CLINICAL-PHARMACOLOGICAL EVALUATION OF CERTAIN ANABOLIC STEROIDS

by

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Introduction

It is difficult to determine the protein- and calcium-saving effect of an anabolic hormone on the human subject. The best criterion would be the demonstration of a clinical effect in patients who are in a “catabolic” condition. To meet this criterion however one has to treat a large number of comparable patients over a considerable period with each of the preparations which one wishes to test; one must then be able to measure their improvement according to objective criteria and compare the results statistically.

In order to gather quantitative data as to the action of anabolic substances within a reasonable time it is thus necessary to employ clinical-pharmacological methods. Until we find a way to investigate the incorporation of amino-acids and bone constituents simply and safely with the help of isotopes, the balance technique will remain the most reliable method for determining the anabolic activity of a given substance in man.

One can argue that the effect of a drug upon the nitrogen and calcium balance is not an absolute criterion for assessing its clinical activity, but in practice it provides a sufficiently strong indication. The advantages of the balance techniques are fourfold.

Firstly, the results are reproducible, can be measured quantitatively and expressed graphically.

Secondly, it enables us to compare the effects of various preparations in different doses.

Thirdly, there can be no objection to the employment of healthy volunteers as test-subjects.

Fourthly, both the anabolic and anti-catabolic effect can be studied and compared.
On the other hand, the method does possess certain drawbacks:

1. The test-subject must be reasonably interested, intelligent, reliable and mentally stable, and he must be willing to submit to a strict hospital regimen for months on end.
2. The nitrogen and calcium balance technique is time-consuming for all concerned.
3. A separate dietary kitchen and laboratory are required.
4. Stringent demands are made upon the accuracy of the dietician and the analyst.

Test-Subjects

Since October 1958 we have had the opportunity to carry out more than 40 balance studies, each lasting for between 60 and 160 days. At first our test subjects were agastatic patients in poor nutritional condition, whose weight we hoped to raise by the administration of anabolic steroids. For our studies of their build-up effect on bone we employed mainly women suffering from post-menopausal osteoporosis. More recently we have carried out balance studies on young and healthy girl students who have volunteered to act as test subjects. Finally, we have found it possible to study the anticatabolic effect on rheumatic and asthmatic patients undergoing treatment with corticosteroids.

Method

We will leave the detailed description of our method for another occasion and confine ourselves now to a few salient points. The patients and volunteers in our trials are admitted to hospital for a period of three or four months. Together with the dietician they select a diet which is subsequently maintained for the entire period of the trial. This diet contains as a rule 50 grams of protein per day and usually provides sufficient calories to maintain body-weight at a constant level when allowing for mild physical exercise. With an eye to the calcium balance all meals and drinks are prepared with demineralized water. The food is carefully weighed each day and the nutritional content calculated with the help of the Netherlands Table of Foodstuffs. As a check, duplicate meals are prepared and analysed once every six days. The results of these analyses are found to correspond closely to the values given in the Table.

The nitrogen content of 2 x 24-hour urines and of samples of the total faeces collected over 6 days is determined by Kjeldahl's method, and the calcium content of the same samples with the complexon method. As a check that all the daily urine is actually being collected we determine the total creatinine content each day. The patient is weighed every day at the same time and in the same clothing. Following the method advocated by Albright & Reifenstein (1948) the analysis of our observations is carried out over six-day periods. As soon as an equilibrium
has been attained, which is generally the case after two or three weeks, the study of the effects of anabolic steroids upon the nitrogen balance can begin.

Results

We have examined the following steroids for their anabolic and anti-catabolic effect:

a. Nandrolone phenylpropionate (Durabolin)
b. Nandrolone decanoate (Deca-Durabolin).
c. Ethylestrenol (Orgabolin)

The effects of various doses of these steroids were investigated and compared with each other and with testosterone propionate (Neo-Hombreol), nor-ethandrolone and methandienone.

The results of these investigations are shown with the use of a number of diagrams. Although this type of graph will be familiar to many readers it may be worthwhile my reminding you of the system employed.

Fig. 1 shows the older method, the method advocated by Reifenstein et al. (1945), and the illustrations devised by Moore & Ball (1951). In our view the last of these is to be preferred since both the food intake and the positive balance are traced above the base-line (in other words as positive quantities) whereas the losses are expressed by a tracing in the negative direction, in other words below the base-line.

Various ways of charting metabolic data. In the charts in this study the method devised by Moore & Ball (1951) is used.
The next four figures illustrate the anabolic action of nandrolone phenylpropionate and nandrolone decanoate.

