tween the anti-folic acid activity of these compounds and their spermatocidal effect(12). The possibility is thus raised that the spermatocidal effect of folic acid antagonists is due to a displacement of folic acid in the sperm cell. The importance of nucleic acids in the sperm cell and the function of folic acid in purine and pyrimidine synthesis lend more interest to this possibility. The purine and pyrimidine analogs tested were generally ineffective, although a few, particularly 2,4,5-triamino-6-hydroxy-pyrimidine, had appreciable activity. This had an M.E.C. of 0.1 mg/cc. Hitherto studies on the effect of inhibitors on spermatazoan metabolism have been concerned mainly with glycolytic mechanisms; the results discussed above suggest the utility of further study on purine and pyrimidine metabolism.

The group of therapeutic substances tested included representatives of the classes of diuretics, antihistamines, analgesics, and adrenolytics. The results obtained presented no coherent picture, and it would appear that spermatocidal activity in this group is a function of chemical structure rather than of therapeutic effect.

It is worthy of note that, among a number of compounds tested which do not fit into any of the above classifications, coumalic acid was particularly effective, having an M.E.C. of 0.01 mg/cc.

Summary. A number of compounds of different chemical structure and physiological effects were tested to determine their spermatocidal properties. Several were found to be active, including a group of pteroylglutamic acid analogs.

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Renotrophic-Androgenic Properties of Orally Administered Androgens.* (19633)

CHARLES D. KOCHAKIAN. (With technical assistance of Dwight L. Smith.)

From Oklahoma Medical Research Institute and Hospital,† Oklahoma City.

Previous studies(1,2) have indicated that among the androgenic steroids the 17β-hydroxyl group is essential for maximum renotrophic activity and the 3-ketone group for androgenic activity in the castrated mouse. On the basis of these observations an attempt(3) was made to obtain further separation of these two properties of the androgens by studying compounds with a functional group in only one of these two positions. Such compounds administered parenterally, however, proved to be very insoluble in the tissue fluids. It seemed that another route of administration might prove more efficacious. Therefore, since one of these compounds, 17-methylandrostan-17β-ol, was still available, it was studied by oral administration and its properties compared with

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several other available 17-methyl androgens administered by the same route. At the same time a few of the non-methylated steroids were studied, for although it is assumed that these compounds are inactivated by the liver, there is ample evidence(4,5,6,7) which indicates that androgens can be converted to more potent androgens by incubation with liver slices or homogenates.

Experimental. Male white mice, from the Maple Grove Rabbitry, Springfield, Mo., were castrated at 17 to 19 g body weight. The mice were kept 2 in a glass jar containing a false screen bottom in a room air-conditioned at 24-26°C. They were fed and weighed at the same time on Monday, Wednesday and Friday of each week. The amount eaten was determined by weighing the food at the beginning and end of each interval. The regular diet consisted of casein 16.7, sucrose 61.2, hydrogenated vegetable oil 7.4, yeast (Fleischmann's 2019) 9.2, Celluflour 1.8, and Wesson's salt mixture 3.7. At each feeding 2 drops of Patch's cod liver oil and 1 drop of 34% tocopherol‡ concentrate from wheat germ oil diluted 10-fold with Wesson oil were mixed with the food.

The androgens§ were dissolved in 10 to 15 ml ethyl alcohol, and were mixed thoroughly with the food by rotating the glass container. The amount necessary for the experimental period was prepared at one time and kept at 3 to 5°C. This mixture was substituted for the regular diet 30 days after castration and the mice were autopsied 30 days later. The organs were weighed on Roller-Smith torsion balances. *Results.* The amount of food eaten by the mice in the various groups was roughly identical.

As expected, 17-methyltestosterone proved to be the most effective steroid. The steroid of greatest interest, however, is 17-methylandrostan-17β-ol which has no group at the 3 position. At the lower dose it demonstrated a renotrophic potency roughly equivalent to that of 17-methyltestosterone and at 0.8 mg‖ /day was almost as effective as 17-methyltestosterone at 2.0 mg/day. Furthermore, in both instances the androgenic activity of 17-methylandrostan-17β-ol was much less than that of 17-methyltestosterone.

The non-methylated steroids were all effective except Δ^4-androstene-3,17-dione at the lower dose level. Testosterone and androstane-3α,17β-diol, however, were not as potent as their 17-methyl derivatives.

An increase in the dose of the androgens resulted in a further increase in androgenic activity without a concomitant increase in renotrophic activity. This phenomenon is not peculiar to the oral administration of the androgens, but is also very evident after parenteral administration(2,7).

The thymus was decreased in size by the various androgens in roughly reverse proportion to the increase in size of the seminal vesicles and prostates.

