AN ANABOLIC STUDY WITH NORETHANDROLONE IN FOUR ELDERLY UNDERWEIGHT MALES

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It has long been recognized that a substance which would bring about increased protein tissue synthesis in the body would be of considerable value to the clinician. The search for such a substance has been in progress for many years, and most of the work has been concerned with the steroid testosterone and its derivatives (Drill and Saunders, 1956). Testosterone, an androgen, was known to have powerful protein anabolic properties, but unfortunately the androgenic effects of this hormone regularly occur when the dose is sufficient to promote protein synthesis. This fact makes testosterone unsuitable as an anabolic agent except for very short periods of treatment. It seemed logical to make modifications of the testosterone molecule in an attempt to dissociate the androgenic from the anabolic property. Early experiments in this direction indicated that a significant degree of separation of the two activities of the androgens was possible.

Amongst the modifications investigated were methyl-testosterone, testosterone propionate, and a number of 19-nortestosterone compounds. The 19-nortestosterone compounds appear to be by far the most satisfactory, having a relatively low androgenic potency and yet retaining the high anabolic potency associated with testosterone itself (Hershberger *et al.*, 1953; Barnes *et al.*, 1954). A substance with a very high anabolic/androgenic ratio is the steroid norethandrolone (17 α -ethyl-19-nortestosterone). In animal studies it was shown to possess only about 6% of the androgenic potency of testosterone propionate although having a similar anabolic effect (Saunders *et al.*, 1957). Much work has been carried out with this substance, and it has been shown to be anabolic for both animals and man (Weston *et al.*, 1956; Saunders and Drill, 1956; Kory *et al.*, 1957; McSwiney and Prunty, 1957).

McSwiney and Prunty (1957) carried out an intensive study of the anabolic effects of norethandrolone and reported marked nitrogen retention and either an increase in body weight or a check in the fall of weight. They also observed a tendency to calcium retention; moreover, the phosphorus balance agreed with that calculated from nitrogen and calcium balance, which is considered to be evidence that the retained nitrogen is used in the formation of lean body tissue. According to Goodman and Gilman (1955), "the most familiar example of the anabolic effect of the androgens is the rapid growth and muscular development of the adolescent male. However, this anabolic action is also prominent in elderly and cachectic individuals. It probably provides a partial explanation of the symptomatic relief

afforded by androgen therapy in certain debilitating diseases." This latter action is of particular interest since many elderly and undernourished patients fail to gain weight in hospital after treatment despite an adequate and well-balanced diet and absence of any active pathological lesion.

The object of this study was to investigate the anabolic effect of the steroid norethandrolone. Its structure and that of the parent steroid, testosterone, are as follows:

Material and Methods

Four elderly men, age range 56–80, who were awaiting admission to Part III accommodation were chosen for this investigation because they had all recovered from the illnesses for which they had been admitted but had consistently failed to gain weight on an adequate diet of approximately 2,000 calories daily, containing 75 g. of protein. All were underweight for their height.

Before beginning the investigation they were examined to exclude the presence of any active disease, and it was confirmed that in each case the renal and liver function was not impaired. Serum bilirubin, alkaline phosphatase, thymol turbidity and flocculation, gold flocculation, and plasma protein estimations were used as indicators of liver function.

In order to estimate changes in metabolism brought about by treatment with norethandrolone, the following measurements were made: (1) naked body weight daily; (2) state of nitrogen balance throughout the study; (3) total body water or urea space and extracellular water or thiosulphate space before and after treatment.

Body Weight.—This was measured at the same time each day, the same scales being used throughout.

Nitrogen Balance.—All food and fluid taken during the study was recorded and the nitrogen content assessed from standard food tables. All urine was kept and analysed in three-day lots for its total nitrogen content by the micro-Kjeldahl method. The faecal nitrogen was assumed to be 1 g. daily in all cases.

