

## "ANABOLIC" EFFECTS OF METHANDIENONE IN MEN UNDERGOING ATHLETIC TRAINING

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**Summary** After failure to confirm an anabolic action of testosterone and its derivatives in rats, methandienone ('Dianabol', an "anabolic steroid" used by athletes) has been given to 11 athletic men during a course of weight-training, in a double-blind, crossover experiment. The dose of methandienone was 100 mg/day for 6 wk. Body weight and composition, muscular strength and performance, and indices of endocrine function were studied. Compared with the placebo period, on methandienone the subjects gained weight (mean  $3.3 \text{ kg} \pm 0.6 \text{ kg}$ ) and accumulated a disproportionately large amount of potassium ( $420 \pm 68 \text{ mmol}$ ); the increase in weight was confined to the lean part of the body, and the muscles increased in size. Strength and performance improved over each training period, but not significantly differently on drug and placebo. On the drug, plasma-cortisol concentration and urinary cortisol excretion increased, and plasma-testosterone decreased. Although the weight and body-composition changes may demonstrate an anabolic action of methandienone in man, they may alternatively have been caused by an increase in intracellular fluid, and the question of anabolic action therefore remains open.

### Introduction

THE concept of a class of drugs known as "anabolic steroids" has been generally accepted. It is based on the report of Kochakian and Murlin<sup>1</sup> that the hormone testosterone possesses an "anabolic" action and later

reports that synthetic analogues of testosterone, which have become known as the anabolic steroids, have essentially only this action.<sup>2</sup> Since the early 1960s anabolic steroids have been taken by athletes with the intention of increasing muscle size and strength. The extent of such use is probably substantial.<sup>3,4</sup> Athletes take the drugs in doses which may be ten times greater than are used in medicine. Many athletes believe that the introduction of steroids led to a marked improvement in athletic performance.<sup>5</sup> This belief, in conflict with considerations of sporting ethics, possible harmful effects, and the efforts of administrative bodies to ban the use of steroids, creates a dilemma for athletes.

The concept of an anabolic action of testosterone is *prima facie* reasonable, but the original evidence for it is open to criticism. Anabolism means increase in the amount of the body's normal lean tissue. Where whole animals were studied, the body-weight records do not in fact show sustained increases; change in lean tissue was assessed from urinary nitrogen excretion, which has been a misleading index in other contexts such as the weight-gains of pregnancy<sup>6</sup> and progesterone treatment;<sup>7</sup> carcass analyses were seldom reported. The bulk of pharmaceutical research relied on the "rat levator ani" assay; this, although convenient, tests a clearly sexual structure, also known as the dorsal bulbocavernosus, and does not reflect the changes in weight of striated muscles or of the body generally.<sup>8</sup> In controlled experiments based on carcass analysis Hervey and Hutchinson<sup>9</sup> could not find any circumstances in which giving testosterone or anabolic steroids led to maintained weight-gain, nor did they find any evidence for anabolic action, in adult rats of either sex, entire or gonadectomised. In the rat the role of testosterone in producing larger body-size in males seems to be exerted early in life, in a way comparable to the determination of subsequent gonadotrophin release patterns and sexual behaviour.<sup>10</sup>

The existence of an anabolic action in man, therefore, is actually inconsistent with the animal evidence. A number of researchers have tried to test the effect in humans, sometimes using controlled "blind" trials, and always "clinical" doses of the test compounds. Some conclude that the drugs do help athletes to increase their strength<sup>11</sup> or body-weight<sup>12,13</sup> or both,<sup>14-19</sup> others report no effect.<sup>20-22</sup> Side-effects have been noted.<sup>22,23</sup> The effect of body-composition has not been much studied: Munson<sup>13</sup> found weight-gain was accompanied by reduction in skinfold thickness; Johnson et

al.<sup>17</sup> and Freed et al.<sup>19</sup> found weight-gain without change in skinfold thickness; Casner et al.<sup>12</sup> found no change in body-density; Ward<sup>15</sup> found density increased.

