ase. While remaining significant, all studies with the non-specific enzyme are in need of repetition with the specific form which is the *in vivo* controlling homeostatic factor. There are few reports in the literature of chemicals active *in vivo* in inhibition of specific or induced histidine decarboxylase. Kahlson *et al* (7) found α-methylhistidine an *in vivo* inhibitor of histamine formation. The method employed measured urinary excretion of C^{14}-histamine following injection of known amounts of C^{14}-histidine. A second active molecule has been reported effective in animals(8) and clinically(9). Quercetin is the third. The clinical results of Bezian and Pautrizel(9) offer much encouragement for utility of histidine decarboxylase inhibitors. The agent they used, 1-(3-amino-4,5,6-triethyoxyphthalidyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline, was effective in pollinosis, aperiodic rhinitis, Quincke's edema and urticaria but proved disappointing in asthma and eczema. While the series was small (22 cases) and uncontrolled, the study offers hope that agents of this type will prove non-toxic and effective in therapeutics.

Summary. Quercetin by an isotopic method has been shown to be an effective inhibitor of non-specific and specific (induced) histidine decarboxylase both *in vivo* and *in vitro*.

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Hypocholesterolemic Effect of an Androsterone Analogue. (29315)

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Interest in androsterone and androsterone-like steroids for treatment of hypercholesterolemia was initiated by the report of Hellman *et al*(1) who observed that androsterone administered parenterally to hypercholesterolemic patients reduced the serum cholesterol level about 20%. They further noted that the most pronounced reductions in circulating cholesterol levels were observed in myxedematous patients and proposed that androsterone possessed some ill-defined "thyromimetic" activity. These observations have been confirmed by Cohen *et al*(2), and Furman and Howard(3), and others.

The implication that androsterone is thyromimetic(1) must be true only in an indirect sense. Certainly, all groups(1-3) have reported the most profound effects of androsterone to occur in hypothyroid individuals; but Cohen *et al*(2) found the steroid had no effect on serum protein-bound iodine. It is well established that the thyroid hormone promotes the conversion of testosterone to androsterone(1). Thus, either a deficiency of the circulating thyroid hormone or of androsterone precursors might lead to a reduction in amount of androsterone available for normal sterol metabolism. Therefore, it seems logical to propose that the hypocholesterolemic response to androsterone therapy may be the result of supplementation of an un-

usually small body pool of endogenous androsterone.

Because androsterone is not effective as a hypocholesterolemic agent when given by mouth(2) it seemed desirable to discover an analogue of androsterone which was orally active and which exhibited some of the endocrine properties of the natural steroid. One of a series of compounds synthesized by Counsell and Klimstra(4) fits these criteria, and this report describes some of the biological properties of this new steroid, 3α-methoxy-17α-methyl-5α-androstan-17-ol (SC-12790).

Methods. One of the problems in evaluating the hypocholesterolemic effect of androsterone and its analogues has been the difficulty of eliciting this response in laboratory animals(5). From the clinical data, however, it would seem reasonable that a significant response to the steroid might be obtained in animals whose thyroid function had been modified. Preliminary studies indicated that the hypocholesterolemic effect of androsterone could be detected in male rats given as drinking water a solution of 0.02% 6-propylthiouracil. At this concentration no thyroid hypertrophy was observed but plasma cholesterol levels were about 15% greater than those of untreated control animals. This is in agreement with Boyd's data on the effect of thiouracil on cholesterol metabolism(6).

The procedure for evaluating androsterone, SC-12790, and a number of related steroids was to treat 250-280 g male rats (eight per group) daily for a period of 10 days, simultaneously giving them 0.02% 6-proplythiouracil as drinking water. All animals were fed Purina chow *ad libitum*. In lipid studies SC-12790 was administered *per os* as a suspension in 20% aqueous propylene glycol to which a small amount of Tween 80 (0.5%) had been added as a suspending medium. Androsterone was administered subcutaneously as a corn oil solution. At the end of the treatment period animals were anesthetized with ether and blood withdrawn from the abdominal aorta. Serum cholesterol levels were measured by the method of Zlatkis *et al*(7). Statistical evaluation of data was by the rank-sum test of Wilcoxon(8).

Evaluation of the androgenic activity of SC-12790 was carried out as described by Saunders and Drill(9), of the estrogenic effects according to Edgren(10) and of the progestational activity by the Clauberg assay (15). In these assays all compounds were administered in corn oil.

Results. Lipid studies. The effects of SC-12790 and androsterone on serum cholesterol levels in propylthiouracil treated rats are exhibited as dose-response curves in Fig. 1. It is evident that both androsterone and SC-12790 were effective in lowering the serum cholesterol levels of these animals. Although the hypocholesterolemic response to SC-12790 treatment appeared to be greater than that due to androsterone, a precise measure of the relative potency of SC-12790 with respect to the natural hormone could only be made if both compounds were tested simultaneously, which was not the case.