Total Body Water and Extracellular Water Volumes.—The total body water was measured by the distribution of orally administered urea (McCance and Widdowson, 1951), and the extracellular water by the distribution of intravenously administered sodium thiosulphate (Cardozo and Edelman, 1952). All urea determinations were made with the Van Slyke manometric apparatus, and thiosulphate levels were determined potentiometrically with standard potassium iodate.

Control Period.—Each patient underwent a control period of from two to three weeks on an adequate diet providing 2,000 calories and 75 g. of protein daily. During this time a record was kept of the daily body weight. When the weight was constant and the patient was in nitrogen balance the measurements of total body water and extracellular water were made.

Treatment Period.—After successful measurement of the total body water and extracellular water the treatment period was begun. Two of the cases (J. R. and H. F.) were given 30 mg. of norethandrolone daily, but this dosage was subsequently increased to 50 mg. daily. The remaining two cases (H. C. and J. McK.) were given 50 mg. of the drug daily throughout the whole of the treatment period. The total

body water and extracellular water determinations were repeated when the gain in body weight appeared to have ceased.

RESULTS

Body Weight

As can be seen from Figs. 1 and 2, in all four cases there was a marked rise in body weight within a few days of the beginning of treatment. This increase in weight continued for a varying period of time—three days for H. F., nine days for J. R., and about 14 days for both H. C. and

FIG. 1.—Diagram showing the relationship between body weight and nitrogen balance. Both cases began treatment with 30 mg. of norethandrolone daily (N3), but this was later increased to 50 mg. daily (N5).

J. McK. After this period of pronounced gain the body weight remained more or less constant. At this stage the daily dose of the drug was increased in patients J. R. and H. F. from 30 mg. to 50 mg. Within several days both patients showed a further increase in body weight, then again the body weight became more or less constant. The two patients (H. C. and J. McK.) who had 50 mg. of norethandrolone daily from the commencement of the treatment period appeared to gain weight more rapidly than did those who started with 30 mg. daily. In these patients, too, the body weight eventually reached a relatively steady state. Unfortunately, in the case of J. McK., measurements had to be interrupted owing to diarrhoea as a result of Sonne dysentery, and, although administration of the drug was continued, no body weights were recorded or urine collected until the infection was controlled.

The increases in weight, expressed as percentages of the body-weight levels during the control period, were 9% (J. R.), 4% (H. F.), 5% (H. C.), and 7% (J. McK.).

Nitrogen Balance

The state of nitrogen balance is shown in Figs. 1 and 2. Nitrogen retention is depicted by the shaded area above the balance line and nitrogen loss by shading below the line. No urines were collected where the balance line is represented by a broken line.

During the control periods all four patients were considered to be in nitrogen balance, within the limits ± 0.5 g. of nitrogen daily, but during treatment there was marked nitrogen retention in three of the cases. The fourth case

(J. McK.) shows marked nitrogen retention until the onset of his diarrhoea, and finally a second nitrogen retention as he gained weight. As expected, in all cases the strongest nitrogen retention occurred where the body weight was increasing most rapidly.

Total Body Water and Extracellular Water Measurements

Total Body Water.—As can be seen from the Table, all four cases showed an absolute increase in the total body water, although in the case of J. McK. this increase was not a significant one. The relative total body water—that is, total body water percentage of body weight—was increased in two cases (H. F. and H. C.); it was unchanged in the case of J. R. and decreased in J. McK.

The Extracellular Water.—The absolute extracellular water increased significantly in three of the four cases but was less for J. McK. The extracellular water percentage of body weight was increased slightly in two cases (J. R. and H. P.), unchanged in one (H. C.), and decreased in one (J. McK.).

Side-Effects

The drug, which was administered orally three times a day in a total dosage of 30–50 mg., was well tolerated. No patients suffered from nausea or vomiting, nor were there any noticeable androgenic effects. An increase in appetite occurred during the treatment period, and the *non-protein* portion of the diet was increased slightly to cater for it. At the time of maximum gain in weight on the 50-mg. dose all patients were fully satisfied by the amount of food, and it was noted that occasionally some was refused, though all denied having nausea and none vomited. On this evidence it is doubtful whether a further increase in dose would have been well tolerated or desirable.