Balance study in a 66 year old man who had had a total gastrectomy. The 48 hours nitrogen balance, the cumulative nitrogen balance curve, the changes in body-weight and the urinary creatinine excretion are illustrated. The arrows indicate intramuscular injections of the hormones mentioned.

Fig. 2 shows a study on a 66 year old male patient who had undergone a total gastrectomy eighteen months previously on account of carcinoma of the stomach. In October 1958 this patient was in a poor condition but he did not present - and he still does not present - any evidence of recurrence or metastasis. He was admitted to hospital in order to be treated with anabolic hormones. During a balance study the nitrogen balance was slightly positive when the trial began, probably because we were allowing him a generous diet for therapeutic reasons (12 grams of nitrogen, corresponding to 75 grams of protein, and a total of 2200 calories).

During the observation the nitrogen balance shifts gradually into equilibrium. Giving 50 mg of nandrolone phenylpropionate causes on two occasions the nitrogen balances to become evidently more positive. The effect is comparable, in degree and
duration, to that produced by 6 daily injections of 25 mg of testosterone propionate. The anabolic effect can also be seen in the cumulative nitrogen balance, in which the daily fluctuations have been added and in the weight chart. The testosterone propionate probably gives rise to more marked retention of salt and water than does Durabolin, perhaps because of the greater quantity of hormone administered. The total gain in nitrogen over the entire period of study is 80 g which corresponds to 2.4 kg of “lean tissue” whilst the increase in body weight is actually a little more than 2 kg. The anabolic steroids had no effect on the creatinine excretion, a well-known fact which has been confirmed in all our studies.

The second trial which I would like to describe was also carried out on an agastric patient (Fig. 3). This intelligent and active man found his confinement to the ward boring and against our advice he took an increasing amount of exercise, sometimes walking for hours at a time. Under these circumstances his diet, which contained 1700 cal. was inadequate to maintain his body-weight. The balance which was at first negative, shifted into equilibrium during the period of observation. Following the administration of 100 mg of nandrolone phenylpropionate and later, following administration of 100 mg of nandrolone decanoate, the nitrogen balance

![Figure 3](https://via.placeholder.com/150)

**Fig. 3**

Balance study in a 56 year old agastric patient, with nandrolone phenylpropionate and nandrolone decanoate.
became clearly positive and remained so - in the first case for 12 days and in the second for 20 days. The evaluation of this case is complicated by the fact that the nitrogen balance was already tending to become more positive before steroid administration began. Nevertheless, the effect of the nortestosterone derivatives can be quite clearly seen; it is also obvious if one looks at the cumulative balance.

This rising curve contrasts oddly with the falling weight curve. Although a theoretical gain of 38 g of nitrogen is registered, corresponding to 1.1 kg of lean tissue (muscle, for example), the body weight is seen to decline by 2.6 kg during the same period. Apparently fat has been broken down in an effort to supply the missing calories whilst at the same time there is an increase in muscle (and bone) tissue, partly as a result of the influence of the anabolic steroids. This case shows how careful we have to be in drawing conclusions as to the action of the anabolic steroids on the basis of weight changes alone. The interesting observation, which as you will see is confirmed in a number of later studies, may also have important consequences in practice, for example in the treatment of obesity with low-calorie diets in combination with anabolic steroids. We are currently studying this point further.

Fig. 4

Balance experiment in a healthy volunteer, a 24 year old girl student. This study includes the calcium balance. 48 hours calcium balance curve and cumulative calcium curve are shown.

The fourth diagram concerns a 72 day balance study carried out on a healthy 24 year old girl student (Fig. 4). At the beginning of the study she was in nitrogen equilibrium, and the calcium balance was also around the zero line. Following the administration of 50 mg of nandrolone phenylpropionate a strongly positive nitro-
gen balance appeared (as is also evident from the cumulative curve). 50 mg of nandrolone decanoate had a slightly less marked but longer-lasting effect on the nitrogen balance, yet it had a stronger effect on calcium retention, as seen also from the cumulative calcium balance curve. In this subject too body weight fell, this time by 1.3 kg, while the cumulative nitrogen balance once again points to a nitrogen gain of 34 g, in other words 1.0 kg of lean tissue.

