

Personal practice

Management of constitutional delay of growth and puberty

R STANHOPE AND M A PREECE

Department of Growth and Development, Institute of Child Health, London

Constitutional delay of growth and puberty (CDGP) is not a disease but a common condition in which puberty and its associated growth spurt occur at an age which is near the extreme of the normal range. Growth at puberty is intimately related to the stage of pubertal development and this is why, quite appropriately, both growth and puberty are implicit in the name, although it could be argued that they occur in an incorrect order. It is an important condition to recognise as many such children only need reassurance although some will require, if only for psychological reasons, therapeutic intervention to improve their short term growth. There is much information available about the anthropometric progress of children with constitutional delay of growth and puberty and we have attempted to correlate this with our more recent understanding of possible options for the manipulation of the endocrinology of puberty.

Definition

Constitutional delay of growth and puberty is defined by Prader as: 'constitutional delay of growth occurring in otherwise healthy adolescents with stature reduced for chronological age but generally appropriate for bone age and stage of pubertal development, both of which are usually delayed'.¹

As growth potential is related to the degree of epiphyseal maturation, it is this delay in bone age which permits a final stature within the normal range. It is the 'tempo' of growth (and puberty) which is significantly delayed.² In this article, we shall use the terms 'constitutional delay' and 'growth delay' as synonymous with CDGP as they are almost certainly manifestations of the same condition, although presenting at different ages (see below). CDGP is more common in boys than girls and tends to have a familial pattern. The anthropometric, as well as the psychological, sequelae of delayed

puberty are more dramatic in boys on whom we shall concentrate most of our discussion.

Endocrinology of puberty

The initial endocrine event of puberty is high amplitude pulsatile gonadotrophin secretion from the pituitary gland in response to pulsatile gonadotrophin releasing hormone (GnRH) secretion from the hypothalamus.³ These events occur predominantly at night, as does growth hormone secretion. It is interesting that the secretion of these hormones is intimately related to the night during puberty and that this relationship continues throughout reproductive function; the onset of the luteinising hormone surge in women, which is an essential prerequisite to ovulation, occurs in the early hours of the morning. The diurnal secretion of these hormones during early puberty has important implications for their therapeutic administration⁴; oestrogen in girls should be administered in the morning, oral testosterone in boys as well as growth hormone in both sexes are usually given during the evening.

There is a sex difference in the pituitary response to GnRH which may explain the characteristic differences between the timing of the onset of puberty in girls and boys; girls more readily release gonadotrophins to a given GnRH stimulus.⁵ This may explain why the onset of puberty is earlier in girls than boys, why central precocious puberty is more common in girls, and why constitutional delay of growth and puberty is more common in boys.

Although both sex steroids and growth hormone are required for the growth spurt of puberty, the pattern of secretion of sex steroids alone does not explain the growth acceleration of puberty. In girls, oestrogen secretion is at its peak just before menarche, when the growth spurt is waning. In boys, sex steroid secretion increases progressively

throughout puberty and yet initially growth decelerates and the onset of the growth spurt occurs relatively late between genitalia stage 3 and 4. Both sex steroids and growth hormone are synergistic during the growth spurt and it has been appreciated for many years that boys with delayed puberty before the onset of the growth spurt, as well as girls in late prepuberty, have physiological growth hormone insufficiency,⁶ which can be reversed by exogenous administration ('priming') with sex steroids.⁷ We have recently appreciated, however, that growth hormone pulse amplitude and not sex steroid secretion correlates with changes in growth velocity during puberty in both girls and boys.⁸ Short term use of sex steroid 'priming' in boys in early puberty temporarily increases growth hormone secretion, and the administration of sex steroids for greater than three months induces a sustained increase in both growth hormone secretion and growth that continues after the cessation of treatment. This is the principle for short course treatment with anabolic and sex steroids for boys in early puberty with CDGP.

