EFFECTS AND SIDE EFFECTS OF ANABOLIC STEROIDS IN CHILDREN

by

J. R. Bierich

The modern synthetic testosterone derivatives have achieved considerable importance in nearly every field of medicine. In general, they stimulate the formation of protein, induce a positive balance of all cell constituents and lead to a general weight increase. They are therefore used in the treatment of cachexia, anorexia, and dystrophy whatever their origin; particular indications for their application are derived, in addition, from their protein-anabolic action on certain organs, especially on muscles and bones. Anabolic steroids are therefore primarily indicated in disorders of growth, osteoporosis and muscle metabolism.

However, these steroids have a number of unwelcome side effects which become apparent especially in longterm therapy:
1) virilising action
2) early skeleton maturation in children, resulting in early epiphysial closure and cessation of growth
3) possible pituitary inhibition
4) possible progesterone-like effects
5) pharmacological side effects, particularly on the liver.

In our investigations we dealt with a part of these problems only. We were particularly interested in the action of the hormones on skeletal growth, both on increase in height as well as on bone maturation. In addition, we were interested in the treatment of osteoporosis resulting from corticosteroid therapy. With regard to the side effects we paid particular attention to the signs of virilisation and disturbances of liver function.

Influence on skeleton development

Before I discuss the action of the anabolic steroids on bone development I would like to review briefly the action of the various hormones on bone growth.
The growth hormone. This is a strongly anabolic hormone, stimulating the endochondral ossification and promoting growth in height without changing the epiphysial appearance. For this reason the pituitary dwarf shows a most marked retardation in bone growth whereas the maturation is less influenced.

The thyroid hormones. Bone maturation on the other hand is dependent on the thyroid hormones. These hormones stimulate the normal processes of bone transformation occurring during growth. The skeleton of the hypothyroid dwarf is very poorly differentiated. His bone age lies well below that corresponding to his height. The thyroid hormones do not have any direct anabolic action. Nevertheless growth in height is dependent on the presence of the thyroid gland. The reason for this is that the pituitary is unable to produce growth hormone in the absence of the thyroid hormones.

The androgens. The anabolic action of the androgens is in part on growth in height which is seen, for example, in the growth spurt in puberty. The more pronounced action, however, is on bone maturation. This acceleration of bone development is mediated through pathways other than with thyroxine. Thyroid produces an increase of osteoblast activity causing a rise in serum alkaline phosphatase. Androgens on the other hand lead if anything to a fall in phosphatase. Prolonged treatment with testosterone causes epiphysial closure, whereas thyroxine does not.

The oestrogens have only minimal anabolic effects even though they produce a positive calcium and phosphorus balance. In contrast to the androgens they act entirely on bone maturation and epiphysial closure. The main actions of these hormones are summarised in the following table.

<table>
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<th>hormone</th>
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<th>differentiation</th>
<th>epiphys. closure</th>
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<td>Thyroxine</td>
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For the treatment of growth retardation, growth hormone would be better than testosterone derivatives as these involve the danger of premature epiphysial closure. As human growth hormone is not available in large quantities one uses anabolic steroids which have a minimal action on epiphysial closure.

Over the last few years we have treated 8 pituitary dwarfs with Nor-testosterone-phenylpropionate (NTPP).
We also treated 5 children with gonadal dysgenesis, a number of cases of dystrophy of various origin and children with retarded growth and osteoporosis as a result of corticosteroid therapy. The next figures show a part of the results.

![Fig. 1A](image1.png)

**Fig. 1A**

Increase in height (upper part) and weight (lower part) before (white columns) and after treatment (black columns) with NTPP. Each column represents 6 months. The interrupted line shows normal values for the individual age. Patient 1-6: pituitary dwarfs; pat. 7 and 8: gonadal dysgenesis; pat. 9 and 10: dystrophic infants.

These figures demonstrate the good results that may be obtained following NTPP. The question is whether these immediate results are not achieved at the
expense of premature epiphysial closure with cessation of growth, if the steroids
are given over any length of time. What may happen can be seen from Fig. 2.

The presented data were taken from observations on children with congenital
adrenogenital syndroms. The diagonal of the diagram represents the progress of
normal growth and bone age in normal children. The drawn out curve shows
the growth in height of our patients which lies up to three years ahead of the
normal values of healthy persons during the first eight years of life. At about
9 years of age the curve gradually flattens and then maintains a constant level at
11 years of age. The reason for this cessation of growth is due to the fact that
androgens stimulate skeletal maturation more than growth in height as demon¬
strated by the interrupted line. With 11½ years the bone age is 18 years and the
epiphyses have fused.

We have tried to demonstrate these relationships mathematically (Fig. 3).