The present trial was planned to use a double-blind, crossover design to examine the effects on men in athletic training of taking one of the commonly used drugs in a dose typical of those used by athletes. The primary emphasis was on measurement of body composition; selected indices of athletic performance and endocrine function were also recorded.

### Subjects and Methods

The subjects were male volunteers aged 19–25 years, weight range 63.5–91.2 kg and height range 1.69–1.92 m. All were studying physical education in a teacher training course. They embarked on a standardised programme of weight-training and trained for 2 weeks without medication. Then half of them began taking 100 mg methandienone ('Dianabol') per day and the others took an indistinguishable placebo. After 6 weeks all subjects stopped training and medication for 5 weeks, then trained for 1 week without medication and then undertook 6 more weeks of training and medication with the treatments crossed over.

At the beginning and end of each 6-week training period the following measurements were taken: plasma concentrations of growth hormone (G.H.), follicle-stimulating hormone (F.S.H.), luteinising hormone (L.H.), and testosterone (by radioimmunoassay), and cortisol (by protein-binding assay); urinary cortisol; body composition and athletic performance were also assessed at these times. Before and during the study blood-pressure and plasma bilirubin, glutamic-pyruvic transaminase (G.P.T.), and glutamic-oxaloacetic transaminase (G.O.T.) were measured.

Full details of the subjects and methods are available from the authors.

### Results

Table I shows the initial values and changes in body measurements over control and drug treatment periods, and the significance of the differences between the changes in the two periods. Body-weight increased significantly on steroid treatment, by a mean of 3.3 kg (S.E.  $\pm 0.6$  kg). Total body-potassium also increased significantly, by 420 mmol ( $\pm 68$  mmol). So also did muscle widths as seen by X-ray, and limb circumferences. On the other hand body-density, aggregate skinfold thickness by caliper, and fat-width as seen by X-ray did not change significantly. None of the measurements changed significantly over the period on placebo.

TABLE I—INITIAL VALUES AND CHANGES IN BODY MEASUREMENTS DURING THE TWO PERIODS OF 6 WEEKS

Body measurement	Control period		Drug period		Difference between changes
	Initial value	Change	Initial value	Change	
Body-weight (kg)	77.7	-0.2	76.8	+ 3.3†	†
Total body potassium (mmol)	4659	-72	4552	+420‡	†
Body density (kg m <sup>-3</sup> )	1073.0	-1.0	1072.6	-1.8	N.S.
Sum of four skinfold thicknesses (mm)	26.3	0.0	26.4	-0.8	N.S.
Sum of three muscle widths (mm)	302.5	+ 4.3	300.7	+15.3‡	•
Sum of three fat widths (mm)	36.9	-0.6	38.2	-1.5	N.S.
Arm circumference (mm)	308.6	+ 0.3	307.0	+13.3‡	•
Thigh circumference (mm)	570.1	-1.2	566.0	+13.4†	•
Calf circumference (mm)	374.5	-0.8	371.6	+ 8.0‡	†

All values are means of 11 paired data.

• Changes significant at the 5% level; †, 1% level; and ‡, 0.1% level (also for tables II and III).

TABLE II—INITIAL VALUES AND CHANGES IN CALCULATED BODY COMPOSITION

	Control period		Drug period		Difference between changes
	Initial value	Change	Initial value	Change	
<i>F.F.M. calculated from:</i>					
Potassium	70.2	-1.1	68.5	+6.3‡	†
Density	68.8	-0.4	67.9	+2.4†	†
Skinfolds	69.1	-0.1	68.3	+3.5‡	•
<i>Fat calculated from:</i>					
Potassium	7.6	+0.8	8.0	-2.5	N.S.
Density	8.9	+0.2	8.9	+0.9	N.S.
Skinfolds	8.6	-0.1	8.5	+0.1	N.S.