Data from postmortem examination,⁹ pelvic ultrasound,¹⁰ and hormone profiles⁵ have suggested that the endocrine events which we associate with puberty probably have their origin very much earlier in childhood. Gonadotrophin secretion progressively increases throughout childhood and when sufficient sex steroids are secreted to induce secondary sexual characteristics, then phenotypic puberty begins. These low concentrations of sex steroids secreted during early childhood, however, may have great significance for the physiology of growth delay. After the second year of life, when growth has become dependent on growth hormone,⁶ low concentrations of sex steroids may result in secondary growth hormone insufficiency and low growth velocity but with contemporaneous retardation of epiphyseal maturation; this is the exact scenario observed in growth delay.

Pubertal development

It is important to distinguish puberty that is normal, except that the onset is delayed, from absent pubertal development or arrested puberty (no progress for 18 months or more). In contrast to CDGP, hypogonadotrophic hypogonadism is a spectrum which may present clinically as absent puberty, arrested puberty, or failure to attain reproductive function depending on the degree of GnRH insufficiency. Thus children who have *no* signs of puberty at 2.5 SD or greater from the mean (14.0 years in a girl and 14.5 years in a boy) require appropriate endocrine and radiological investigation of the hypothalamo-pituitary axis.

Progress through puberty can take a considerable length of time; 3% of normal girls and boys take longer than five years to progress from genitalia/breast stage 2 to 5.^{11 12} For example, a boy who enters puberty at 14 years may not complete his puberty (and therefore his growth) until 19 years and perhaps considerably later as children who enter puberty later tend to progress through puberty more slowly.¹

Pattern of growth

CDGP is more common in boys than girls for reasons we have discussed. Even when this becomes a clinical problem in a girl, it is self limiting because as soon as the onset of puberty occurs (breast development) and they commence their growth spurt, girls will attain peak height velocity between breast stage 2 and 3. By contrast, the problem is exaggerated in boys because their growth spurt only occurs towards the end of puberty. The growth spurt commences at 10 ml testicular volume (genitalia stage 3 to 4) and attains a peak velocity at 12 ml (genitalia stage 4 to 5). Thus the growth of a boy who enters puberty at 14 will continue to decelerate for many years, until the growth spurt starts at perhaps 17 or 18 years of age, by which time he is considerably shorter than his peers. The later the growth spurt occurs, the lower the peak height velocity that is attained, as final height attainment is not dependent on the timing of the onset of puberty (except in precocious sexual development).^{13 14} This dictum has recently been affirmed as the use of a GnRH analogue to delay the puberty of short normal children does not improve final height prognosis.¹⁵

An example of a boy with CDGP is shown in fig 1. Although he entered puberty at 14 years, his growth continued to decelerate at an extended 50th centile velocity. This may imply a growth velocity of only about 2–4 cm/year by the age of 16 years, and although this may induce considerable concern in his medical attendants it is important to appreciate that this is normal for chronological age and stage of puberty. By the age of 16 years, at the commencement of the growth spurt, his height was 15 cm below the 3rd centile on the 'distance' chart.

Diagnosis of constitutional delay of growth and puberty

The characteristic feature of normal puberty is that there is a relationship between the pattern of acquisition of the various stages of sexual maturation and the growth spurt. Loss of this normal harmony of growth and puberty points to an

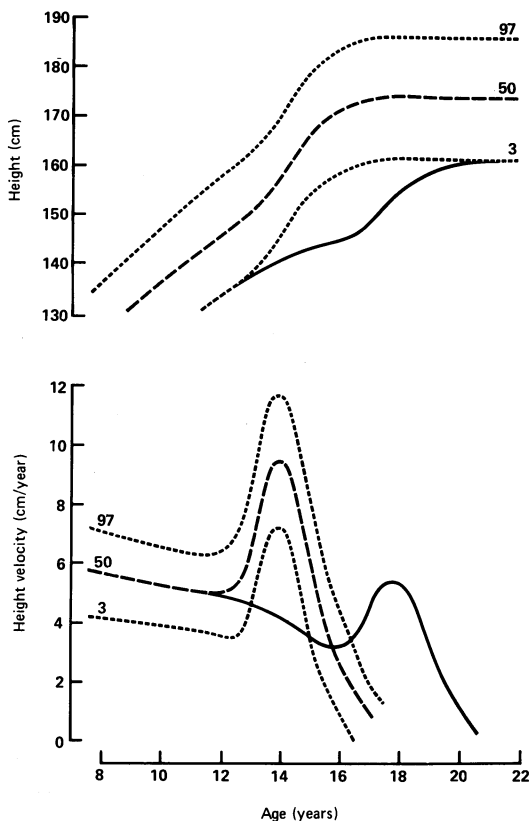


Fig 1 Distance (above) and velocity (below) charts from a boy with constitutionally delayed puberty. The onset of puberty was at 14 years and he continued to grow at an extended 50th centile velocity until the onset of the growth spurt at 16 years. The typical pattern of growth is shown on the 'distance' chart.