In a 5 year old normal child the developmental age (ordinate) is the same as
the chronological age (abscissa): They are both 5 years. The relationship of the
2 values expressed as tangent (Tan) α is 1 : 1 = 1 and the angle is 45°. In a 5
year old patient with adrenogenital syndrome the age in height is 7.5 years. The
value of Tan α is 7.5 : 5 = 1.5. The bone age on the other hand is 9.6 years.
The Tan α is 9.6 : 5 = 1.9 The values of Tan α, and Tan α, show variations
corresponding to the slope of the curves. However, the relationship between Tan
α, and Tan α, remains constant up to the age of 8, that is to say 1.9 : 1.5 =
1.27. This quotient between increase in bone age and increase in height is a
similar constant characteristic of the anabolic steroids as is the quotient between
their androgenic and anabolic action. The higher the quotient the poorer is the
therapeutic value of the particular steroid in the treatment of retarded growth; the
lower the quotient the greater is its usefulness.

Let us now turn to the therapeutic use of the androgens, first testosterone
itself. Detailed studies have been carried out by Sobel et al. (1956) who treated
27 children suffering from retarded growth with methyltestosterone. In the
following two figures 1 have depicted two groups of these children, with the
assumption that hormone treatment was started in all children at the age of 6.
The first group comprises children whose bone age was reduced more than their
height age (Fig. 4).

With doses of 5 mg methyltestosterone daily the growth in height increased
markedly by a Tan α, = 2, even more strikingly however was the increase in bone
maturation, showing a Tan α, = 2.7. The index “b” was 1.35. If the treatment
had been continued a bone age of 18 years and epiphysial closure would have
both been reached at 11 years of age. The final height would have corresponded
to about that of a 16 years old child.

In the 5th group of Sobel et al. 1956) (Fig. 5) only growth was retarded.
Bone age (b) and growth in height (h) in children with congenital adrenogenital syndrome. The diagonal of the diagram represents the progress of normal growth and bone age in normal children.

Effect of methyltestosterone on bone age and height age in children whose bone age was more retarded than their height age (same presentation as in figure 2).

Effect of methyltestosterone on bone age and height age in children, retarded in growth; skeletal maturation was slightly accelerated (same presentation as in figure 2).
The skeletal maturation however was slightly accelerated. Under 40 mg methyltestosterone daily an increase in height was observed with a Tan αₜ of 2.1, while the increase in skeletal maturation amounted to a Tan αₑ of 3.1, the quotient “b” being 1.43. Since the skeletal maturation was relatively far advanced to start with, the outcome of treatment was particularly unfavourable in this group. Had treatment been continued, growth would have come to a stop at the age of 10 years, the child having then attained the height of a healthy 11½ year old.

From these 2 examples one may conclude that result of the therapy depends very much on the relation between the state of skeletal development and height present at the beginning of steroid therapy. We obtained some years ago similar results when we began to treat our pituitary dwarfs with methyltestosterone.

The 12.9 year old boy (K.K.) had the size and skeletal development of a child of exactly half his age. At first he received HCG, later on 6 mg methyltestosterone daily. As a result of this treatment the bone age increased much more than the

![Image](Fig. 6) Effect on height age and bone age of HCG, methyltestosterone and nor-testosterone-phenylpropionate (NTPP); (same presentation as in figure 2).

![Image](Fig. 7) Effect on bone age and height age of thyroid, methyltestosterone and nortestosterone phenylpropionate (same presentation as in figure 2).
height age, the quotient of the Tan α's being 1.65. Had this treatment been continued the growth would have come to an end when the patient had reached the size of a normal 12 years old boy. We therefore discontinued the treatment. At the age of 15½ years we began treatment with NTPP in a dosage of 1.5 mg/kg/month. This resulted in an increase of growth which was slightly greater than the increase in bone maturation. The quotient of the two Tan α's was 0.84. This was below 1 which warranted further good possibilities for growth.

Similarly we treated a 13½ year old girl (Fig. 7), a pituitary dwarf with secondary hypothyroidism and hypogonadism, first with exsiccated thyroid. Later we added methyltestosterone. Following this a rapid acceleration of growth rate and an even greater acceleration of ossification took place. If therapy had been continued growth would have ceased when the patient reached the size of a healthy 13 year old girl. Following discontinuation of therapy both curves flattened out. Using NTPP growth increased more than ossification.

Fig. 8 shows a girl with growth retardation due to a craniopharyngeoma which had in part been removed surgically. From the age of 14 years onwards NTPP was given (2.7 mg/kg/month). Growth and bone maturation increased at almost the same rate.

Table 2 summarises the results. Reading from top to bottom the patients received increasing amounts of NTPP. Tan αh is either 1 or greater than 1, that is to say the growth is in most cases greater than that expected for the age.