In the liver-function tests repeated after treatment there was no impairment of function.

FIG. 2.—Diagram showing the relationship between body weight and nitrogen balance. Both cases had 50 mg. of norethandrolone (N5) throughout the treatment period.

Comparison of Total Body Water, Extracellular Water, and Derived Intracellular Water Values Before and After Treatment with the Steroid Norethandrolone

Patient	Age	Surface Area (Sq. m.)	Time of Measurement	Body Weight (Kg.)	Total Body Water		Extracellular Water		Intracellular Water*	
					Litres	% Body Wt.	Litres	% Body Wt.	Litres	% Body Wt.
J.R.	68	1.43	At end of control period	40.2	28.9	72	9.4	23	19.5	48
			After 42 days' treatment	43.7	31.4	72	11.0	25	20.4	47
			Difference	+3.5	+2.5	0	+1.6	+2	+0.9	-1
H.F.	56	1.35	At end of control period	39.5	26.4	67	8.1	21	18.3	46
			After 22 days' treatment	41.2	28.5	69	8.9	22	19.6	48
			Difference	+1.7	+2.1	+2	+0.8	+1	+1.3	+2
H.C.	80	1.60	At end of control period	48.4	32.8	68	11.1	23	21.7	45
			After 25 days' treatment	50.6	35.2	70	11.6	23	23.6	47
			Difference	+2.2	+2.4	+2	+0.5	0	+1.9	+2
J.McK.	77	1.56	At end of control period	56.0	29.9	53	13.5	24	16.4	29
			After 28 days' treatment	60.0	30.6	51	12.8	21	17.8	30
			Difference	+4.0	+0.7	-2	-0.7	-3	+1.4	+1

* Intracellular water volume obtained from the difference of the total body water and the extracellular water volumes (i.e., T.B.W. - E.C.W. = I.C.W.).

Discussion

The object of this study was to investigate the anabolic properties of the steroid norethandrolone in elderly underweight patients who consistently failed to gain weight on an adequate diet. From the results it would appear that this substance has definite anabolic properties. The four patients studied showed significant weight gain accompanied by marked nitrogen retention—two necessary requisites for the laying down of new lean body tissue. That this weight gain was in fact due to an increase in the lean body mass and not merely due to fluid retention should be more obvious after consideration of the total body water and extracellular water volumes before and after treatment.

Lean tissue gain is associated with an increase in both the absolute and the relative total body water values, and our results appear to follow this course. In all four cases there is an increase in the absolute total body water; there is an increase in the relative total body water in two of the cases (H.F. and H.C.), one is unchanged (J.R.), and the other (J.McK.) shows a slight decrease. The extracellular water values also support the view that the gain in body weight was lean body tissue and not merely fluid retention, since if the latter were the case we would expect large increases in the extracellular water. The increases which occurred, however, were not large, and in fact are compatible with the weight gain being totally accounted for as lean body tissue. The extracellular water percentage of body weight was increased slightly in two of the cases (J.R. and H.F.); it remained unchanged in one case (H.C.), and was slightly decreased in one (J.McK.). If the weight gain had been due to fluid retention we should have expected the extracellular water percentage of body weight to have increased by as much as 5 or 6% and not only 1 or 2% as we have found.

Fluid retention unaccompanied by an increase in the lean body mass would have had little effect, if any, on the absolute intracellular water volume. Our evaluation of the intracellular water volume—the difference between the total body water and extracellular water volumes—shows an absolute increase in the four cases studied. The intracellular water percentage of body weight is increased in three of the cases and decreased in one case (J.R.). It was unfortunate that J.McK. had acute diarrhoea during part of his treatment period, and this undoubtedly accounts for the decrease in the absolute and relative extracellular water values observed and also for the decrease in the relative total body water. Nevertheless, the increase in the intracellular water volume, together with the marked increase in body weight, shows that in this patient too an increase in the lean body mass occurred.

