

METABOLIC EFFECTS OF ANABOLIC STEROIDS*

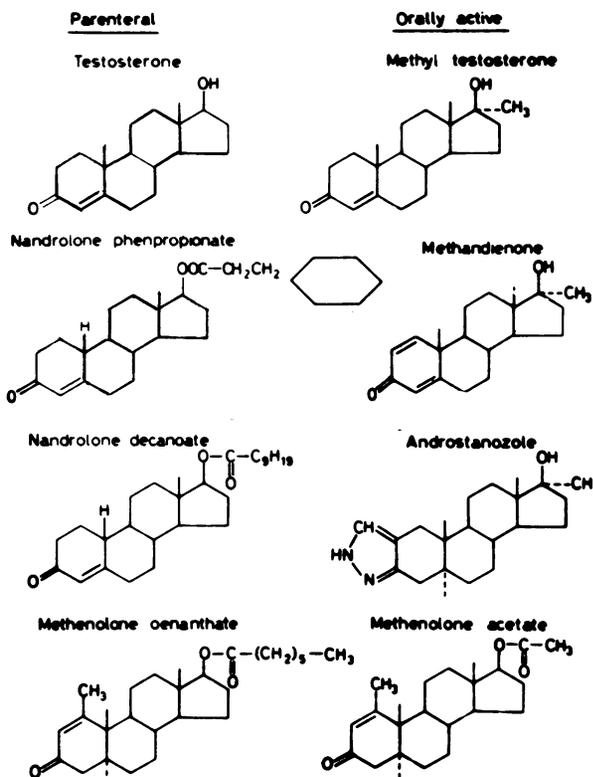
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Everyone is familiar with the rapid weight gain which occurs in both boys and girls with the onset of puberty. At this time there is also a spurt in the rate of growth. These effects are brought about by increased secretion of the sex steroids, testosterone in males and oestrogen and progesterone in females, which occurs at puberty and is maintained thereafter. The physical difference between men and women is also fairly well recognised by most people. The more muscular male owes this mainly to testosterone. The female curves, mainly due to adipose tissue, are an oestrogen effect. The protein anabolic effect of testosterone is well recognised and can be exploited therapeutically. The term 'anabolic' implies that the substance under consideration is being synthesized and stored. In the context of today's discussion the term 'anabolic steroid' refers to compounds which increase the production of protein in the body. Testosterone is the most powerful of the anabolic steroids in humans and as already mentioned, is responsible for the greater muscle mass of men compared to women. Women who are given testosterone develop masculine characteristics, namely increased muscle mass, beard growth, greasiness of the skin, deepening of the voice, loss of hair from the scalp and other changes which need not be referred to here. These latter effects are referred to as the virilising action of testosterone. In the adult male who is secreting normal amounts of testosterone, additional amounts given by injection do not produce virilising effects, but testosterone may be anabolic if enough is given and the individual may gain weight and increase his muscle mass. Women are more sensitive to the effects of testosterone and it cannot be given for any significant length of time without producing both anabolic and virilising effects.

Much of the action of testosterone is lost if it is taken by mouth and consequently testosterone, if it is employed therapeutically, is usually given by injection. An orally active form of testosterone, however, can be produced by a simple chemical modification, described below.

A further modification of testosterone can be made which renders the compound less virilising while preserving its anabolic action. Thus, it is possible, by chemical changes, to produce compounds which are both active when taken by mouth, and strongly anabolic, but with reduced virilising action. These compounds are the com-



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Fig. 1

monly used and abused anabolic steroids. Figure 1 shows the chemical structure of some anabolic steroids. The compound at the top lefthand is testosterone, the natural hormone, that is anabolic, virilising, largely inactive if given by mouth and needs to be given by injection.

On the top righthand part of the figure the closely related compound, methyl testosterone, an orally active form. Oral activity is conferred by a simple chemical modification, the insertion of an alkyl group in the 17-alpha position, referred to as 17-alpha-alkyl substitution. Most orally active steroids, whether they are anabolic steroids or oral contraceptives, have a similar chemical modification.

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This modification of testosterone not only produces an orally active compound which has the anabolic and virilising action of testosterone, but most significantly and, in my opinion, dangerously, it confers metabolic actions on this compound which are not possessed by the original hormone. This orally active compound, methyltestosterone, produces structural changes in the liver and in the liver's function which can be dangerous and even fatal.