In 3 cases the quotient B is less than 1, that it is to say it is optimal. The high value obtained in case 5 is due to the fact that this boy not only received hormone
therapy but also reached puberty and started to form his own androgens. This unexpected puberty apparently was initiated by bone maturation following hormone therapy. In a healthy boy puberty is triggered off once the bone age has reached 12 to 13 years. That in a pituitary dwarf puberty can be initiated in the same manner, is a particularly satisfying result of steroid therapy. In patient 7 the dose of NTPP was probably too high, thus possibly invalidating the results: index “b” is 1.25. On the other hand the dose of 0.6 mg/kg/month which was used in the first patient was too low. Patients 8 and 9 are children with gonadal dysgenesis. When the very high doses of NTPP are taken into consideration, then the Tan $a_h$ is relatively low. In contrast to growth in height, ossification is greatly accelerated, index “b” reaching a maximum value.

Fig. 9 demonstrates these relationships for patient 8 in graphical form.

Apparently the bone reacts poorly as regards growth in height to the hormone therapy. Similarly the osteoporosis and Scheuermann’s disease which so often accompanies Turner’s syndrome do not react to the anabolic hormone. Bone seems to be just as refractory to the steroids as to the action of the body’s own growth hormone. Both Gemzell and we ourselves have been able to demonstrate high plasma values for growth hormone in children with gonadal dysgenesis. From these results one may conclude that the growth retardation found in Turner’s syndrome is due to a skeletal abnormality and not to an endocrine insufficiency. In addition, we are of the opinion that very probably there exist constitutional dwarfs with a very similar growth disturbance. Three months ago we obtained ethylestrenol to treat such children who were constitutionally small and in whom there was for the most part not only a decrease in height age but also in skeletal

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**Table 2**

| Case | $tg\ a_h$ | $tg\ a_l$ | $tg\ a_h$ | $tg\ a_l$ | $tg\ a_h'$ | $tg\ a_l'$ | Doses NTPP $mg$ $kg^{-1}$|mo |
|------|-----------|-----------|-----------|-----------|-----------|-----------|-----------------|
| S.N. ♀ | —         | —         | 1.25       | 0.27      | 0.38      | (1.41)     | 0.6             |
| R.M. ♂ | 0.42      | 0.53      | 1.25       | 1.00      | 1.38      | 1.38       | 1.4             |
| K.K. ♂ | 0.45      | 0.47      | 1.04       | 1.38      | 1.15      | 0.84       | 1.5             |
| A.S. ♀ | 0.34      | 0.45      | 1.32       | 1.19      | 0.79      | 0.81       | 1.6             |
| W.S. ♀ | 0.47      | 0.60      | 1.29       | (1.12)    | (1.88)    | (1.67)     | 1.6             |
| J.L. ♂ | 0.42      | —         | —          | 1.91      | 1.66      | 0.87       | 2.6             |
| C.D. ♀ | 0.40      | 0.45      | 1.12       | 1.33      | 1.66      | 1.25       | 2.7             |
| M.A. ♀ | 0.34      | 0.40      | 1.17       | 1.19      | 2.61      | 2.19       | 3.0             |
| K.B. ♂ | 0.58      | 0.55      | 0.95       | 1.00      | 1.43      | 1.43       | 2.8             |

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age. The period of observation, however, is too short to draw exact conclusions as to the results of therapy. With regard to the indication for the use of anabolic steroids we feel that such cases form a particularly suitable group, that is, cases where not only the size but the bone development also is retarded so that the risk of early cessation of growth is particularly small. The epiphyses of the hands should be regularly controlled by X-rays. We recommend doses of not more than 1.5 mg/kg/month.

![Fig. 9](image)

Effect of nortestosterone phenylpropionate on bone age and height age in a girl with gonadal dysgenesis.

**Osteoporosis**

A further indication for the use of anabolic steroids is osteoporosis resulting from corticosteroid therapy. Long-term therapy with these hormones is used particularly frequently in pediatric practice. If these children are not given adequate amounts of anabolic steroids, then osteoporosis especially of the vertebral column and pelvis is inevitable. Yet it is known that osteoporosis of the vertebrae is not recognisable, until the calcium content of the bone has been reduced by thirty percent or more, in other words when the process is already far advanced. In children one observes not only the appearance of osteoporosis but also retardation or cessation of growth.

Children treated with corticosteroid have a negative nitrogen balance. This is in
contrast to those patients with retarded growth which we have discussed above. For this reason large amounts of anabolic steroids are needed to restore a positive balance, the amount of which will vary in accordance with the amount of corticosteroids given. We are of the opinion that one should not wait for the first signs of osteoporosis before giving anabolic steroids. If corticosteroid therapy is expected to last for longer than two or three months, anabolic steroids should be given simultaneously from the start. Under such a regimen it is sufficient to give 2-3.5 mg per kg per month of NTPP, provided that corticosteroids are given in not too large amounts of about 10 mg a day.

![Developmental diagram of a girl treated with prednisone; later in combination with nortestosterone phenylpropionate.](image)

Fig. 10
Developmental diagram of a girl treated with prednisone; later in combination with nortestosterone phenylpropionate.