All values are in kg.

TABLE III—INITIAL AND FINAL VALUES OF HORMONE MEASUREMENTS DURING THE TWO PERIODS OF 6 WEEKS

Hormone	Control period		Drug period		Difference between changes
	Initial value	Final value	Initial value	Final value	
Plasma-cortisol (nmol/l)	324	356	290	401*	N.S.
Urine cortisol (nmol/24 h)	221	196	248	452*	†
Plasma-testosterone (nmol/l)	19.9	17.5	19.6	8.1†	•
Plasma-F.S.H. (I.U./l)	3.4	3.2	2.9	2.3	N.S.
Plasma-L.H. (I.U./l)	19.8	18.2	18.1	15.4	N.S.
Plasma-G.H. (mU/l)	6.1	7.3	7.3	8.6	N.S.

Each value is the mean of 8 paired determinations.

Table II shows the initial values and changes in fat-free mass (F.F.M.) and fat, calculated from total body potassium, body weight and density, and body-weight and skinfold thickness. Results from all three methods indicate that F.F.M. increased significantly on steroid treatment, according to the computations by between 2 and 7 kg; and that body fat did not change significantly.

The subjects' performances in the weight-training exercises improved significantly over both training periods, but the improvement when the steroid had been given was not significantly greater than that over the control period. There was no significant improvement in the peak force exerted on the force platform during a standing jump, or in maximum oxygen uptake, over either period. Full details of the subjects' athletic performance are available from the authors.

Table III shows the result of the hormone measurements. Plasma-cortisol increased significantly over the treatment period and non-significantly over the control period, and the difference between the changes was not significant. The 24 h excretion of cortisol, however, almost doubled over the treatment period and this change was significantly different (at the 1% level) from the insignificant change over the control period. Plasma-testosterone decreased significantly over the treatment period, but the final values were clinically abnormal in only two subjects; the precision of this assay, however, was unusually low, and the drug may have interfered with it. Some earlier measurements suggested that plasma F.S.H. and L.H. also decreased, but in the final experiment the difference between control and treatment groups was small and not significant. Plasma-G.H. did not appear to change.

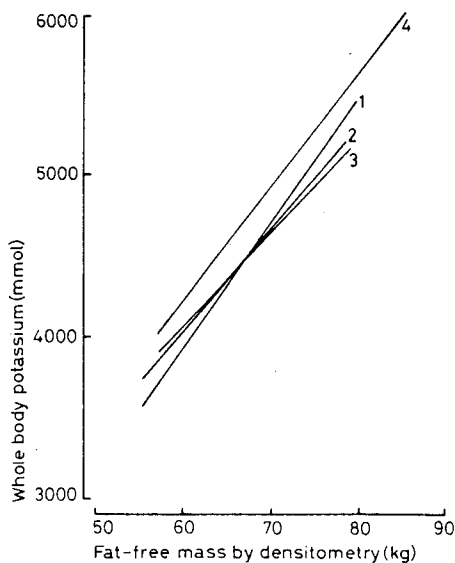
Regular clinical examination showed no changes of consequence in general health, blood-pressure, or plasma concentrations of proteins, alkaline phosphatase, bilirubin, G.P.T., or G.O.T.

### Discussion

The results confirm the widely held belief that anabolic steroids cause weight-gain in young men undertaking regular but unaccustomed weight-training. They are thus in contrast with Hervey and Hutchinson's<sup>9</sup> findings for unexercised rats. The gain in weight appears to have been in the fat-free part of the body, since density, skinfold thicknesses, and thickness of subcutaneous fat measured radiographically showed no consistent changes, and estimations of F.F.M. from potassium, density, and skinfold thickness all showed marked increases. The increase in muscle width on radiographic measurement further localised the weight-gain to the muscles.