A second modification renders the orally active methyltestosterone less virilising. It is the reduction of the steroid A ring in the 1/2 position. This compound, methandianone, or Dianabol (CIBA), is a widely used anabolic steroid. It possesses all the actions of methyltestosterone but is less virilising and can therefore be used by women who want the anabolic effect without the moustache, beard, hoarse voice etc. that goes with the use of methyltestosterone. I would stress, however, that Dianabol has all the metabolic disadvantages of methyltestosterone and after lengthy use is dangerous, as described later.

The removal of the 19-methyl group produces the so-called 19-nor steroids. This modification renders testosterone less virilising while retaining the full anabolic action. The compound illustrated here does not have a 17-alpha alkyl substitution and it is therefore necessary to give it by injection, so this compound is an injectable form of anabolic steroid. It produces an increase in muscle mass but is less virilising than testosterone. I would like to stress that as far as our investiga-

tions have gone the injectable forms of the anabolic steroids, whether testosterone or modifications of testosterone, have far fewer unwanted effects than the orally active class of compounds.

Let us look briefly at the anabolic effect produced by Dianabol in an underweight individual. Figure 2 shows a metabolic balance study carried out in an underweight girl consuming 3,000 calories a day on a high protein diet. She suffered from self-inflicted emaciation. For the first 10 days there was only a weakly positive nitrogen balance, but when the anabolic steroid, methandianone, or Dianabol, was used the positivity of the nitrogen balance increased at least threefold and persisted for the 34 days of the drug's administration. There was an associated satisfactory gain in weight. When the drug was withdrawn the positive nitrogen balance ceased and no further weight gain occurred. These data show clearly the powerful anabolic effect of the steroid in this patient. A similar effect is shown in a second patient, figure 3. This was a boy of 16 who was considerably underweight as the result of self-induced emaciation. Again the same effect is shown. On a 4,000 calorie a day diet and a very high protein intake there was only a modest positive nitrogen balance for the first 12 days of the study. When the anabolic steroid Dianabol was given there was also a threefold increase in the positivity of the nitrogen balance which persisted for the next 26 days while the drug was given. There was a very satisfactory gain in weight. When the drug was withdrawn weight gain ceased and the nitrogen balance became zero. Here again the patient exemplified a strongly anabolic effect of this orally active anabolic steroid.

Fig. 2

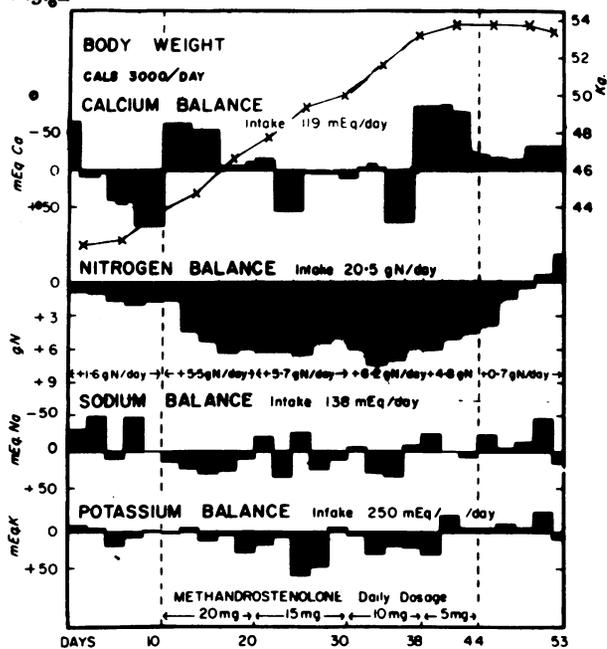
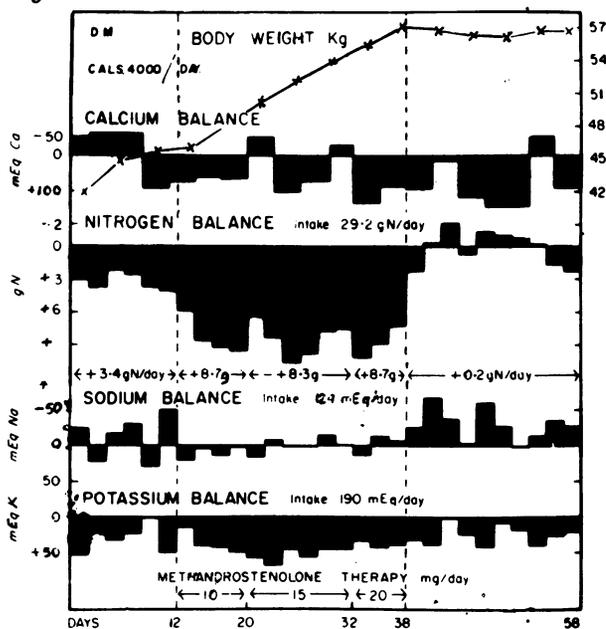