endocrinopathy.¹⁶ The absence of a growth spurt associated with the acquisition of a 10 ml testicular volume; a growth velocity of 2 cm/year in a boy in early puberty that is appropriate at 17 years but not at 13 years; and a large testicular volume in relation to inadequate virilisation are all examples of loss of the normal consonance of growth and puberty and necessitate investigation. In contrast, the normal consonance of growth and puberty is usual in children with CDGP and this mitigates against special investigations.

Growth delay often occurs in children with severe systemic disease such as asthma, renal disease, coeliac disease, inflammatory bowel disease, or after the chronic use of corticosteroids. It is important not to overlook these possibilities as they can mimic some of the features of CDGP.¹⁷

The distinction between CDGP and partial hypogonadotropic hypogonadism can be difficult as both show the normal consonance of growth and development. In order to distinguish between these two conditions puberty may have to be induced (see below) for a period of two to three years and then progress observed after the cessation of treatment. Congenital growth hormone insufficiency is not usually confused with CDGP because by this age children with the former are very much shorter than the latter. Acquired growth hormone insufficiency secondary to an intracranial tumour, however, must always be considered. In girls, Turner's syndrome and its variants should be excluded by a karyotype. Children with primary hypothyroidism usually have a growth rate that is inappropriately low for their age and stage of puberty, and moreover may have inappropriate sexual maturation.¹⁶ Children with mild skeletal dysplasias, such as spondyloepiphyseal dysplasia seldom have a delayed bone age and usually exhibit limb-trunk disproportion. The diagnosis is confirmed by skeletal survey.

If pharmacological tests of the hypothalamo-pituitary axis are carried out these usually require sex steroid 'priming' (see above) and, in the clinical situation of delayed puberty, are difficult to interpret. In our experience the anthropometric data are more reliable. If sex steroid 'priming' is required, however, then it is appropriate to use stilboestrol (1 mg twice a day for three days), which can be used in either sex and does not interfere with the anthropometric data.

Psychological sequelae

The delay of both growth and puberty can have considerable psychological sequelae, especially because this is such a critical time for social, emotional, and educational development and, importantly, the onset of relationships with the opposite sex. At no other time during life is peer group pressure so important and influential than at adolescence. In an analogous way to facial acne, there is little consolation in the advice that all will be well if the boy waits long enough and that growth will be complete in his early 20s. This is highlighted by the following extracts from a letter written by an intelligent 17 year old boy with delayed puberty.

'... I often get very upset, but I find it very difficult to release my tension. When I do, this results in huge arguments, often over petty inconsequential things. I do not wish to be told to leave pubs, and 'X' certificate films when I am 18. I lose a great deal of my confidence with girls—I feel fine talking to them normally, but asking to go out with someone is something I

wouldn't consider, as I can't understand many 17 year olds wishing to go out with someone who looks like a 14 year old. It is certainly difficult for me to convey how I feel, but all I can say is that I feel utterly powerless, and I often feel quite depressed over this matter. This, I fear, will begin to affect my work which is very important as I am approaching my 'A' Level examinations'.

This summarises many of the difficulties that such boys commonly experience, although it is unusual to have such depth of insight. Many boys with CDGP are subject to bullying and some develop antisocial behaviour such as shoplifting or vandalism, which may bring them into conflict with the authorities. They require therapeutic help and not unnecessary investigation. It is surprising that when boys with CDGP are asked whether growth or puberty is their primary concern, most indicate the former and it is to this aspect that the therapeutic approach should be aimed.