An obese 65 year old woman with arthrosis deformans of both hips was put on a reducing diet of 1100 calories so that here too the body-weight slowly decreased (Fig. 5). While she was in nitrogen equilibrium 50 mg of nandrolone phenylpropionate was administered by injection, the result being a strongly positive nitrogen balance. There is a slight rebound-effect. Thereafter we gave her 50 mg of nandrolone decanoate. Not knowing at that time that the protein-saving effect to this steroid sometimes continued for more than eighteen days we were rather too early in giving the third injection, which was of 50 mg of nandrolone phenylpropionate. This unintended, premature early injection of nandrolone phenylpropionate proves however that it is possible to maintain the positive nitrogen balance for as long as 36 days with two such injections, a point which is
further shown by the cumulative nitrogen curve. The calcium balance taken over the whole period is negative, as you will also see from the cumulative balance, probably because the calcium supply (less than 400 mg a day) was inadequate. Nevertheless the administration of the nor-steroids did influence the calcium balance inasmuch as it tended to shift in a positive direction. Once again one sees the remarkable contrast between a strongly positive nitrogen balance and a decline in body-weight. Whilst the latter fell by more than 3 kg the nitrogen balance points to a theoretical gain of about 2 kg of “lean tissue”. The clinical data supported these findings: the pain in the hip joint decreased as a result of the loss of weight, whilst the patient felt fitter and stronger and her walking quite noticeably improved. This study illustrates clearly the fact that a medical treatment and a balance study can perfectly well go hand in hand. A total study period of several months (in this case an adjustment period of 14 days followed by 78 days of balance study, making a total of 3 months) will not in such cases be opposed by the patient.

Our conclusion from these cases then, is that nandrolone phenylpropionate and nandrolone decanoate in doses of 50 to 100 mg bring about a definite and constant retention of nitrogen and calcium, lasting 14 and 24 days respectively.

The next three figures illustrate the anti-catabolic effect of these two nor-steroids.

Balance study with nandrolone phenylpropionate and nandrolone decanoate in a 41 year old woman, treated with prednisolone for rheumatoid arthritis.
A 41 year old woman received 5 mg tablets of prednisolone (Di-Adreson-F), at first three tablets daily and later two tablets three times daily (Fig. 6). The preparation had a very favourable effect upon her rheumatic symptoms. The nitrogen balance became only very slightly negative but when 100 mg of nandrolone phenylpropionate was given it became strongly positive; 100 mg of nandrolone decanoate had a similar but longer-lasting effect. This latter response was perhaps less than it would otherwise have been because of the higher doses of prednisolone given simultaneously, but it is very clearly seen in the cumulative nitrogen balance and the weight curve. One sees that after the nandrolone phenylpropionate effect has worn off something of a rebound occurs, but the cumulative curve shows that by this rebound a very small part of the spared nitrogen is lost again.

![Figure 7](image-url)

**Fig. 7**

Balance study in a 55 year old rheumatic woman, treated with prednisolone (orally), nor-steroids and testosterone propionate (intramuscularly).

We were able to carry out a balance study over a period of 124 days in this 55 year old patient (Fig. 7). The administration of prednisolone in the form of three 5 mg tablets daily brought about such a striking improvement in her rheumatic symptoms that, after having spent years confined to her bed, she could gradually be mobilized and could take some exercise. In this case the corticosteroid treatment produced a clearly negative balance; the administration of nandrolone phenylpropionate, followed by nandrolone decanoate and then by further nandrolone phenylpropionate produced a positive balance once more.

For the sake of comparison we finally administered seven daily injections of
25 mg of testosterone propionate. The nitrogen-saving effect of this treatment was of the same order of magnitude as that of the nor-steroids.

The cumulative nitrogen curve fell steadily throughout the entire period of study. One must probably attribute this partly to the constant administration of prednisolone and partly to the strict 1600 calory diet which necessitated the use of a part of the ingested protein to supply energy. This perhaps explains why the protein-saving effect of all the steroids administered to this patient seemed to be less than in many other test subjects. On the other hand it may be that this patient was simply less reactive. Various authors, among them Liddle & Burke (1960), have indeed pointed to the great variation in response to anabolic hormones between one individual and another.

Balance study in a 49 year old woman, treated with prednisolone for rheumatoid arthritis.

In a 49 year old female patient the results were more marked (Fig. 8). A negative nitrogen balance following the administration of 3 doses of 5 mg of prednisolone was abolished during a period of 18 days by a single injection of 100 mg of nandrolone phenylpropionate and for as long as 24 days by 100 mg of nandrolone decanoate. These effects are very clearly seen in the cumulative curve and in the weight curve. There is a total increase in body-weight of 2 kg and a theoretical increase of 1.4 kg of lean tissue.
We may therefore conclude that nandrolone phenylpropionate and nandrolone decanoate are capable of abolishing a negative nitrogen balance brought about by the administration of corticosteroids. They apparently thus possess an anti-catabolic effect lasting also for 14 and 24 days respectively.