These results, together with the marked nitrogen retention, indicate that the gain in weight results from an increase in lean tissue and is not due to simple fluid retention. It appears, therefore, that the steroid norethandrolone is an

effective protein tissue-building substance which is well tolerated and has little or no androgenic effects in these aged patients at a dosage of up to 50 mg. daily. According to McSwiney and Prunty (1957), 50 mg. of norethandrolone daily is as effective as 100 mg. Our investigation shows that 30 mg. does not produce the maximum anabolic response (Fig. 2), since a higher level of weight resulted from the administration of 50 mg. daily. The tendency to anorexia observed towards the end of the course suggests that a larger dose might cause nausea and vomiting in patients of the age group and sex investigated in this study.

We were not able to measure the body weight in the immediate post-treatment period, since the subjects were anxious to leave hospital after their prolonged stay, but the two we were able to follow (J.R. and H.C.) have maintained and subsequently increased their weight after seven months. McSwiney and Prunty (1957) reported that after cessation of treatment they have observed immediate nitrogen loss and quote a case in which nitrogen loss after withdrawal of the drug approximated to that previously gained. Kory *et al.* (1957), however, found that in a group of chronically underweight individuals 19 out of 25 subjects, followed for six months after the drug was discontinued, either maintained their weight or continued to gain. Our subjects and those of Kory were chronically underweight individuals, while those of McSwiney and Prunty were well nourished. This may explain the difference in findings. Where there is definite underweight or wasting the nitrogen retention due to treatment is perhaps permanent, but in a well-nourished subject the nitrogen retained may well be lost on withdrawing the drug.

Summary

The anabolic effects of the steroid norethandrolone have been investigated in four elderly underweight patients.

In each case there was a significant gain in body weight associated with marked nitrogen retention.

Total body water and extracellular water measurements were made before and after treatment, and the results supported the view that the weight gain was due to an increase in the lean body mass and not merely due to a simple fluid retention.

No androgenic or other unpleasant effects were observed from use of the drug.

In our opinion norethandrolone has definite anabolic properties and should prove to be of considerable value for increasing the lean body mass in individuals who consistently fail to gain weight on an adequate diet.

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ACTION OF METHALLENOESTRIL ON THE POST-MENOPAUSAL ENDOMETRIUM AND VAGINAL EPITHELIUM A COMPARATIVE STUDY

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Methallenoestril ("vallestril") is a phenolic acid derived from naphthalene that has been shown to be more strongly oestrogenic than oestradiol when administered parenterally in oily solution to castrated female rats (Courrier, Horeau, and Jacques, 1947). It has the descriptive formula 3-(6-methoxy-2-naphthyl)-2,2-dimethylpentanoic acid. It is relatively insoluble in water and gastric contents, but soluble in alcohol, in oil, and in dilute bases such as occur in the intestinal secretions. Sturnick and Gargill (1952) have found methallenoestril to be effective in the control of "menopausal symptoms" and of the pain of post-menopausal osteoporosis, without causing uterine bleeding during treatment or after withdrawal.

Potency studies in the laboratories of the manufacturers have shown that, while the oestrogenic effect of methallenoestril on the vaginal epithelium of spayed mature rats is twice that of oestrone, its influence on uterine growth in immature mice is only one-tenth as potent as that of oestrone. The present investigation was undertaken to determine whether this selective oestrogenic action of methallenoestril was demonstrable in women, and this was done by comparing its action on the endometrium and vaginal epithelium with that of stilboestrol.