Treatment of constitutional delay of growth and puberty

The most important decision is whether, rather than how, to treat a boy with CDGP. This is only indicated when such a boy is experiencing psychological distress. It is important to have the parents present at the initial interview as events such as bullying are more likely to be alluded to by the parents because the admission of this by an adolescent boy may be considered as a sign of weakness. Often the attendance of the adolescent and the discussion about such delicate problems, as perceived by the adolescent, at a clinic appointment is a significant sign in itself.

It is important to emphasise that this condition is just a variation of the normal timing of puberty, and is not an illness. This also indicates the necessity for an effective but safe treatment. Misconceptions about future fertility and manhood may require reassurance. It is unlikely that treatment will improve final height, although this is theoretically possible using growth hormone treatment, but it will allow the boy to achieve final height at an earlier age.

Two therapeutic approaches in the treatment of CDGP are possible. Either the growth spurt can be induced using a low dose of an anabolic steroid or possibly growth hormone, with little alteration in the progress of sexual maturation, or puberty can be induced along with its associated growth spurt by the administration of testosterone or human chorionic gonadotrophin.

ANABOLIC STEROIDS

These have been extensively used for the past three decades in North America but unfortunately their initial use was in high dose regimens for long periods which resulted in side effects of hepatotoxicity,¹⁸ suppression of the hypothalamo-pituitary-gonadal axis,^{19 20} and inappropriate advance of epiphyseal maturation.¹⁸ Sobel noted that virilisation is dose dependent, whereas the growth acceleration was not.²¹ Low doses of anabolic steroid^{22 23} administered orally in a daily regimen induce a growth spurt that is not a placebo effect.²⁴ At the attainment of a 4 ml testicular volume this growth acceleration is sustained, and therefore only relatively short courses are required.^{22 23} At the cessation of treatment this induced growth spurt continues and eventually becomes indistinguishable from the spontaneous growth spurt of puberty at the attainment of a 10 ml testicular volume (fig 2). Such low dose regimens do not cause inappropriate advance in epiphyseal maturation and do not alter final height prognosis.^{22 23} There is a normal advance in secondary sexual characteristics during such short course, low dose regimens of anabolic steroids and testicular volume is not suppressed. Unfortunately, despite the usefulness of anabolic steroids in the treatment of constitutional delay and other growth disorders, fluoxymesterone is now unavailable and oxandrolone can only be prescribed on a 'named patient basis' as it has no product licence in the United Kingdom.

TESTOSTERONE AND HUMAN CHORIONIC GONADOTROPHIN

An alternative approach is to induce secondary sexual characteristics and thereby their associated growth acceleration by using either testosterone or human chorionic gonadotrophin. Testosterone is usually administered by deep intramuscular injection of a depot preparation at monthly intervals or orally, as testosterone undecanoate, during the evening.⁴ Unfortunately such oral preparations have variable absorption from the gastrointestinal tract that limit their usefulness. Depot testosterone esters are certainly effective,²⁵ although unfortunately they are often used in excessive doses, but they probably do not reduce final height attainment.²⁶ Although testosterone administration suppresses the hypothalamo-pituitary-gonadal axis, with reduction in testicular volume, this is only temporary. Testosterone treatment often produces a rapid rise in serum testosterone concentrations and also wide fluctuations in concentrations between injections which can, in themselves, produce emotional lability and may become counterproductive to the indications for treatment. An alternative and