Let me now show you some balance studies with ethylestrenol (Orgabolin). At first we administered this substance in quantities of 25 to 50 mg daily, but we later reduced this quite drastically to between 3 and 6 mg a day, in other words less than 0.1 mg per kg of body-weight. We will look first at the anti-catabolic effect since our first studies with this preparation were carried out on patients with chronic rheumatism.

![Graph](image)

**Fig. 9**

Balance study in a 55 year old woman with rheumatoid arthritis; she was treated with prednisolone and consecutively with norethandrolone, ethylestrenol (Orgabolin), nandrolone decanoate and methandienone.

A 55 year old rheumatic patient received 5 mg of prednisolone twice daily, as a result of which she acquired a negative nitrogen and calcium balance (Fig. 9). During the investigation an equilibrium was gradually obtained in both balances. Besides you can see the nitrogen-saving effects of norethandrolone and ethylestrenol both in a dosage of 50 mg daily and of one injection of 50 mg. Finally we administered methandienone, also in a dosage of 50 mg daily - a little too early, un-
fortunately, since the nitrogen balance was still positive under the influence of nandrolone decanoate given 18 days previously. All the same, one can see some effect. The influences of norethandrolone, ethylestrenol and nandrolone decanoate on the calcium balance are clear that of methandienone is dubious as also seen from the cumulative curve. The weight record indicates that both nandrolone decanoate and methandienone cause some water retention.

![Graph showing nitrogen and calcium balance](https://example.com/graph)

**Fig. 10**

Balance study in a 58 year old woman with rheumatoid arthritis; she was treated with prednisolone and received consecutively: norethandrolone, nandrolone decanoate and ethylestrenol (Orgabolin).

A 58 year old woman suffering from rheumatoid arthritis had similarly acquired a negative nitrogen and calcium balance following 15 mg of prednisolone (Fig. 10). However, 50 mg of norethandrolone and ethylestrenol daily produced a strongly positive nitrogen balance. The same effect was produced by one injection of 50 mg of nandrolone decanoate. These effects are extremely clearly shown in the cumulative balance. The calcium balance, which remains on a whole negative because of the low calcium intake, shows the same reactions.

I would like to turn now to a group of balance studies in which no prednisolone was given and which thus illustrate the anabolic effect of ethylestrenol.
The balance study illustrated by Fig. 11 and carried out on a healthy 21 year old girl student was twice interrupted. Nevertheless the effect of 25 mg of ethylestrenol and 50 mg of nandrolone decanoate emerges clearly, particularly in the cumulative curve. The girl had a strong spontaneous negative balance, probably as a result of a strict diet of 1700 cal. and a great deal of exercise; she lost in all more than 3 kg. No influence on the menstrual cycle was recorded.

Finally, here are two more studies concerned with the use of lower doses of ethylestrenol, namely 6 mg daily in a patient weighing 79 kg, in other words 0.08 mg per kg of body weight (Fig. 12). We see that ethylestrenol works well even at these low doses. Its nitrogen-saving effect is of the same order of magnitude as that of methandienone as is also shown by the cumulative curve. The cumulative calcium curve also seems to show a favourable effect. Methandienone proves both in the nitrogen and calcium balance to give rise to a rebound effect. All three steroids apparently cause water retention as shown by the weight curve. The menstrual cycle was not influenced.

Finally, I would like to show you a study, carried out on a healthy woman student, in which we compared ethylestrenol, methandienone and nandrolone phenylpropionate with each other (Fig. 13). In spite of the very low dose of 3 mg
Balance experiment with ethylestrenol (Orgabolin) and methandienone in a 21 year old healthy volunteer.

daily which we employed corresponding to 0.05 mg per kg of body-weight, one sees a definite effect, be it a small one, on the nitrogen balance.

Increasing the dose of ethylestrenol to 10 mg however does not noticeably increase the effect, whilst the reaction to 100 mg of nandrolone phenylpropionate shows that this test subject belonged to the group of "low reactors" which I mentioned earlier. It was however clearly shown that ethylestrenol in such very small doses does have an anabolic effect.