Fig. 10 shows the development diagram of a girl who was treated with corticosteroids for four years because of acquired haemolytic anaemia. The dose corresponded on the average to 10 mg of prednisone daily. During the first 2½ years the child received no anabolic steroids leading to a complete cessation of growth, although no osteoporosis was detected on X-ray. Following this, NTPP was given which led to a satisfactory increase in the girl’s height and further avoidance of osteoporosis.

Higher doses of NTPP become necessary under certain circumstances: 1) when the amounts of corticosteroids given are greater than an equivalent of 10 mg prednisone per day; 2) when the anabolic steroids are used not prophylactically but therapeutically in the treatment of manifest osteoporosis.

The following case represents an example of this. A boy 12 years of age who over two years had received large amounts of corticosteroids in another hospital for severe rheumatoid arthritis. Anabolic steroids were not given.

When we admitted the patient, we were also at first forced to give large amounts of corticosteroids in the region of 20 mg triamcinolone daily.
Because of the severe osteoporosis which we found the patient received 6 mg/kg/month of NTPP for the next 8 months. Despite this it was impossible to prevent an increase of the osteoporosis. The decalcification of the vertebral column was maximal at the end of these 8 months, the vertebræ appeared flattened to show “a codfish” appearance, the discs became increased in volume and complete collapse of a number of vertebræ appeared imminent.

We decided to reduce the dose of triamcinolone which was achieved with the greatest difficulty; at the same time we increased the amount of NTPP during the first 4 months to 12 mg/kg/month, later decreasing to 8 mg. These doses were well tolerated. Under this regimen a definite improvement was noted in the next half year and this has since continued.

Despite the enormous doses of hormone used the bone maturation of the hand has shown only little progress. It is therefore apparent that in such cases one can greatly increase the dose of NTPP without running into complications and indeed one is obliged to do so.

The exact relationship between the amount of corticosteroid and the amount of anabolic steroid that is needed can only be determined by nitrogen-balance-studies.

Virilization

I now come to the side-effects of the anabolic steroids and will deal first with virilization. If one uses NTPP over long periods, virilizing symptoms generally appear after 3-4 months. The most regularly occurring signs are the growth of pubic hair as well as a change in voice pitch. The voice becomes deeper and rougher. If steroid therapy is then discontinued the voice will regain its original pitch. However, if therapy is continued the voice will break, eventually assuming an even low quantity. Other virilizing phenomena which become disturbing in girls, and may indeed force one to discontinue therapy, are an increase in the breadth of thorax and shoulders as well as a coarsening of the face, and the occurrence of acne.

We have seen only two girls with more marked virilization of the genitalia. Here there was hypertrophy of the clitoris together with the development of a scrotum-like appearance of the labia majora. These children were treated with 2.5 mg/kg/month of NTPP for over a year (Fig. 11). Nowadays we would not use such high doses except in the treatment of osteoporosis.

Doubtless one must regard the action of the steroids on the genitalia as a true virilizing effect. As regards the change in voice one may discuss whether the enlargement of the larynx is due to the androgenic or the anabolic action of the steroids. One may question whether the stimulation of bone growth produced by steroids does not necessarily lead to an enlargement of the larynx.
Hypertrophy of the clitoris in a girl treated with nortestosterone phenylpropionate 2.5 mg/kg per month for over a year.

**Disturbances of liver function**

The testosterone derivatives as well as producing hormonal side effects may also cause pharmacological side effects, which I am finally going to discuss. The most important of these are the disturbances of liver function.

Werner (1947) and Kinsell (1948) for the first time reported the occurrence of icterus following the use of methyltestosterone. Since then a large number of similar observations has been published.

This has also been seen during the last year following the treatment with a number of testosterone derivatives, of fluoxymesterone and methandrostenolone. Studies carried out recently by Liddle & Burke (1960) on patients treated with methandrostenolone showed that mild changes occurred fairly regularly, especially delayed excretion of bromsulphalein. The question as to how the steroids cause alteration of the liver, whether the icterus is due to liver cell damage, haemolysis or cholestasis, can nowadays be regarded as settled. Evidence for degenerative liver cell damage has as a rule not been found from biopsy nor could be produced experimentally in animals (Schaffner et al. (1959); Drill (1958); Post (1958)). Popper et al. (1959) found that the actual site of disturbance is in the smallest biliary ducts, the so-called canaliculi. This results in biliary stasis and leads to the formation of biliary thrombi and in certain circumstances to periportal cell infiltration. This morphological picture corresponds to the biochemical results obtained experimentally. Besides a rise in bilirubin which is found in severe cases there is a moderate rise in serum transaminases and a more or less definite rise in alkaline phosphatase. As a rule there is a delay in bromsulphalein excretion.

In the series of the derivatives of nortestosterone this type of damage has frequently been observed after treatment with 17α-methyl- and ethyl-nortestoste-
Icterus has never been described following the use of NTPP. We ourselves have observed the appearance of icterus in two children suffering from leukemia treated with NTPP. However both children were also receiving mercaptopurine which may have a toxic effect on the liver. Laboratory findings did not support the presence of biliary stasis. We therefore believe that the icterus was due to the mercaptopurine and not the NTPP. Wernze (1960) carried out systematic studies with NTPP and found no biochemical evidence for liver damage.