Fig. 3



With anabolic steroids there are unwanted side effects. The injectable forms of anabolic steroids produce few unwanted effects unless large amounts are given, in which case in women virilisation will occur. It is quite a different matter, however, with the orally active anabolic steroids. These show a host of unwanted effects and should really be regarded as highly dangerous compounds which should not be used except under careful medical supervision and even then they have only a restricted place in therapy. The orally active anabolic steroids are hepato-toxic and cause cholestatic jaundice. Long continued use may be associated with liver tumours, including cancer (Farrell 1975). It is, however, the potential atherogenic risk of these compounds that I wish to stress. The accelerated development of atherosclerosis which leads to heart disease, stroke and peripheral vascular disease can be anticipated when drugs cause disturbances in carbohydrate and lipid metabolism. The orally active anabolic steroids do this.

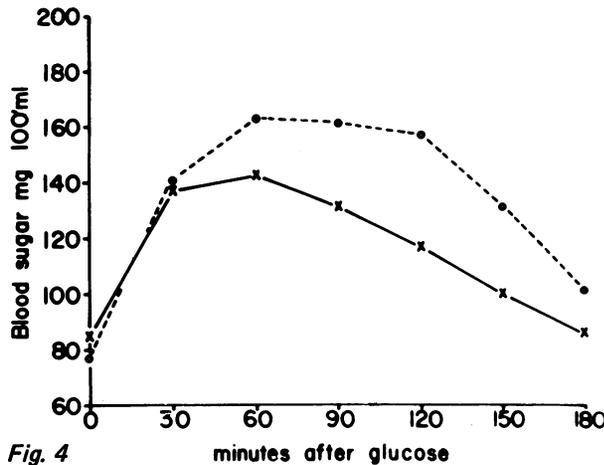


Figure 4 shows the effect of the orally active anabolic steroid, Dianabol, on oral glucose tolerance in a group of 10 healthy subjects. The drug produces a decided deterioration in glucose tolerance associated with a significant fall of the fasting blood sugar.

Figure 5 shows that intravenous glucose tolerance is significantly impaired by anabolic steroids such as Dianabol, in the same group of subjects. The mechanism of the impaired oral and intravenous glucose tolerance is not understood fully but is associated with marked insulin resistance as shown in Figure 6. In a group of 7 healthy subjects treated with 10 mg. a day of the anabolic steroid, Dianabol, a relatively low dose and much less than would be used for example by a male athlete wishing to gain weight, there is deterioration of the oral and intravenous glucose tolerance and, most strikingly — a marked increase in insulin secretion associated with the use of this compound. One cannot look at this with

Fig. 5 The effect of methandienone on the intravenous glucose tolerance test.

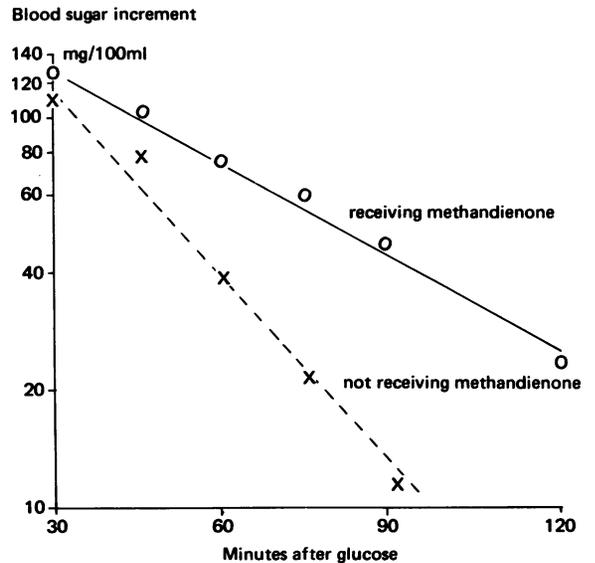
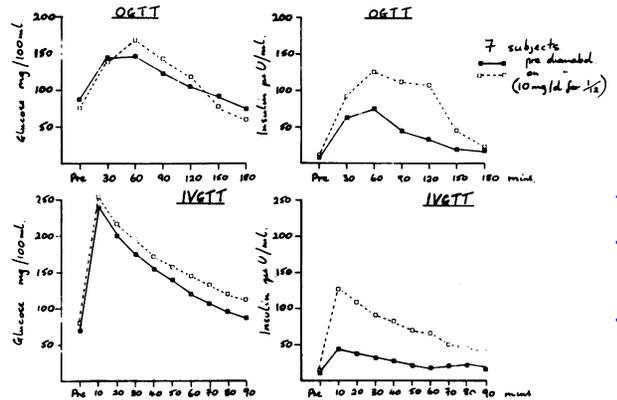