*Our conclusions are that ethylestrenol (Orgabolin) proves to possess a nitrogen saving effect not only in daily doses of 25 to 50 mg but also in far lower doses, i.e. less than 0.1 mg per kg of body weight.*

One last remark as to these low doses may be in order. During our balance studies with anabolic steroids we have noticed that comparatively large doses are required if one is to produce effects which are sufficient to exceed the spontaneous daily biological variations and which occur in all subjects - in other words, effects
Balance experiment with ethylestrenol (Orgabolin), methandienone and nandrolone phenylpropionate. Basal rectal temperature is charted. m = menstruation.

which are both significant and reproducible. The doses of hormones which we have employed exceed the levels which are therapeutically necessary. The reasons for this discrepancy are in our view threefold:

1. We maintained the food intake rigidly at a constant level, although in practice all anabolic steroids stimulate the appetite and thus the intake of food.
2. We employed only one single injection every 3 to 4 weeks and administered the oral preparations only during 6 days, whilst in practice one usually gives repeated injections and long courses of treatment.
3. The balance study is a comparatively coarse instrument which can only provide us with information as to the sum total of metabolic events within the body.

Under these circumstances one may consider it quite remarkable that as little as 3 mg of ethylestrenol has a demonstrable effect on the nitrogen balance.

Summary

The anabolic and anti-catabolic effect of nandrolone phenylpropionate (Durabolin), nandrolone decanoate (Deca-Durabolin) and ethylestrenol (Orgabolin) was demonstrated in 12 metabolic balance studies. The strength and duration of this effect was determined and was compared with the effect of other anabolic steroids at various dosage levels.
REFERENCES


DISCUSSION

Tausk: Thank you, Dr. van Wayjen, for your presentation of this enormous mass of data which must have taken a great deal of work. This paper is now open for discussion.

Lambrechts: I should like to make three comments on this lecture. I well know what cost of chemical, clinical and psychological work so many balances represent. I congratulate Dr. van Wayjen on his excellent work. My second comment is a question. You did not mention phosphorus balances in your work? I think that phosphorus is very important in this connection. The relation between nitrogen, phosphorus and calcium for example gives one an indication of the fate of nitrogen retention. According to the relations established by Stearns et al., you can guess, from the value of the relation between nitrogen and phosphorus retention, whether either bone or muscle tissue is formed when the treatment has stimulated growth. My last comment is a theoretical objection to the procedure of using two substances successively for the study of nitrogen metabolism. If you have a substance A and another substance B and if you observe the nitrogen retention on the substance B, after having observed the retention on substance A, this may be incorrect as a nitrogen balance depends on at least two factors: nitrogen intake and the previous nitrogen depletion. During the balance studies, time is passing and the depletion may be corrected; then the quantitative response on the second substance may not be quite what would have been expected if it had been given first.

Van Wayjen: Of course we wished to perform analyses of phosphorus, sulphur, sodium, potassium, and perhaps also of magnesium but when we began these balance studies, we had to limit ourselves. We chose the two most important parameters: nitrogen- and calcium-excretion. It was shown by Albright & Reifenstein that the phosphorus balance is rather parallel to the calcium and nitrogen balances and can be calculated from these knowing that in bone the calcium/phosphorus rate is about two and in muscle the nitrogen/phosphorus ratio is approximately 15. Gram for gram, much more nitrogen than calcium is retained during treatment with anabolic hormones. So, I cannot see that phosphorus can add much information in balance studies concerning anabolic hormones. Secondly, you mentioned the influence of a previous nitrogen depletion. It was shown from carcase analyses that the nitrogen content of the body without fat does not fluctuate.
very much. The body may be depleted in “metabolic protein”, but during our balance studies we could not observe any marked changes in serum protein. Nevertheless, I agree with you that the body may be in another “state” following a period of starvation than after a period of positive nitrogen balance. With a view to preventing any great change in the nitrogen and calcium equilibrium we always chose a diet close to the diet of the test subject’s home diet. This constant diet had to be taken for some weeks before we commenced our balance studies. In order to eliminate the influence of the time factor during the study we used to change in the various experiments the order of the substances being tested and where possible we employed the A-B-A method in each balance study.

Tausk: In fairness to the other speakers on this programme I would ask you to be fairly brief in your further remarks. Have you any other questions or remarks?

Nowakowski: I have two short questions with regard to your studies with ethylestrenol and with nortestosterone decanoate. In the two cases where you did not see a rise in calcium retention, as far as I could see, you gave a rather low calcium intake with the food. Do you believe that this explains why you did not see an effect with ethylestrenol? Because, in my experience which is particularly with a combination of androgens and estrogens, the effect on calcium retention depends on the intake. Many patients have a negative calcium balance before they receive the hormones and sometimes one is unable to make it positive unless they are supplied with sufficient calcium in their food.

