THE INFLUENCE OF ANABOLIC STEROIDS ON GROWTH

by

A. Prader

Children with stunted growth or growth retardation are a frequent problem in pediatric practice. However, it is rare to find an underlying cause such as under-nutrition or hypothyroidism which can be corrected. In most cases the diagnosis is hereditary small stature or constitutional delay of development neither of which can be influenced by traditional therapy. We all wish to know for the benefit of these children an overall effective growth stimulating therapy which is devoid of undesirable side-effects.

The only compounds which really stimulate growth in children are the anabolic steroids, that is testosterone and its derivatives, and human pituitary growth hormone. Since human growth hormone, which might be the ideal therapy, is not yet available for practical purposes we are restricted to the anabolic steroids.

Of a growth promoting drug we would like to know:
1. What is the immediate effect on growth and what will be the ultimate effect on growth?
2. Does the growth response depend on endogenous factors such as heredity, age and disease? In other words: Where can we expect a good growth response and where shall we get no response?
3. Are there any side-effects and what are they?

Our experience in this field is based on the treatment of 64 children with stunted growth (all below the third percentile) with nandrolone phenylpropionate (Durabolin) given intramuscularly and with methandrostenolone given by mouth for periods ranging from 5 months to more than 3 years. A small number of patients have also been treated with testosterone or with nandrolone decanoate (Deca-Durabolin). 11 of these children have pituitary insufficiency of a more or less severe degree. A complete report will be published elsewhere. Height and weight age have been determined from the tables of Stuart & Stevenson (1950) and of Heimendinger (1958a, 1958b), bone age from the atlas of Greulich & Pyle

78
Growth prognosis has been calculated from age, height and bone age with the help of the tables of Bailey & Pinneau (1952). Several variables do not allow a meaningful statistical treatment of our results. Among these variables are dosage, duration of treatment, duration of the follow-up period, age of the patients and the cause of growth retardation. We have therefore preferred to draw our conclusions from a study of the many individual growth curves, considering in every case as far as possible all individual peculiarities.

Fig. 1.

Idiopathic pituitary dwarf (Bruno B.) with proven thyroid and adrenal insufficiency. The administration of testosterone isobutyrate during a few months at the age of 12 accelerated growth, weight gain and bone maturation. The effect on bone maturation is more marked and continues for a longer period of time than the effect on growth. This discrepancy leads to a decrease in predicted adult height. Height age is shown in this and in the following figures by a heavy full line, weight age by an interrupted line, bone age by a dotted line and growth prognosis by a double line.

Fig. 1 demonstrates the effect of a moderately intensive short treatment with testosterone on growth. It shows some of the basic problems of therapy with anabolic steroids. The patient, a pituitary dwarf, was treated with testosterone for a few months at the age of 12 and has been followed without any other treatment up to the age of 21. This short period of therapy had a profound influence on height and bone age for many years, in fact for the rest of the total growth period. This shows that a long follow-up is necessary to evaluate fully the ultimate effect of such a treatment. The immediate results of a short treatment do not give the full information we need and may even give a completely wrong impression. In the patient of Fig. 1 the immediate effects are a moderate acceleration of growth, a relatively greater gain in weight, a very marked ac-
celeration of bone age and the appearance of pubic hair. After withdrawing testosterone the acceleration of height-, weight- and bone age continues for some months, bone maturation being again faster than growth. The fact that the increase in bone age is much more marked than the increase in height age means a decrease in future adult height (Fig. 1).

The conclusion is that the immediate growth improvement has only been achieved at the expense of a decreased adult size. To summarize: Fig. 1 shows clearly the three main effects of testosterone in children: 1. the anabolic, growth stimulating effect; 2. the stimulating effect on bone maturation and 3. the virilizing or androgenic effect.

Today we no longer use testosterone to stimulate growth because we are afraid of its virilizing effects. We prefer the newer anabolic testosterone derivatives because in animal experiments these steroids have relatively more anabolic and less androgenic effects. The results gained from animal experiments are impressive but not too helpful for the clinician. They have not yet given any information about the effect on bone maturation which is clinically so important. In addition the dissociation between anabolic and androgenic effects seen in the animal is not necessarily the same in the human. So far we have no direct evidence that in children these drugs really have a relatively less androgenic and more anabolic effect than testosterone. On the other hand children are more sensitive to androgenic effects than adults. All this shows that the experience in animals and in human adults cannot be applied to children. Only the long term, direct experience in children will give us ultimately the full information.

From the still incomplete information we have gained I wish to discuss the following problems:
1. Is there a dosage which stimulates growth in children without producing virilization?
2. Is it possible to stimulate immediate growth without decreasing adult height?
3. Which endogenous factors determine the extent of growth response in the individual?

In our experience virilization is rare if the dosage does not exceed 1 mg/kg/month of nandrolone phenylpropionate intramuscularly and 0.04 mg/kg/day of methandrostenolone by mouth. These doses stimulate growth in most children of small stature and rarely lead to virilization. However, it is important to follow all patients closely and to stop treatment as soon as virilization appears. Some children are more sensitive than others to the virilizing effect. The reason for this is usually obscure. From a few single cases we have got the impression that brain damage and hypothyroidism may be among the sensitizing factors.

