitted for publication).

The effect of high-dose estrogens on lipid metabolism was evaluated in several studies (178, 204). The changes of serum lipids and lipoproteins during estrogen therapy were reversible after cessation of treatment.

Malignancy was not reported in our follow-up study (175). Although there have been no reported cases of ovarian, uterine, vaginal, or breast malignancies in girls treated for tall stature, the risk of cancer in young women receiving estrogens remains uncertain. The possibility of a dose-dependent effect and a relationship with OC use at a young age and duration of OC use with increased risks of breast cancer (205) point to the need for long-term follow-up of patients treated with pharmacological doses of estrogens.

IX. Alternative Treatment Modalities and Future Research

An alternative strategy to limit growth in children with tall stature utilizes interference in the regulation of GH secretion. It is based on the assumption that tall stature is related to GH hypersecretion. Bromocriptine therapy has been proposed as a means to suppress endogenous GH secretion. Bromocriptine is a dopamine agonist and inhibits GH secretion in patients with acromegaly by binding to pituitary dopamine receptors (206). In the 1980s, studies on the effectiveness of bromocriptine in reducing final adult height in children with CTS revealed conflicting results. The studies of Evain-Brion and colleagues (207–210) reported marked decreases in height prediction in a group of about 30 adolescents after a treatment period of 9–15 months. It was stated that the reductive effect on height prediction was mainly due to an increase in bone maturation rather than a decrease in height velocity; IGF-I and IGF-II levels remained unchanged. In contrast, other studies did not substantiate the effect of bromocriptine treatment on height prediction or skeletal maturation in children with tall stature (211–213). Recently, research has focused on somatostatin analogs for the management of tall stature. Somatostatin is a neurohormone produced at the hypothalamic level that has potent inhibitory properties on GH release in the pituitary via the vascular network of the portal system (214). Preliminary data revealed an effective suppression of GH secretion in small groups of tall children and a significant reduction in growth rate and predicted adult height (215–218). In addition, plasma IGF-I levels decreased whereas bone maturation accelerated in many of the treated children (216). The effect of somatostatin on bone maturation suggests that somatostatin acts not only by systemic hormonal effects on GH and/or IGFs but also by local regulatory effects on bone growth and metabolism. This hypothesis is supported by the observation of Lamberts (219), who found symmetrical bands of increased radioactivity by means of *in vivo* somatostatin receptor-imaging techniques at the epiphyseal surfaces of children with neuroblastoma. Final results on height reduction by somatostatin therapy have not yet been established, and the possibility of serious side effects such as gall stones must be considered.

Strategies to limit final height of tall children have centered around the peripubertal years. This is mainly due to the use of high doses of sex steroids to advance skeletal maturation. Hindmarsh *et al.* (218) suggested that in the management of children with tall stature, attempts should be made to reduce the prepubertal contribution to stature. Since prepubertal growth is largely GH dependent, somatostatin analogs might be used to reduce the actual height from which the pubertal growth spurt will commence. In addition, sex steroid therapy may be applied as an adjuvant during puberty to optimize the ultimate height-reducing effect. Other possibilities are low-dose sex steroid treatment starting at an early prepubertal age (106), or orthopedic modalities such as bilateral epiphysiodesis around the knee (220) or femoral shortening (221).

X. Conclusions and Recommendations

Treatment of CTS is generally based on psychological grounds. Children and adults with excessive growth may suffer considerably from being much taller than their peers. Although psychosocial factors form the main reason for

treatment, extensive psychological investigation before or during height-reductive therapy has never been performed. There are no objective prospective data indicating lifelong psychosocial damage as a result of tallness. In two retrospective studies men and women previously treated with high doses of sex steroids because of CTS showed no major psychological maladjustment compared with tall controls (180, 181). Nevertheless, many tall individuals experience practical problems concerning clothing and shoes, are teased, and are subject to hurtful remarks and jokes about their height. Thus, careful attention should be paid to the psychosocial problems related to tallness especially in relation to the sociocultural environment when considering treatment.

Prospective controlled studies that answer the main question of whether treatment with pharmacological doses of sex steroids is effective in reducing final height have never been performed. As claimed effectiveness is based on height prediction, a critical appraisal of the quality of the various prediction methods is in order. Height prediction in tall girls is more accurate than in boys.

It is suggested that height prognosis in children with excessive growth is more accurate when based on growth data derived from untreated tall children (101). It must be emphasized that although prediction techniques may have small mean errors of prediction, in individual cases considerable errors in height prognosis may be made. This is reflected by the presence of the relatively large SDS of the mean errors of the prediction method applied (191). It is preferable, therefore, to give predicted adult height as a height with a confidence limit using the residual SDS of the prediction technique for calculation (see Table 5). Repeated measurements at intervals of 4–6 months will improve the clinical relevance of the prediction. Treatment with supraphysiological doses of sex steroids has been advocated for final height reduction since 1950.

When the many reports in the literature on the height-limiting effect of sex steroid treatment are analyzed, one may conclude that height reduction is dependent on the BA at the time of start of treatment. In our experience, tall girls benefit more from sex steroid therapy than tall boys, but data from the literature are not consistent.

As shown in Figs. 1 and 2, the period during which effective height reduction is to be expected is quite limited. The upper limit of this period is determined by BA (Greulich and Pyle) of <14 yr in boys and of <13.5–14 yr in girls. The lower limit is determined by psychosocial constraints, as treatment clearly induces puberty. Posttreatment growth caused by cessation of treatment before complete closure of the epiphyses may cause a significant reduction of the height-limiting effect of treatment. The optimal dose of sex steroids is not known. In the course of time the dosage of oral ethinyl estradiol for girls has been reduced gradually from 500 μg/day to 100–200 μg/day. In boys, long-acting T esters, 1000 mg/m^2/month, is most often recommended administered ip once per 1 or 2 wk. For late maturing individuals, it is advisable to initially prescribe a reduced dose with subsequent gradual increments.

To date, no evidence of long-term side effects of high doses of sex steroids have been demonstrated after 8–10 yr. This limits the need for a prospective trial to assess the effectiveness of a lower dosage regimen. On the other hand, in view of a relationship with OC use at a young age and duration of OC use with increased risks of breast cancer (205), there is a need for long-term follow-up of individuals treated with pharmacological doses of estrogens. Similarly, while no hard evidence of testicular damage has been established after androgen treatment in tall boys, the finding in one study of marginally elevated FSH levels along with normal sperm counts, testicular volume, and endocrinological parameters including inhibin B levels, warrants further study.

In conclusion, it is recommended first to refer constitutionally tall children in the late prepubertal period (8–10 yr) to secure proper pretreatment evaluation of growth and bone maturation. Second, to restrict treatment to excessive tallness or a very outspoken professional desire where height forms a clear limitation (*e.g.*, pilot, ballet dancer). Third, treatment should be initiated at an early 'bone age,' psychosocial constraints permitting. Treatment should not start before an age corresponding to the 10th percentile of the first stage of pubertal development. Moreover, although retrospective studies have not provided hard evidence of testicular damage, it should be realized that in boys androgen treatment might interfere with pubertal testicular development. Finally, treatment should be continued until complete closure of the epiphyses has been established radiologically.

In view of the crucial role of GH during the pubertal growth spurt, it is tempting to speculate on other treatment modalities that might be as effective or perhaps even more effective than the current practice. There may be new ways of effectively suppressing GH secretion not only by somatostatin analogs (223), but also by GHRH or GH antagonists (224–226).

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