Bromsulphalein excretion remained normal in all cases. We have therefore only carried out systematic investigations with ethylestrenol. 20 children were treated with this preparation. In 12 of these we have observations over a period of 4-16 weeks, with an average of 8 weeks. Some children received the preparation to stimulate growth and others to counteract the catabolic action of corticosteroids. Children below 6 years of age received 1 mg daily, those between 6-10 years 2 mg, and those over 10 years 3 mg daily. Serum was examined for bilirubin, thymol turbidity, phosphorus and alkaline phosphatase, glutamate-oxalate-transaminase, glutamate-pyruvate-transaminase; urine was examined for bile pigments. As these were treated on an outpatient basis bromsulphalein excretion was not determined regularly but only 8 times.

Icterus did not occur in any case. Serum bilirubin remained unchanged except in 1 case, where it rose from 0.8 mg% before treatment to 1.2 mg%.

No other pathological changes were observed in this case. Thymol turbidity remained normal in all cases. At no time was there an increase in bile pigments in the urine.

However, we observed in 4 of 12 children a moderate rise in SGOT (Fig. 12). In one case there was a definite rise in SGPT, which was accompanied by a raised SGOT, which was not, however, above the upper limit of normal. We found a significant rise in the alkaline phosphatase in the 2 most severe cases. In both cases these changes were observed over a number of weeks. In the child with the most marked alterations a bromsulphalein test was performed, which showed a perfectly normal excretion.

In 5 out of 12 cases under ethylestrenol in not too high doses, we found mild changes such as have previously been observed with a number of other testosterone derivatives. We have no doubt that a similar process is involved here. On the whole, serum phosphatase did not rise greatly and occurred late: observations which were also made by Watson et al. (1959), Schaffner et al. (1959) and Wernze (1960). These authors only very occasionally observed a rise in serum phosphatase prior to the appearance of icterus under methyltestosterone and ethyl-nortesto-

Arsene et al. 1959; Wernze (1960). The authors only very occasionally observed a rise in serum phosphatase prior to the appearance of icterus under methyltestosterone and ethyl-nortestosterone treatment. A rise in serum phosphatase can therefore not be used as a sensitive indicator of biliary stasis resulting from androgenic steroids.

Apparently ethylestrenol also can lead to moderate cholostasis in a certain

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number of patients. This action is almost entirely confined to those testosterone derivatives in which a methyl- or ethyl-group is substituted at C₁₇ (Wernze (1960)). In these cases the hydroxyl-group at C₁₇ is altered to a tertiary alcohol group, thus preventing the oxidative degradation of the molecule, a fact which is of prime importance for the oral effectiveness of the steroid.

Thus this preparation may carry with it a certain risk in producing icterus.

We ourselves have not observed any cases of jaundice, although in 3 cases in whom there were pathological test results, we continued treatment with ethylestrenol.

As I understand, up to this moment, nobody at all has observed jaundice with ethylestrenol. As I mentioned yesterday, hepatologists are using very similar preparations in liver cirrhosis without any harm. So the risk just mentioned seems to be slight.
REFERENCES

Kinsell, L. W.: Gastroenterology 11 (1948) 672.

DISCUSSION

Tausk: Thank you, Dr Bierich. The two papers are now open for discussion.

Houtsmuller: I would like to ask Dr Bierich whether he has ever observed corticosteroid diabetes in children and if he has had any experience with anabolic steroids in this disturbed mechanism?

Bierich: We have observed in the last 10 years only one case of steroid diabetes. That was 2 months ago. The diabetes ceased following the withdrawal of the corticosteroids. This child had a maximal excretion of half a pound sugar a day. We have no experience with anabolic steroids in the treatment of this kind of diabetes.

Prader: Did you say half a pound?

Bierich: Yes, it seems fantastic, but it is true.

Houtsmuller: Is it possible to stop the growth in young girls who are likely to be excessively tall with these high doses of anabolic steroids, without incurring any harmful effects?

Prader: High doses of testosterone or other anabolic steroids will certainly decrease the expected adult height but in addition will also virilize and depress gonadal function. In girls I would rather use oestrogens to avoid virilization but in the high doses which are necessary, gonadal depression will also result. Though I have seen patients where this depression was reversible (Fig. 8 in my paper), I am not prepared to recommend this therapy for tall girls. We do not really know whether gonadal function will always recover.

Kopera: I have two questions for Dr Prader. Firstly I would be interested to know whether the clinician regards it as an advantage to have an injectable preparation for the treatment of growth disturbances? Secondly: the voice changes produced by high doses of norsteroids do not return to normal again after discontinuing treatment. Now this is in contradiction to what Dr Bierich has said. He said that when he stopped treatment the voice changes disappeared too. I would like to know your opinion on that.