On the other hand, the results did not support the belief that anabolic steroids increase strength and performance. Although the subjects increased their weight-lifting performance over each period of training, the improvement was not significantly greater on the drug than on the placebo, and was rapidly lost between periods of training. We thus agree with previous negative reports.<sup>21 22</sup> We also agree with others<sup>13 17 22</sup> in finding no change in maximal oxygen uptake. Freed et al.<sup>19</sup> suggested that gain in strength was seen when steroids were given in clinical doses to trained subjects eating high-protein diets; we made no attempt to control or assess diets, but these undoubtedly provided an excess of protein over maintenance requirements, and there is no evidence that very high protein intake promotes anabolism.

The increase in total body potassium by 420 mmol, measured by a direct and reliable method, was striking. The gain in F.F.M., calculated from this on the assumption of a constant concentration of potassium in the F.F.M. of 66.6 mmol/kg, was, however, 6.3 kg, 3 kg more than the gain in body-weight. If the subjects had lost 3 kg of fat, this would have been evident in the skinfold thickness, which would have changed by about -8



Regression lines of total body potassium on F.F.M. calculated from body-density at the beginning and end of the control period (lines 1 and 2) and at the beginning and end of the steroid period (lines 3 and 4).

Statistical analysis shows that data groups 1 to 3 could be represented equally well by a single line, but a separate line is required for group 4.

mm, whereas the observed change was only  $+0.8 \pm 0.7$  mm. Alternatively, the overall concentration of potassium in the F.F.M. may have increased; the regressions of total body potassium on the estimates of F.F.M. from density are suggestive of this (see accompanying figure). This could reflect an increase in intracellular potassium concentration in the F.F.M., and/or an increase in the amount of a particularly potassium-rich component of the F.F.M. The latter could be muscle, and we have radiographic evidence that muscles did increase in size. If the whole weight-gain of  $3.3 \pm 0.6$  kg were muscle of normal composition—i.e., containing about 90 mmol potassium/kg— $300 \pm 54$  mmol total gain of potassium would be expected. If, however, the gain was intracellular water, containing about 160 mmol potassium/l, the total gain of potassium would be  $530 \pm 96$  mmol. The observed value is of the right order for either of these possibilities, but does not distinguish between them.

A high dose of a steroid might cause increase in intracellular potassium accompanied by water. Casner et al.<sup>12</sup> suggested that their subjects' weight-gain might have been due to water retention, since they (like ours) showed no increase in strength; Munson<sup>13</sup> and Freed et al.<sup>19</sup> repeated the suggestion without further evidence. Direct measurement of body nitrogen content might resolve the important question whether muscle protein is increased. If the evidence from rats, which led to the introduction of anabolic steroids into human use, was unsound, it would be remarkable if the anabolic action nevertheless does occur in man.

The increase in cortisol excretion might reflect increased production, decreased catabolism, or changes in plasma-binding or renal handling. The increase in plasma-cortisol, if accepted as real, could account for the rise in excretion, and reduces the possibilities to increased production, or, as has been suggested by James et al.<sup>24</sup> and Linet,<sup>25</sup> decreased catabolism due to the anabolic steroid competing for metabolic pathways. In either case the observation may be relevant to the belief, expressed by some athletes, that the value to them of taking anabolic steroids lies in reduction of fatigue during the training period, which allows more training to be done; and also to the subjective impression that some athletes, particularly participants in "heavy" events such as shot-putting, show changes in appearance which resemble those of Cushing's disease. Reduction of plasma-testosterone is not surprising, for large doses of anabolic steroids may be expected to have sufficient androgenicity to suppress gonadotrophin output, although this was not demonstrated.

The effects of any steroids taken in large doses are likely to be complex. Athletes who take anabolic steroids may experience diverse actions which we have not attempted to measure—e.g., on the central nervous system. In a few sports they may desire increase in body-weight irrespective of the composition of what is gained. There are also undoubtedly possibilities of harmful effects.<sup>23 26 27</sup> We believe, however, that the existence of an anabolic action, which must be the principal basis for consumption by athletes, should be regarded as an open question.