Discussion. A comparison of the results obtained by oral administration of androgens with the previous results(1,2) obtained after subcutaneous implantation of pellets of these steroids indicates that the oral route is much less efficient. But those steroids which are only slightly soluble in tissue fluids(1,2,3) show a much greater comparative potency when administered by mouth.

This is specially true for 17-methylandrostan-17β-ol, which, though ineffective by parenteral administration(3), proved not only to be highly active by mouth but also showed preferential renotrophic activity. This property of this compound is of special interest for, by removal of an active group from the 3 position, a further reduction in androgenic activity without impairment of the renotrophic activity has been obtained. Thus, the relationship of the chemical group at the 3 position to androgenic activity can be extended to give the following sequence: C = O > α OH > β OH > no group.

Summary. Orally administered non-methylated as well as methylated androgens are able to stimulate an increase in size of the kidney and the seminal vesicles and prostates and decrease the thymus of castrated mice. The

‡ Provided by Distillation Products Inc. through the courtesy of Dr. P. L. Harris.

§ The androgens were generously made available by Ciba Pharmaceutical Products, Inc.

‖ The amount of this steroid available was not sufficient to permit an experiment at the 0.5 mg/g food (2 mg/day) level.

TABLE I. The Renotrophic and Androgenic Effect of Orally Administered Androgens.*

	Mice No.	Body wt — Initial, g	Body wt — Change, g	Food intake, g/day	Thymus, mg	Kidney, mg	SVPr, mg	Iner.† K/SVPr, mg/mg
		.1 mg steroid/g food, 30 days						
Control (castrated)	8	31.2	4.4	3.7	64±5	355±13	16±1	—
17-Methyltestosterone	7	28.6	5.1	4.2	36±6	478±36	112±8	1.28
17-Methyl-Δ^5-androstene-3β,17β-diol	7	30.4	4.7	4	38±4	452±27	42±6	3.73
17-Methylandrostan-17β-ol	4	29.9	3.7	3.8	34±9	446±29	40±7	3.80
Testosterone	6	29.4	5.5	4.1	52±4	426±26	51±10	2.32
17-Methylandrostane-3α,17β-diol	6	28.6	5.6	3.9	34±4	412±21	57±9	1.43
3β,17β-diol	5	29.6	5.5	3.8	39±5	399±20	34±8	2.45
17-Methylandrostan-17β-ol,3-one	4	27.2	3.3	3.7	29±8	395±23	59±9	.93
Androstane-3α,17β-diol	6	30.2	4.7	3.9	50±5	394±20	25±4	4.33
Δ^4-Androstene-3,17-dione	6	30.4	5.2	3.8	52±6	379±27	17±2	—
		.5 mg steroid/g food, 30 days						
Control (castrated)	8	29.7	4.1	4	47±5	367±18	15±3	—
17-Methyltestosterone	6	31.4	4.1	4	6±1	565±36	307±26	.68
17-Methylandrostan-17β-ol‡	4	31.4	7	3.9	37±5	523±26	100±16	1.84
17-Methylandrostane-3α,17β-diol	6	30.8	4.5	4.3	8±3	514±14	232±27	.68
17-Methylandrostan-17β-ol,3-one	4	30.2	4.1	4.3	4±3	488±29	226±26	.45
17-Methyl-Δ^5-androstene-3β,17β-diol	6	31.7	6	3.9	23±8	482±16	189±48	.66
Androstane-3α,17β-diol	7	31.8	7.3	4	35±3	455±32	90±18	1.49
17-Methylandrostane-3β,17β-diol	8	31.4	3.5	4	27±5	451±15	137±20	.70
Testosterone	6	31	4.8	3.9	30±8	420±26	160±19	.36
Δ^4-Androstene-3,17-dione	6	31.3	6.3	4	44±6	398±23	36±6	1.43

* The values for the organ weights are given with the stand. error of the mean $\sqrt{\frac{\overline{X^2}}{N} - \overline{X}^2} \Big/ \sqrt{N-1}$.

† Increase in kidney wt divided by increase in seminal vesicles and prostates wt.

‡ This steroid was at only .2 mg/g of food because of unavailability of further material.

absence of a functional group in the 3 position, *e.g.*, 17-methylandrostan-17β-ol resulted in a marked decrease in androgenic, but not renotrophic, activity.

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Fetal X-Irradiation and Fertility.* (19634)

ROBERTS RUGH.

From the Radiological Research Laboratory, Columbia University.

It is important to determine, with experimental animals, the effect on subsequent fertility of high but sub-lethal exposures of the fetus. For this study the Swiss mouse was used, the pregnant female receiving chronic exposures for 6 days prior to delivery. The offspring were then tested at 6 months (the height of normal reproductive activity) for fertility. There have been numerous reports of the effect on the mammalian gonad of di-

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