Prader: As a clinician I wish to have both an injectable preparation and an oral
preparation. The age of the patients, the reliability of the parents and of the patients, the distance of the patients home from the doctor, the psychological and other aspects make it preferable to give injections to some patients and tablets to others.

Some virilizing symptoms are reversible, others are not. The most sensitive sign of beginning (and still reversible) virilization is the increased frequency of erections in boys. In girls there is not such a sensitive sign. Hypertrophy of the clitoris and a deep voice belong to the irreversible symptoms. This is a regular experience in adrenogenital patients treated with cortisone and a regular experience in patients who have received high doses of anabolic steroids. The change of voice is only reversible at the onset, when the new low range of voice and the normal high range are both still present. The return to normal is than achieved by unconscious training, that is by suppressing the low range and training the normal high range.

_Tausk:_ May I interject one question with respect to these changes of voice? Is it in your joint opinion possible that the mild changes of the voice which are reversible are perhaps due not to an actual growth of the cartilages of the larynx but to a change of the vocal cords? It has been suggested - this is not my original idea - that maybe the anabolic effect of these steroids might influence the muscles of the vocal cords and thereby influence the voice. Could it be that that is perhaps more easily reversible than actual changes in the cartilage structure of the larynx? Do you have any opinion on this, Dr Prader?

_Prader:_ No, I have not.

_Tausk:_ Have you, Dr Bierich?

_Bierich:_ Looking for an explanation myself I have reasoned along the same lines as you have; it cannot be an increase of tissue formation in the cartilage because then it would be irreversible. But I am not aware and I do not know whether you are, of observations on actions on any other of these tissues apart from the cartilages. In the beginning of treatment with anabolic steroids one does not observe a deepening of the voice but the voice does become more rough and fortunately this is reversible.

_De Toni:_ We have much experience with this problem as we treat our muscular dystrophy patients with very high doses of Durabolin and other anabolic steroids. We have observed the change of voice in every case. I think that there are two different factors: one is the change in the cartilage which does not disappear and the other is the change in the vocal cords which can decrease when the treatment is stopped. We have had occasion to observe this voice change after the end of treatment.

_Hortling:_ I have some experience in treating stunted growth in pituitary dwarfs and high grade infantilism, where the bone age was very much delayed (Acta endocr.
(Kbh) 32 (1959), 563). Their age was somewhat higher than that of the patients studied by Dr Prader and Dr Bierich. I used very small doses of anabolic hormones as Hellinga did with methyltestosterone (Acta endocr. (Kbh) 18 (1955), 536). My observations lead me to the conclusion that during treatment with androgens the bone age, which at the beginning of treatment is much behind, increases rapidly. The bone age now comes nearer to the chronological age. However this accelerated increase slows down and the bone age does not increase at the same rate although the same or an even greater dose of androgens is used than in the beginning of treatment.

**Prader:** In eunuchoid boys, therapeutic anabolic steroids stimulate bone age in the same way as do endogenous androgens in the normal pubertal boy. In other words bone age increases normally in this situation. In younger boys however the same accelerating effect of therapeutic anabolic steroids on bone age is greater than normal because the normal (pre-pubertal) young boy is not under the massive influence of endogenous androgenic steroids as is the pubertal boy. As bone age can only be evaluated in relation to the normal, it is understandable that anabolic steroids do seem to accelerate bone age in smaller children much more than in pubertal children. Observers who deny the stimulating effect of anabolic steroids on bone age have probably only treated patients who were just prior to or actually in puberty.

**Nowakowski:** I would like to discuss how far it is possible to damage the gonads by steroid therapy. I know that you can depress gonadal function in the male and in the female but, as far as I know, nobody has seen any irreversible damage during treatment with steroids, androgens and estrogens or even with the new compounds. Consequently I think that you pediatricians should not be too anxious about gonadal function. From our experience of patients with adrenogenital syndrome we know that as soon as we administer corticosteroids gonadal function is restored.

**Prader:** I agree with Prof. Nowakowski on theoretical grounds. However, until we have more experience in treating tall children, either just before or during puberty, with high doses of anabolic steroids in order to decrease expected adult height, we cannot recommend such a therapy.

**Overbeek:** First of all I would like to say how very much impressed I am by the accurate data of Dr Prader and it is therefore perhaps even more alarming that the dissociation between the anabolic and androgenic effects observed in animals and also observed in adult human beings do not appear in children. Perhaps you could say a few more words about that. First of all to prove your point which is of course extremely important and secondly as to the possible explanation. I might add a few observations from our animal experiments where we certainly did not see any difference in the sensitivity between young and old animals and between young and old castrated animals. Of course we saw the different reaction between the young
castrated animals which we used in our levator ani assay and for example, the grown up mature animals which still have their testicles. This is because the pituitary inhibition plays a rôle and thus one sees a different effect both on the levator ani and also on the seminal vesicle. I could well imagine this to be a suppression of endogenous testosterone production.