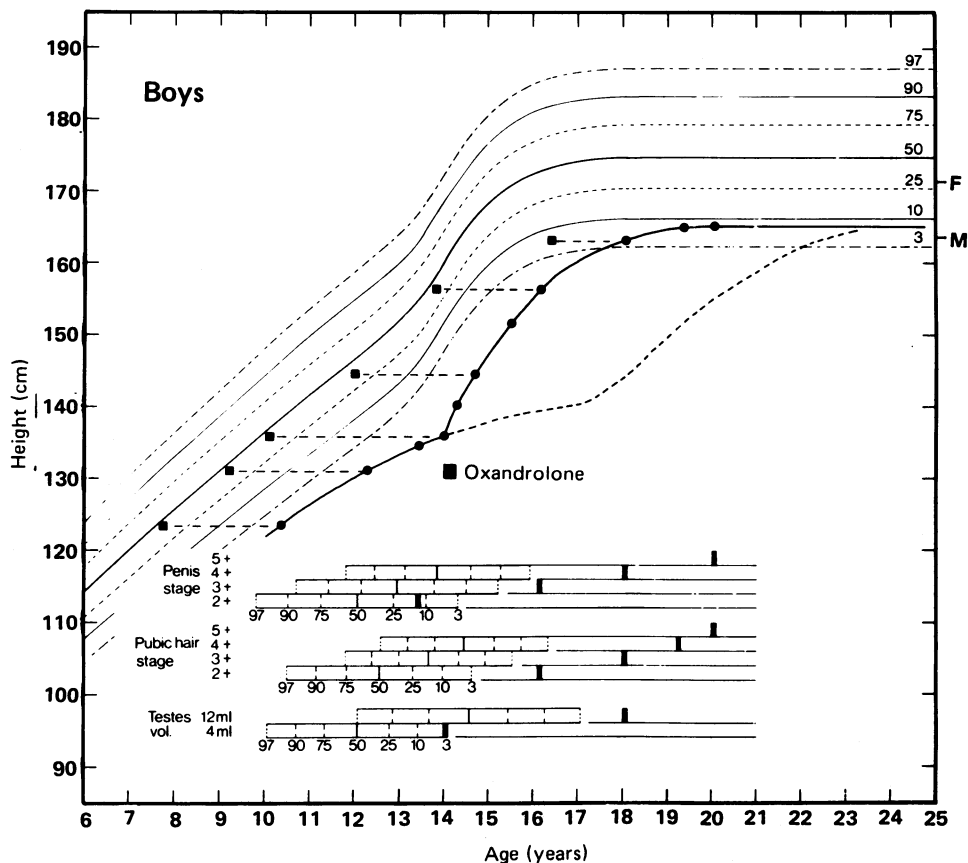


Fig 2 Growth data from a boy with constitutional delay of growth and puberty. Bone age is shown by the solid squares. Parental centiles are indicated on the right hand border. His expected pattern of growth is indicated by the dotted line. At the age of 14 years, he was treated with a three month course of oxandrolone (1.25 mg daily), and the induced, sustained growth acceleration became indistinguishable from the growth spurt of puberty at the attainment of a 10 ml testicular volume.

more physiological treatment is human chorionic gonadotrophin, but this has to be administered in two to three injections a week, which limits its use. Both testosterone and human chorionic gonadotrophin need to be given for a minimum of three months in order to attain a sustained growth spurt. Of course, unlike anabolic steroids, both testosterone esters and human chorionic gonadotrophin have to be given by injection.

For girls who require treatment low dose oestrogen, such as ethinyl oestradiol 2 µg daily, can be administered as this induces a growth acceleration. When an advance in puberty has occurred which is inappropriate for the dose of exogenous oestrogen, then the medication can be withdrawn with the probability that spontaneous puberty has started. Human chorionic gonadotrophin cannot be adminis-

tered in girls because of the likelihood of ovarian hyperstimulation syndrome.

GROWTH HORMONE

From the discussion about the mechanism of the growth spurt of puberty, it is not surprising that the administration of growth hormone can improve short term growth in boys with CDGP²⁷ and this could theoretically improve their final height prognosis. Because of the increase in growth hormone secretion which occurs during puberty, however, larger doses may have to be used than are administered in the treatment of growth hormone deficiency in prepubertal children.²⁸ From experience of the management of children with hypopituitarism, growth hormone treatment has little effect during late puberty. Treatment is expensive and may

have to be continued for a long period of time because of the possibility of 'catchdown' growth.²⁹ Growth hormone is certainly not the primary choice of treatment for children with CDGP; as they have physiological growth hormone insufficiency it seems more appropriate to use an androgen in boys or an oestrogen in girls to induce increased endogenous growth hormone secretion.

A practical regimen

The normal harmony of puberty is the characteristic of CDGP. Indeed, endocrine investigations in delayed puberty are notoriously difficult to interpret and are more often misleading than they are helpful. Most patients with psychological distress due to CDGP require an effective safe treatment, rather than investigations. If puberty is disordered or if there is an inappropriate anthropometric response to treatment,³⁰ however, then the patient should have neuroradiological and endocrine assessment of the hypothalamo-pituitary axis.