Figs. 2 to 6 illustrate the effect on immediate growth and on virilization and show also the effect on bone maturation and on growth prognosis.
Fig. 2.

Pituitary dwarf (Antoine P.) with a craniopharyngeoma, operated at the age of 8. There is definite adrenal and questionable thyroid insufficiency. The combined treatment with thyroid and nandrolone phenylpropionate (Nor-Test-P.P.) or nandrolone decanoate (Nor-Test-Decanoate) in small doses during 3 years improved growth and bone maturation without compromising expected adult height. Same presentation as in Fig. 1.

Fig. 3.

Idiopathic pituitary dwarf (Anna S.) with proved adrenal insufficiency and questionable thyroid insufficiency. The combined treatment with thyroid and nandrolone phenylpropionate during 1½ years improved growth and bone maturation without compromising expected adult height. Same presentation as in Fig. 1.
Delayed development in a boy with ventricular septum defect (Kurt G.). Treatment with nandrolone phenylpropionate (Nor-Test-P.P.) and methandrostenolone (Dehydro-Meth. Test.) during 3 years improved growth, weight gain and bone maturation. Transitory overdosage of methandrostenolone explains the unusual speed of bone maturation during a short period. Same presentation as in Fig. 1.

Constitutional delay of development (Robert K.). Treatment with nandrolone decanoate during 1 year improved growth, weight gain and bone maturation in a harmonious way. Same presentation as in Fig. 1.

Delayed development in a girl with multiple malformations (Anneliese St.). Treatment with nandrolone phenylpropionate (Nor-Test-P.P.) and methandrostenolone (Dehydro-Meth. Test.) during 1½ years improved growth, weight gain and bone maturation. Massive overdosage of methandrostenolone during 4 months was followed by a tremendous acceleration of bone age and by the transitory appearance of pubic hair. Same presentation as in Fig. 1.
The effect on bone age and on growth prognosis can be summarized as follows. The acceleration of bone age is not seen until a few months after treatment has begun and continues frequently long after therapy is discontinued, so that the long term effect on growth can only be fully evaluated after a long follow-up period. The recommended low, non-virilizing doses accelerate bone age in general not more or only slightly more than height age. In other words: immediate growth is improved without seriously compromising future adult height. Higher doses lead not only to virilization but also to such a marked acceleration of bone age that growth prognosis is definitely decreased. In all our patients the growth prognosis is either unchanged or decreased. There is no patient with an increase of growth prognosis. Apparently this type of treatment cannot improve future adult height.

Let us now consider how the growth response is influenced by age and by the factors causing dwarfism. We have a large experience with children between infancy and puberty, less experience with children in puberty and practically none with infants. As long as we do not know more about the immediate and the long term effect of these anabolic steroids we hesitate to use them in infants. However, there are a few indications in the newer literature that growth in premature and new-born babies can perhaps not be stimulated with either anabolic steroids (Meadows et al. 1960) or with pituitary growth hormone (Du-charmé & Grumbach 1961).

The growth response in puberty is seen in Fig. 7. This patient and others show either a doubtful or no growth response during the growth spurt of spontaneous puberty and show at the same time that the recommended low dosage does not interfere with normal pubertal development and with normal testicular growth. This is in contrast to high doses of anabolic steroids which definitely depress gonadal function as judged from gonadotrophin excretion and from testicular size. Fortunately the depression of gonadal function seems to be reversible (Fig. 8).

Fig. 9 shows another problem of anabolic steroids and puberty. Since puberty appears normally at a specific stage of bone maturation (bone age of 11 in girls and of 13 in boys) the artificially induced acceleration of bone age before puberty leads to an earlier onset of spontaneous puberty and to an earlier cessation of growth. In other words it is possible to hasten the appearance of spontaneous puberty by treating prepubertal children with anabolic steroids. This secondary effect should not be mixed up with the primary virilizing effect caused by overdosage of the same steroids.
Hereditary short stature in an adolescent boy (Beat St.). Administration of nandrolone phenylpropionate in a small dosage during puberty has no influence on the normal puberty growth spurt, which began before treatment, and does not disturb normal pubertal growth of the testes. Same presentation as in Fig. 1.

Poliomyelitic tetraplegia in an adolescent boy (Peter S.). Treatment with methandrostenolone in a very high dose for 3 months in order to prevent hypercalciuria and nephrolithiasis was followed by a transitory decrease in gonadotrophin excretion and in testicular size. Apparently the gonadotrophic suppression caused by this treatment was fully reversible.

Concerning endocrine and other causes of stunted growth we have found so far three situations in which the normal growth response seems to be absent or very slight. Probably there exist others which we have not yet examined.

The first is severe pituitary insufficiency. Fig. 10 shows the growth and bone age response in 11 pituitary dwarfs. Most of the 11 patients have a good response and only a few a bad response. These few are mainly those who have been operated for a craniopharyngioma and who have the most marked pituitary insufficiency.