Another point is this pituitary inhibition. We carried out a number of experiments in animals where the inhibition of pituitary function with 19-norsteroids, for example Durabolin, and also with substances like ethylestrenol or other estrenols was studied. There we could really observe, as you did in this one case, that in the males the testicle is rapidly restored to normal weight and also to a normal function. I do not think there is a really great difference even in young animals. In young animals the development is much more easily inhibited than is the function of the mature animal depressed. So in this way they are more sensitive than the older ones. This is a different thing of course to the sensitivity towards androgenic activity but it is surprising how quickly the normal function and weight of the gonads are restored. In the females it is the same thing. When the oestrus cycle is suppressed by using these steroids it is surprising to see that after stopping treatment the first cycle may be somewhat abnormal but the second cycle is already normalized. So the restoration is extremely rapid.

Prader: I did not state that the favourable dissociation between the anabolic and the androgenic effect seen in the animal does not exist in children. I only said that such a dissociation has not yet been proved in children. It could only be investigated by comparing a large group of children treated with testosterone to a large group of children treated with the newer anabolic steroids. Nobody has done this and I would be afraid to do it - which shows that I have a high respect for the evidence which indicates that such a dissociation exists in animals.

I would like to say at this point a few words about the high sensitivity of children to androgenic influences. I do not think that the end organ is really more sensitive in children but it is certainly a better indicator of androgenic influences than in the adult. This is easily understood because a normal child has no androgenic symptoms, that is he has no pubic hair etc. Therefore the appearance of very little pubic hair is a striking symptom in a child. In the adult woman it needs a more marked increase of pubic hair, in other words a higher dose of androgenic steroids before the difference is seen. In an adult man even a very high dose of androgenic steroids can hardly increase the already fully developed pubic hair.

Several speakers have implied that I am rather too critical and over anxious in using and discussing anabolic steroids. I feel strongly that with children we have to be more careful than with adults and I wish to emphasize again that the recommended low dosage (nandrolone phenylpropionate 1 mg/kg/month and methandienone 0.04 mg/kg/day) should not be exceeded in children. I am glad
to see that Dr van Wayjen and Dr Bierich recommend similar doses. In the beginning we did use higher doses and many authors still recommend higher doses. These nearly always lead to virilization and we do not yet know enough about the possibly harmful psychological effect of virilization in children. I think we are only allowed to use higher doses if this is the only possible way to improve a desperate situation.

**Tausk:** Would you say that in your opinion this dissociation between androgenic and anabolic effects has not been proven to exist as far as the action on children is concerned? Would you not say that what Dr Bierich showed us goes a long way towards proving it; if you look at the different quotients and the different tangents Dr Bierich showed us, which seem in a way characteristic of the different compounds he has been using.

**Bierich:** I am sure but I should like to ask whether or not the relationship between these quotients of the tangent α’s and the quotient between anabolic action and androgenic action is very close?

**Tausk:** Yes, I can see that. All I wanted to say is this: in the animal studies we definitely find that there are essential differences in the patterns of activity of various steroids. Now those compounds, which in the animal experiments show up as good anabolic compounds measured by our tests and with relatively low androgenicity, have been introduced in clinical studies and in these clinical studies these compounds again differ in certain ways. Dr Prader, with great respect for your very careful attitude, which I admire, you yourself have the feeling that you would not really dare to use testosterone. Yet here comes Dr Bierich who shows another parameter and he also shows that by comparing these quantitative data, there are differences between the compounds. Of course only time will show what quantitative relationship exists between all these clinical parameters and the pharmacological data.

**Prader:** Prof. Tausk, if you say that Dr Bierich’s ratios are related to the ratio of anabolic to androgenic effects you are implying that acceleration of bone age is an androgenic symptom. I would like to ask you whether if the increase of bone age is an anabolic or an androgenic effect? I would like to know the answer.

**Bierich:** This is my question too.

**Tausk:** I am afraid we have not enough time to settle this now.

**Ilzerman:** May I ask Dr Prader two questions? The first one is how exactly do you calculate the growth prognosis? The second thing is that you stated that with anabolic steroids it is impossible to improve future adult height. Am I correct in assuming that this future adult height in many of the cases which you treat is really a rather theoretical adult height which could never have been reached without treatment? You would not reach it with treatment either but you still reach something more with treatment than without it. Or am I mistaken?
Prader: Growth prognosis or expected adult height can be calculated from age, height age, and bone age according to the tables of Bayley & Pinneau (J. Pediat. 40 (1952) 423). These tables have been established from data of normal children. From our experience I have the impression that these tables are rather reliable also for patients with dwarfism. Treatment with anabolic steroids frequently changes growth prognosis but most steroids have not yet been long enough on the market to have had actual observations of the adult height reached after such treatment in childhood.

Izerman: Sorry to interrupt you. What I mean is that if there is a good indication for anabolic steroids to promote growth does that not imply that one thinks that the growth in itself would never have reached the adult height?