Once the diagnosis has been made then reassurance should be given and treatment only offered if there is inappropriate psychological distress. For boys with CDGP for whom short stature is the predominant symptom, then treatment should be given with an anabolic steroid such as oxandrolone 1.25–2.5 mg daily for three to four months. This will induce a growth spurt which, after the attainment of a 4 ml testicular volume, will be sustained. If growth deceleration does occur on cessation of anabolic steroid treatment, then a further three to four month course can be administered. Once a sustained growth spurt is achieved then growth and development should continue without requiring any further treatment. It is important to explain that this treatment is only advancing the timing of the growth spurt without altering final height attainment. In the more unusual case where inadequate sexual development is the predominant symptom then treatment with testosterone esters (such as Sustanon 50) should be administered at monthly intervals for three to four months. Usually, this is sufficient to induce an advance in pubertal maturation with concomitant growth acceleration.

Growth delay can often be recognised many years before puberty and the growth pattern of CDGP can be anticipated and effectively prevented. In the pre-pubertal years and before the attainment of a 4 ml testicular volume, low dose anabolic steroids will induce a growth spurt but this will not be sustained. A course of anabolic steroids, such as oxandrolone 1.25 mg daily, can be administered for a period of about a year without inducing sexual development or inappropriate epiphyseal maturation. This

regimen will improve short term growth, allowing the boy to attain a higher centile on a 'distance' chart.

Growth hormone and human chorionic gonadotrophin have little place in the management of CDGP, particularly as both have to be administered by frequent injection and the former is very expensive.

Conclusion

Constitutional delay of growth and puberty should be recognised clinically and not require endocrine investigation. Treatment by either anabolic steroids or testosterone should only be given when psychological distress is encountered, but the treatment can be administered by either a paediatrician or community paediatrician without the necessity for referral to a specialised growth centre. However, assessment of epiphyseal maturation is essential in the management of children with delayed puberty. Rarely, when inadequate growth acceleration with treatment is observed, referral to a specialist centre is indicated.

We are grateful to Professor HS Jacobs, Middlesex Hospital, London, for allowing us to use clinical data from one of his patients.

References

- 1 Prader A. Delayed adolescence. *Clin Endocrinol Metab* 1975;4:143–55.
- 2 Tanner JM. Developmental age, and the problems of early and late maturers. *Foetus into man*. London: Open Books, 1978: 78–86.
- 3 Boyar RM, Finkelstein R, Roffwarg H, Kapen S, Weitzman E, Hellman L. Synchronisation of augmented luteinizing hormone secretion with sleep during puberty. *N Engl J Med* 1972;287:582–6.
- 4 Stanhope R, Brook CGD. An evaluation of hormonal changes at puberty in man. *J Endocrinol* 1988;116:301–5.
- 5 Stanhope R, Brook CGD, Pringle PJ, Adams J, Jacobs HS. Induction of puberty by pulsatile gonadotrophin-releasing hormone (GnRH). *Lancet* 1987;ii:552–5.
- 6 Brook CGD, Hindmarsh PC, Stanhope R. Growth and growth hormone secretion. *J Endocrinol* 1988 (in press).
- 7 Eastman CJ, Lazarus L, Stuart MC, Casey JH. The effect of puberty and growth hormone secretion in boys with short stature and delayed adolescence. *Aust NZ J Med* 1971;1:154–9.
- 8 Stanhope R, Pringle PJ, Brook CGD. The mechanism of the adolescent growth spurt induced by low-dose GnRH treatment. *Clin Endocrinol* 1988;28:83–91.
- 9 Peters H, Byskov AG, Grinster J. The development of the ovary in childhood in health and disease. Coutts JRT, ed. *Functional morphology of the human ovary*. Lancaster: MTP Press, 1981:26–34.
- 10 Stanhope R, Adams J, Jacobs HS, Brook CGD. Ovarian ultrasound assessment in normal children, idiopathic precocious puberty and during low-dose GnRH therapy of hypogonadotropic hypogonadism. *Arch Dis Child* 1985;60:116–9.