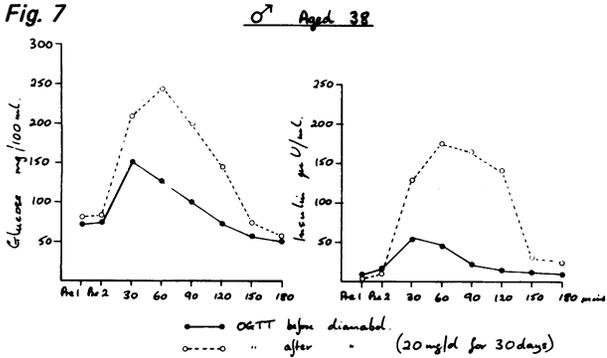
Fig. 6



equanimity. Hyperinsulinism has been identified as a significant risk factor in the development of atherosclerosis, especially of the coronary arteries. The use of orally active anabolic steroids causes an unacceptable degree of hyperinsulinism. In Figure 7 one can note the interference with glucose tolerance which occurred in a healthy male aged 38 taking 20 mg. of Dianabol for 30 days. Not only was he rendered diabetic as judged by the glucose tolerance test, but his insulin secretion was very greatly increased. It should be stressed that these metabolic changes may be symptomless although that does not mean that they are without longer term significance.

Anabolic steroids exert profound effects also on lipid metabolism; hypertriglyceridaemia and hypercholesterol-

Fig. 7



aemia have been identified as being risk factors predisposing to the development of ischaemic heart disease.

Fig. 8

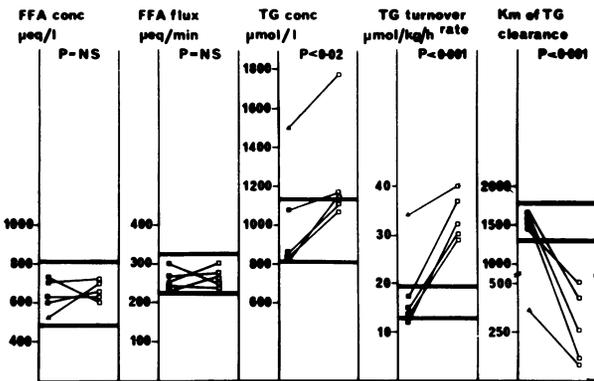


Figure 8 shows the results of a study on the kinetics of triglyceride metabolism carried out on five female volunteers who were given a small amount of Dianabol. One can see that there was a significant increase in the plasma triglyceride level, but more importantly there was a trebling of the rate of production of triglyceride. At the same time there was an increase in the rate of removal of both endogenous triglyceride as demonstrated by the fall in the Km, and exogenous triglyceride as shown in the next figure 9 which shows on the left hand side, the removal rate (K_2) of an intravenous load of a fat emulsion (intralipid). It can be seen that Dianabol increased the K_2 in all subjects, and that this was associated with a significant rise in post-heparin lipolytic activity, which reflects the activity of the enzymes involved in the removal of triglyceride from the plasma in the peripheral tissues. The predominant effect of Dianabol upon the kinetics of triglyceride metabolism, however, was to increase triglyceride production as, in spite of the enhanced triglyceride removal, the circulating plasma levels of triglyceride were raised.