Prader: What you mean is that some endocrine dwarfs might never reach, spontaneously, their calculated adult height and that steroid treatment may therefore damage only the theoretical adult height but at the same time in reality improve the obtainable adult height. I do not know whether this is so. I rather imagine it is not. To give a reliable answer to this question we have to compare growth prognosis and adult height of untreated grown-up pituitary dwarfs and other dwarfs, whose height and bone age have been followed during the whole growth period. Nobody has yet done such a study. In spite of my critical attitude I am the first to admit that anabolic steroids are at the moment the best available treatment to stimulate the growth of pituitary dwarfs, provided that the low doses which I have indicated are not exceeded.

Tausk: I wonder whether the term growth prognosis should not be replaced by the words “maximum attainable height”, which in my opinion is something different from a prognosis? But again I am afraid that we have not enough time.

Van Wayjen: There is one point put forward by Dr Prader about the interaction between growth hormone and anabolic hormones. I understood that he could not obtain any effect on growth with anabolic hormones in a pituitary dwarf who was hypophysectomized by operation. So he came to the conclusion that growth hormone has a permissive action on anabolic steroids. There is a certain doubt though if that holds true. In the first place, I remember from the literature that anabolic effects have been obtained in hypophysectomized rats and in the second place Kochakian proved that anabolic hormones and growth hormone in rats resulted in a summation of effects. He thought that the action of these two hormones were different at the cell-level. In the third place, you could not get an effect in a case of Turner Syndrome where sufficient pituitary hormones, at least gonadotrophins, are present. So I wonder if you could say a little bit more about this interaction?

Prader: First we should not forget that anabolic action as measured by nitrogen retention and anabolic action as measured by a growth response are not neces-
sarily identical. I can visualize a situation where there would be a good nitrogen retention and no growth response. Certainly we have to keep this possibility in mind. I fully agree that the mechanism of growth stimulation by testosterone is probably different to the mechanism of growth stimulation by growth hormone. However I do not think that this is a valid argument against the hypothesis that some growth hormone is necessary to permit a growth response to anabolic steroids. I am fully aware that this question is not settled. The interaction between growth hormone and anabolic steroids is a fascinating problem.

Tausk: You are aware of course of the paper by Wilkins, who treated primordial dwarfs with growth hormone. They did not show any nitrogen retention with growth hormone but did respond to anabolic steroids.

Prader: Was that not a paper by Lipsett et al. (J. clin. Endocr. 21 (1961) 119)? These authors found in patients with acromegaly no nitrogen retention with growth hormone and a good nitrogen retention with testosterone.

Tausk: Sorry, indeed it was.

Overbeek: I think your first item, Dr Prader, is a most intriguing problem: the possible differences and similarities between the action of growth hormone and anabolic steroids.

I think, it may be that growth hormone has a dual effect. Firstly what is called the metabolic effect may be the same, or to a certain extent the same, as that of the anabolic steroids. Secondly the somatotrophic effect which is perhaps responsible for the growth of the long bones - the chondotrophic effect described by Freud and his group. So this may be one of the reasons why there is a reaction, or an absence of reaction to the metabolic effects which are probably at the bottom of everything and a failure of the long bones to grow.

May I also put a question to Dr Bierich?

We have already discussed yesterday liver function and liver damage. If I remember rightly, with growth hormone you can also observe effects on the transaminases, and perhaps also on the alkaline phosphatase. I now see in the course of your paper that practically the only effects which could be interpreted as an impairment of liver function were the effects on the enzymes, whereas the other usual symptoms were absent. So I wonder really if this might or might not be because of the anabolic effect? It would perhaps be very interesting to try and see what human growth hormone does in these cases. Would it not be possible to see whether in similar cases you would have the same effect on the enzyme with growth hormone? If so the results could not be interpreted as an impairment of liver function.

Bierich: It would be really very interesting to perform such experiments but may I say there are differences between the various anabolic hormones. Durabolin does not raise the level of the transaminases as far as I know; neither does it alter the alkaline phosphatase level nor the retention of bromsulphalein. On the other hand
the steroids substituted on C₁₁ do have this effect. It cannot be the anabolic action alone.

Horting: What is the lowest dose with which you get a growth promoting effect? I used very small doses in very young patients (9 years and 11 years old) and I found in these patients on administering very low doses the same phenomenon I mentioned before. During the first two years the bone age increased more rapidly. When the treatment was continued for a longer period the bone age did not continue to increase so rapidly. I suppose that when we use small doses there is no real danger.

Prader: I think that one of Dr Van Wayjen’s pictures showed that 0.7 mg/kg/month of Durabolin still had a good nitrogen retention effect. Some of our patients with only 0.5 mg/kg/month of Durabolin or of 0.02 mg/kg/day of methandienone have shown a clear growth response.

Tausk: I am afraid I shall have to close the discussion at this point.