Two of these bad reactors had subsequently a good growth response to human growth hormone (Fig. 11). This lack of growth response to anabolic steroids in patients with severe hypothalamo-pituitary insufficiency is extremely interesting. It looks as if growth hormone is necessary for the growth effect of these steroids. Growth hormone may have a permissive action for the growth effect of anabolic steroids. This hypothesis is supported by observations in animals (Simpson et al. 1960).
Constitutional delay of development (Walter Sch.). Treatment with nandrolone phenylpropionate in a high dose during 11½ years improved growth and bone maturation. Because of the overdosage bone age acceleration markedly exceeds height age acceleration. This results in the following two consequences: 1. Spontaneous puberty, which appears in boys normally at a bone age of about 13 and which was therefore expected in this boy at the age of about 20, began at age 15. 2. The expected adult height decreased from about 180 cm to about 160 cm. The continuing growth acceleration after treatment has been stopped represents the growth spurt of puberty. Same presentation as in fig. 1.

Growth and bone maturation in 11 children aged 2 to 13 with pituitary dwarfism before and during treatment with nandrolone phenylpropionate for 11 to 32 months. The slope of the lines (normal = 45°) indicates the velocity of growth and bone maturation before treatment (below the horizontal line) and during treatment (above the horizontal line). Before treatment growth and bone maturation are slower than normal in most patients (the fast bone maturation in 3 patients is due to thyroid therapy). During therapy they are in most patients faster than before, and often even faster than normal. The therapeutic response of the 3 patients with an operated craniopharyngeoma (marked with a black point) is smaller than in the other patients.
Pituitary dwarf with craniopharygeoma (René St.). After surgical removal of the craniopharygeoma at 2½ years of age pituitary function deteriorated markedly, leading to a general anterior and posterior pituitary insufficiency. The combined treatment with thyroid preparations, prednisone and anabolic steroids up the point of virilization for 3 years did not stimulate the nearly completely arrested growth, which is in contrast to patients with milder pituitary insufficiency (fig. 1-3). However, as soon as human growth hormone was added, an impressive growth spurt was seen. Same presentation as in Fig. 1.

Fig. 11

Intra-uterine dwarfism (Marlies R.). The girl was born at term and had a birth weight of only 2.46 kg. Methandrostenolone (Dehydro-Meth. Test.) in increasing dosage up to the point of virilization and nandrolone decanoate (Nor-Test.-Decanoate) did not improve growth and weight (unresponsiveness of the end organ?) but accelerated bone maturation. Same presentation as in Fig. 1.
The second situation where we could not get a normal growth response is Turner's syndrome. The patient of Fig. 12 is a typical example. The stunted growth of these patients, the lack of a normal growth response to anabolic steroids and the reported finding of an increased growth hormone level in the blood of such patients (Fraccaro et al. 1960) are best explained by a peripheral resistance to the growth stimulating effect of growth hormone and of anabolic steroids. We feel that the same is true in some patients with intra-uterine dwarfism (or primordial dwarfism) who show a poor growth response to anabolic steroids (Fig. 13).

**Summary and Conclusions**

In children anabolic steroids have multiple effects, which include mainly stimulation of growth, stimulation of bone maturation and virilization. These effects depend on various exogenous and endogenous factors such as dosage and length of time of treatment and biological age and endocrine status of the individual. The use of these steroids in childhood places a great responsibility on the physician. A periodic evaluation of growth, bone maturation and secondary sexual characteristics before, during and after therapy is indispensable.

Children are more sensitive than adults to the virilizing effects of these steroids. However, there seems to be a low dosage range which, in the majority of cases, will stimulate growth without producing virilization. This dosage is 1 mg/kg/month of the intramuscularly administered nandrolonephenylpropionate (Durabolin) and 0.04 mg/kg/day of the orally administered methandrosteneolone. Hypothyroid and brain-damaged children appear to be more sensitive to virilizing effects than other children.

Growth acceleration without virilization can be achieved in the majority of children. None or only a slight growth acceleration is seen in some children with severe pituitary insufficiency, and in some with intra-uterine dwarfism and in Turner's syndrome. In the first situation there is a severe lack of pituitary growth hormone which is apparently necessary to permit the growth promoting effect of anabolic steroids. In the second and third situations there seems to be a decreased peripheral response to anabolic steroids (and probably also to pituitary growth hormone). During the growth spurt of spontaneous puberty and perhaps also during the period of intensive growth in the premature and the newborn baby the growth rate cannot be significantly accelerated by these steroids.

Bone maturation is nearly always accelerated. This effect is easily overlooked in short term therapy because it is not seen until some months after therapy has begun and continues frequently for several months after therapy has ceased. The acceleration of bone maturation leads to an earlier onset of puberty and to an
earlier cessation of growth. With high doses the acceleration of bone maturation exceeds the acceleration of growth. This means that growth acceleration is achieved only at the expense of a decreased ultimate adult height. With low doses as indicated above bone maturation is generally not faster than growth so that the predicted adult height is not affected. It is important to realize that these steroids improve only immediate growth and not predicted adult height and that they may even decrease future adult height when used in high doses or in unusually sensitive individuals. Correct low dosage and regular evaluation of bone maturation are indispensable to prevent this undesirable long term effect.

REFERENCES