The subjects of the investigation were patients awaiting vaginal repair operations for genital prolapse in whom the menopause had occurred five or more years previously. Each of these was given a course of tablets labelled A, B, or C, the nature of which was unknown to the investigators until the study was complete. The course of tablets, one a day, was given for a period of between 40 and 84 days, and the interval between completion of the course and endometrial curettage at the time of the vaginal repair operation was between 4 and 15 days.

The tablets labelled A contained 5 mg. of methallenoestril, those labelled B were inert, and those labelled C contained 0.5 mg. of stilboestrol.

Results

It may be seen from the Table that of the seven patients who received methallenoestril only one experienced withdrawal bleeding. This patient and one other were found to have hyperplastic endometrium. Of the 10 patients in the control group not one had withdrawal bleeding, although in three cases endometrial polypi were found, and in two of these the endometrium was relatively hyperplastic for a post-menopausal woman. Of the eight patients who received stilboestrol, four experienced withdrawal bleeding only, one induced bleeding, and one both induced and withdrawal bleeding. All of these, together with a seventh who did not bleed, were found to have hyperplastic endometrium. One patient had an endometrial polyp.

The diagnosis of "hyperplastic endometrium" was made on the basis of a naked-eye judgment of the amount and thickness of the endometrium confirmed by microscopical evidence of active proliferation or frank cystic hyperplasia. The four endometrial polypi (of which three occurred in the control group) were discrete adenomata arising by slender pedicles within the uterine cavity. They were considered to be innocent neoplasms rather than manifestations of hyperplasia.

The condition of the vagina was compared by noting the presence or otherwise of obvious atrophic changes in the epithelium. This was present in one of the seven methallenoestril cases, five of the 10 controls, and none of the eight stilboestrol cases.

Five patients volunteered the information that they felt better in general health and that their symptoms of prolapse were moderated after taking the tablets. Of these, three received methallenoestril and two the inert tablets.

Tabulated Results

	Age	Years since Menopause	Days of Treatment	Interval before Curettage (Days)	Induced Bleeding	Withdrawal Bleeding	Atrophic Vaginitis	Endometrium		
								None or Scanty	Hyperplastic	Polyp
A. Methallen- oestril										
2117/56	68	16	49	10	—	—	—	—	+	—
30661/54	65	15	63	15	—	—	—	—	—	—
46285/54	62	12	42	10	—	—	—	—	—	—
11174/56	62	10	42	10	—	—	—	—	—	—
13164/54	61	10	46	4	—	—	—	—	—	—
25128/55	58	10	62	10	—	—	—	—	—	—
10982/56	57	5	42	10	—	+	—	—	+	—
B. Control										
26697/54	59	18	44	10	—	—	—	—	+	—
27838/52	56	14	41	10	—	—	—	—	—	—
11349/50	63	11	42	10	—	—	—	—	—	—
2800/49	57	8	43	10	—	—	—	—	+	—
21632/55	57	7	42	10	—	—	—	—	—	+
10316/55	59	5	44	8	—	—	—	—	+	—
392/57	55	7	63	10	—	—	—	—	—	+
5072/57	46	5	73	10	—	—	—	—	+	—
40193/56	59	10	84	10	—	—	—	—	—	—
27136/52	57	5	84	10	—	—	+	—	+	—
C. Stilboes- trol										
35248/53	59	19	40	10	—	—	—	—	+	—
925/49	57	9	44	8	+	—	—	—	+	—
373/56	57	7	41	10	—	—	—	—	+	—
4351/56	57	7	41	10	—	—	—	—	+	+
38570/56	66	14	69	10	—	—	—	—	—	—
23902/56	61	11	68	10	—	—	—	—	+	—
44359/49	61	8	63	13	+	+	—	—	+	—
18427/56	66	16	82	10	—	+	—	—	+	—

Summary

A "double blind" trial of methallenoestril (vallestril) and stilboestrol has been carried out on 25 post-menopausal women awaiting vaginal repair operations.

Abnormal bleeding occurred in six out of eight patients who received stilboestrol and in only one of