The second point is with regard to the anabolic effect of Orgabolin. As far as I could see from your diagrams, you observed a nitrogen retention with 3 mg per day and you observed the same calcium retention with 15 and 20 mg per day. So therefore I can see no difference in the dosage. As far as my experience goes, I have not seen nitrogen retention using 5 or 6 mg ethylestrenol daily.

Van Wayjen: The low calcium intake is partly due to the fact that we tried to choose a diet for each patient that was as similar as possible to their diet at home. Most of these patients, especially the patients with rheumatism, had a rather low calcium intake at home. When you supply a very high calcium intake (higher than the subjects have at home) they usually change to a marked positive calcium balance. The evaluation of the anabolic drugs is then of course very difficult. I admit you must give an amount of nitrogen and calcium, that exceeds the daily minimum. We saw that 400 mg calcium per day was sometimes sufficient, but in osteoporosis cases we usually gave 800 and 1000 mg per day. Of the relation between dose and nitrogen retention with Orgabolin I cannot give you an answer. There seems to be a discrepancy between your results and ours.

Tausk: Perhaps Prof. Nowakowski was a little bit unlucky, because he had some poor reactors too. Or have you any other evidence that they were good reactors? I mean by this, that you said you had two cases on whom you carried out balance stu-
...dies; you gave low doses of ethylestrenol and saw very little or no effect on the nitrogen balance. Now Dr. van Wayjen has shown that in his group of patients there were some whom he termed poor reactors as they did not respond very well to these anabolic steroids. So I wonder whether perhaps you were a little unlucky in the selection of just two cases or do you have some evidence (for example from injection of other steroids) which shows that they were good reactors.

**Nowakowski:** I have also seen patients who have not reacted to anabolic steroids but the incidence of these patients is very low. Most of the patients we tested reacted well.

**Van Wayjen:** I have said already that you must give higher doses in balance studies than are ordinarily given. In the case of Deca-Durabolin we usually gave 100 mg. It is indeed remarkable that we saw an effect with such low doses of ethylestrenol.

**Ijzerman:** I should like to ask Dr. van Wayjen whether it would be advisable to try a large number of cases in these balance studies with these new oral compounds, against prednisolone, in prednisolone-treated patients. It is quite evident from the whole series of graphs which you have shown us that in those cases where you used the injectable anabolics in patients treated with prednisolone, the effects were better, more clear-cut and easier to interpret than in the cases where you used healthy volunteers, (perhaps with one exception), or patients with a gastrectomy or patients who were not in a clear negative balance before you started treatment. I think that the effects are far better controlled if these studies are carried out in patients treated with corticoids.

**Van Wayjen:** Yes, I agree very much and it is a pity that we could not perform more of these investigations. We planned metabolic studies in rheumatic patients with a combination of prednisolone and low doses of Orgabolin. One of these is still in progress but unfortunately I cannot show you the results yet.

**Kopera:** As regards the relation between the dosage used and the response of the nitrogen retention I think one has to bear in mind that there is probably a maximum effect which cannot be exceeded. This maximum effect is achieved with say 5 or 10 mg ethylestrenol and even if the doses are raised to 15 mg or more the effect cannot be further increased. This might be the reason why no increase in N-retention was seen with 15 mg compared with that of 5 mg.

**Tausk:** Well, in animal studies of course we try to establish a dose response curve and then we make sure that we are on the steep part of the curve.

**Prader:** What Dr. Kopera said has been well documented for methandienone. The dose response curve is very steep and then becomes flat with increasing dosage.

**Overbeek:** I would like to add that this proves that it will be extremely difficult in the human to find real dose response curves. This is certainly the case, as Dr. Prader said, when you have a very steep curve. Then the small differences in sensitivity will make it impossible to see any difference since the maximum is reached very quickly.
The only possibility would be to give the \textit{same} patient varying doses but this presents some practical difficulties. Whereas if you give \textit{different} patients different doses you have very little chance to observe differences in response. Fortunately, with our animals we are in a pretty good position.

\textit{Tausk:} Well Gentlemen, I am afraid we are already half an hour behind our schedule and as usual it is the fault of the chairman when the meeting is not on time. I hope however you will forgive me. There were so many interesting questions and it was such a pleasant discussion that I would have felt ashamed if I had interrupted it. I think we should now close for our coffee-break and I propose that we meet here again at 11.15.