Carbohydrate and triglyceride metabolism are closely interrelated. Insulin increases the conversion of glucose

Fig. 9

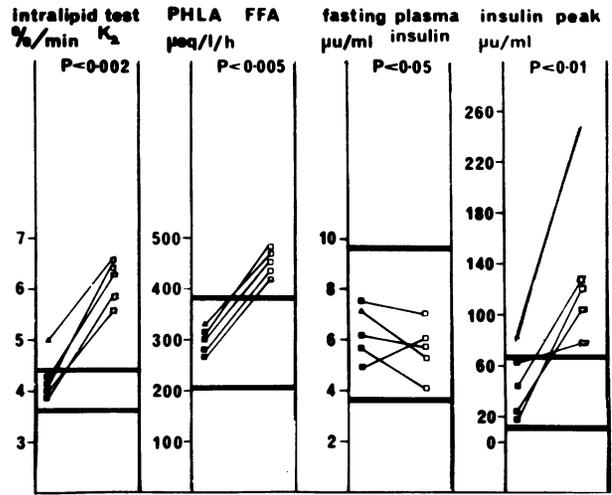
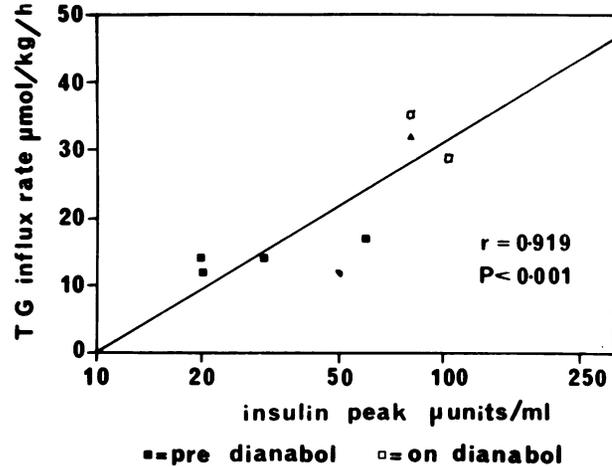


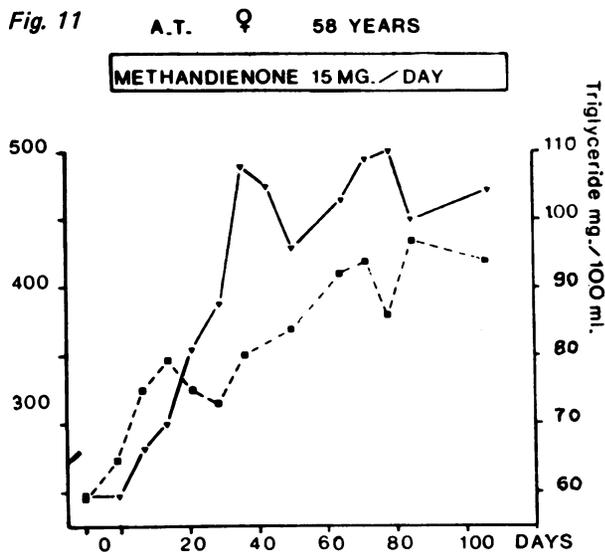
Fig. 10



into triglyceride precursors. Figure 10 shows the close correlation between the peak plasma insulin responses observed during an oral glucose tolerance test and the triglyceride production rate in the five female volunteers studied before and then during Dianabol administration, and that hyperinsulinism, as induced by Dianabol, is associated with the highest rate of production of triglyceride.

While it may superficially seem to be satisfactory that a drug could increase both the production and removal of triglyceride there are theoretical reasons why this is really not an acceptable metabolic effect. Increased triglyceride production disturbs the metabolism of cholesterol and in susceptible individuals this may well lead to elevated cholesterol levels and atherosclerosis. The last figure, 11, shows such an effect occurring in a

Fig. 11



woman with maturity onset diabetes. Dianabol 15 mg. per day produced a striking rise in serum cholesterol from 250 mg% to 500 mg%.

The serum triglyceride also rose. No one could doubt the great risk to the patients of such a change in serum lipids. As yet we have found this effect in more than 10 subjects predisposed to this abnormality — namely people who already have a mild glucose intolerance — the sort of abnormality which could exist in anyone without obvious symptoms. These data will serve to draw attention to the subtle and potentially harmful effects of orally active anabolic steroids. These effects are not shown by the injectable steroids but these are less active than the oral forms and inconvenient to use.

In conclusion, I would like to stress that in my view there is no justification for the use of orally active anabolic steroids by healthy subjects. They have a very restricted medical usefulness and their use requires close supervision by the doctor.

REFERENCES

Farrell, G. C. (1975), Androgen-induced Hepatoma, *Lancet*, 1, 430-431.