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## CARDIOPULMONARY RESUSCITATION BY LAY PEOPLE

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**Summary** The survival-rate in 75 of 631 patients with cardiac arrest in whom resuscitation was started outside hospital by lay people was 36%. Only 8% survived when attempts at resuscitation were delayed until the arrival of an ambulance team which included an anaesthetist and a specially trained nurse. These data show the importance of anoxia-time (time from cessation of circulation to initiation of resuscitation) to the chances of survival after resuscitation, and support the idea that lay people should be taught and encouraged to perform cardiopulmonary resuscitation.

### Introduction

THE anoxia-time is one of the most important factors (besides underlying pathology) determining the outcome of a resuscitation, and it is defined as the interval between the cessation of the heart beat and the initiation of resuscitation.

About 60% of deaths from coronary heart-disease take place outside of hospitals. This is because many patients who have an acute heart-attack die suddenly and

often unexpectedly. Thus, prevention of unnecessary deaths—i.e., reaching patients who could be saved by resuscitation—is a problem which must also be tackled outside hospitals.

We found that immediate attempts at resuscitation of patients with cardiac arrest from acute coronary heart-disease by lay people increased the chances of survival in such patients.

### Methods

Of 631 patients in whom resuscitation was attempted by the crew of a special ambulance service run by the department of anaesthesia at Ullevål Hospital, fairly reliable information about the anoxia-time was established in 526 patients. This information came from two sources: statements from people who had witnessed the accident; and accurate records of the duration of ambulance runs.

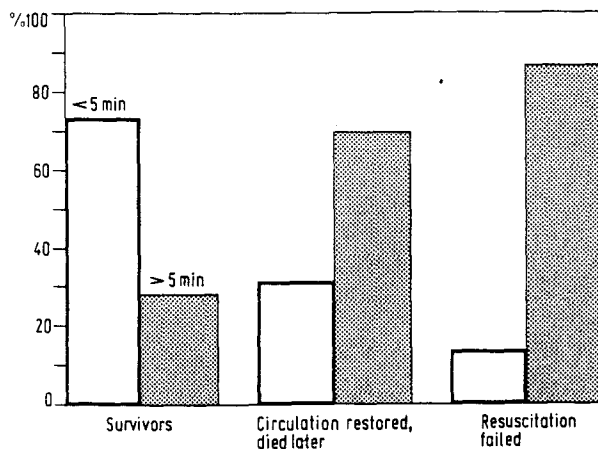
### Results

When the anoxia-time was less than 1 minute, 61% of 59 patients survived to be discharged from hospital. Of the patients in whom anoxia-time lasted from 1 to 5 minutes, 17% survived. When the anoxia-time lasted from 5 to 10 minutes the survival-rate was only 9%. Only 2 (1%) of 218 patients whose anoxia-time exceeded 10 minutes survived.

Division of the patients into two groups according to whether the anoxia-time lasted less than or more than 5 minutes demonstrated the advantage of initiating resuscitation immediately (see accompanying figure).

70 patients (11%) out of the 631 survived to be discharged from the hospital. 376 did not respond to resuscitation. 185 patients in whom circulation was restored later died in hospital. Thus, a total of 561 patients did not survive (table I).

8 of the 70 patients who survived and left hospital had severe cerebral damage after resuscitation. 6 others had symptoms of slight cerebral dysfunction, but they could resume their previous activities (table II). 2 patients who had been resuscitated by lay people were among those with brain damage. Both had had an anoxia-time of less than 1 minute. 1 of these patients received only external cardiac compression and severe brain damage developed. The other was resuscitated with an apparently satisfactory technique, but his memory was



Anoxia-time in survivors, patients in whom circulation was restored, but who eventually died in hospital, and patients who did not respond to resuscitation.