- ¹¹ Marshall WA, Tanner JM. Variation in the pattern of pubertal changes in girls. *Arch Dis Child* 1969;**44**:291-303.
- ¹² Marshall WA, Tanner JM. Variation in the pattern of pubertal changes in boys. *Arch Dis Child* 1970;**45**:13-23.
- ¹³ Tanner JM. *Growth at adolescence*. 2nd ed. Oxford: Blackwell, 1962.
- ¹⁴ Prader A. Paediatric endocrinology, past and future. In: Ranke MB, Bierich JR, eds. *Paediatric endocrinology past and future*. Munich: MD Verlag, 1986:13-21.
- ¹⁵ Stanhope R, Brook CGD. The effect of gonadotrophin releasing hormone (GnRH) analogue on height prognosis in growth hormone deficiency and normal puberty. *Eur J Pediatr* 1988 (in press).
- ¹⁶ Stanhope R, Brook CGD. The clinical diagnosis of disorders of puberty: the loss of consonance. *Br J Hosp Med* 1986;**35**:57-8.
- ¹⁷ Preece MA, Law CM, Davies PSW. The growth of children with chronic paediatric disease. *Clin Endocrinol Metab* 1985;**15**:453-77.
- ¹⁸ Geller J. Oxandrolone effect on growth and bone-age in idiopathic growth failure. *Acta Endocrinol (Copenh)* 1968;**59**:307-16.
- ¹⁹ Hopwood NJ, Kelch RP, Zipf WB, Hernandez RJ. The effect of synthetic androgens on the hypothalamo-pituitary-gonadal axis in boys with constitutional delayed growth. *J Pediatr* 1979;**94**:657-62.
- ²⁰ Marti-Henneberg C, Niirianen AK, Rappaport R. Oxandrolone treatment of constitutional short stature in boys during adolescence. Effect on linear growth, bone-age, pubic hair and testicular development. *J Pediatr* 1975;**86**:783-8.
- ²¹ Sobel EH. Anabolic steroids. In: Astwood EB, Cassidy CE, eds. *Clinical endocrinology 11*. New York: Grunc and Stratton, 1968:789-97.
- ²² Stanhope R, Bommen M, Brook CGD. Constitutional delay of growth and puberty in boys. The effect of a short course of treatment with fluoxymesterone. *Acta Paediatr Scand* 1985;**74**:390-3.
- ²³ Stanhope R, Brook CGD. Oxandrolone in low dose for constitutional delay of growth and puberty in boys. *Arch Dis Child* 1985;**60**:379-81.
- ²⁴ Stanhope R, Buchanan CR, Fenn GC, Preece MA. Double blind placebo controlled trial of oxandrolone in the treatment of boys with constitutional delay low dose of growth and puberty. *Arch Dis Child* 1988;**63**:501-5.
- ²⁵ Wilson DM, Kei J, Hintz RL, Rosenfeld RG. Effects of testosterone therapy for pubertal delay. *Am J Dis Child* 1988;**142**:96-9.
- ²⁶ Zachmann M, Studer S, Prader A. Short-term testosterone treatment at bone-age of 12-13 years does not reduce adult height in boys with constitutional delay of growth and adolescence. *Helv Paediatr Acta* 1987;**42**:21-8.
- ²⁷ Bierich JR. Treatment by hGH of constitutional delay of growth and adolescence. *Acta Paediatr Scand [Suppl]* 1986;**325**:71-5.
- ²⁸ Vanderschueren-Lodeweyckx M, Van Den Broeck J, Volter R, Malvaux P. Early initiation of growth hormone treatment: influence on final height. *Acta Paediatr Scand [Suppl]* 1987;**337**:4-11.
- ²⁹ Preece MA, Tanner JM. Results of intermittent treatment of growth hormone deficiency with human growth hormone. *J Clin Endocrinol Metab* 1977;**45**:169-70.
- ³⁰ Stanhope R, Hindmarsh P, Pringle PJ, Holownia P, Honour J, Brook CGD. Oxandrolone induces a sustained rise in GH secretion in boys with constitutional delay of growth and puberty. *Pediatrician* 1988 (in press).

Correspondence to Dr R Stanhope, Department of Growth and Development, Institute of Child Health, 30 Guilford Street, London WC1N 1EH.