Because certain hypocholesterolemic agents may induce the accumulation of desmosterol in the plasma(12,13), the nature of the nonsaponifiable lipids of the serum of control and treated animals was examined by thin-layer chromatography. No sterol other than cholesterol was found in any of the serum extracts when they were chromatographed according to the method of Wolfman and Sachs(14).

Endocrine studies. In the rats (150-170 g) used for the androgen assay the average weight gains (30 g) over the 7-day treatment period were the same in the control and in the SC-12790, androsterone and testosterone propionate treated animals. The androgenicity of parenterally administered SC-12790 as judged from increases in seminal vesicle weights was 2 to 5% of that of testosterone propionate (Table I). This androgenic activity of SC-12790 is slightly less than that of androsterone. The ventral prostates showed a slightly greater response than the seminal vesicles, resembling androsterone in this regard. The myotrophic activity of SC-12790 as judged by the response of the levator ani muscle was also about 5% of the standard. When SC-12790 and 17α-methyltestosterone were administered by stomach tube in this assay procedure the test com-

pound was found to be nearly as active as this standard (Table II).

In the estrogen assay SC-12790 exhibited a uterotrophic activity only at very high doses; a response commonly observed with androgenic compounds. It did not induce vaginal cornification in spayed rats. SC-12790 administered parenterally in the Clauberg assay showed a progestational activity of about 5% that of progesterone.

Cardiovascular studies. No effects on blood pressure were noted following either intravenous administration (0.1, 1 or 5 mg/kg or oral administration (25 mg/kg) of SC-12790 to normotensive dogs. Likewise there were no effects on the electrocardiogram, heart rate or respiratory rate that could be attributed to SC-12790 when administered orally at a dose of 25 mg/kg to 2 normotensive, unanesthetized dogs.

Discussion. These data indicate that SC-12790 is an orally effective hypocholesterolemic agent as assayed in propylthiouracil treated male rats. This activity in lowering

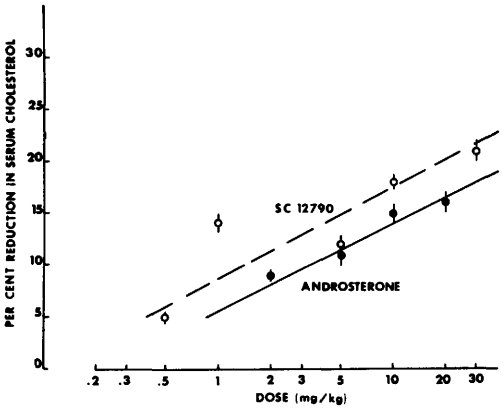

FIG. 1. Effects of SC-12790 and androsterone on serum cholesterol of hypercholesterolemic rats. The per cent reduction is expressed in terms of serum cholesterol levels of simultaneously tested control animals. SC-12790 was given *per os* as a suspension in 20% aqueous propylene glycol; androsterone was administered parenterally as a corn oil solution. Only the value for SC-12790 at 0.5 mg/kg is not significantly different from control value(8). Vertical lines indicate standard errors of means.

TABLE I. Effects of SC-12790 Administered Intramuscularly on Weights of Accessory Organs in Castrated Male Rats.

Compound	Total dose, mg/rat	No. of animals	Body wt, g		Seminal vesicle, mg	Ventral prostate, mg	Levator ani, mg
			Initial	Final			
Oil only	—	24	154	182	7.0	7.9	51.6
SC-12790	5.0	16	152	183	15.8*	31.6*	68.3*
	2.0	8	163	189	10.9*	21.4*	63.9
	1.0	8	160	188	10.1*	15.5*	60.8
	.5	8	148	178	9.0	13.9*	53.1
Testosterone propionate	.2	8	162	195	46.7*	39.8*	88.5*
	.1	8	163	194	25.0*	25.0*	70.0*
	.05	8	167	196	12.8*	16.0*	64.9
	.02	8	162	194	8.0*	10.7*	61.4
Androsterone	10	8	169	201	18.7*	44.1*	73.8*
	5	7	165	201	16.4*	49.7*	76.8*
	.5	7	163	199	10.0*	13.4*	69.9*

* Significantly larger than appropriate controls by the Wilcoxon rank sum method ($P < .05$) (8).

TABLE II. Androgenic Effects of SC-12790 Administered by Stomach Tube.

Compound	Total dose, mg/rat	No. of animals	Body wt, g		Seminal vesicle, mg	Ventral prostate, mg	Levator ani, mg
			Initial	Final			
Oil only	—	16	160	193	7.4	9.6	57.6
SC-12790	10	8	158	190	11.6*	17.5*	70.2*
Methyltestosterone	45	8	156	191	37.6*	44.9*	88.3*
	30	8	156	191	27.7*	30.4*	80.8*
	10	8	159	193	15.4*	19.4*	66.9*

* Significantly larger than controls by the Wilcoxon rank sum method ($P < .05$) (8).

serum cholesterol levels of these hypercholesterolemic animals is comparable qualitatively with parenterally administered androsterone as judged by the similarity of the slopes of the dose-response curves for the two compounds.

The endocrine evaluation of SC-12790 showed it to be a weak androgen of the same order of activity as androsterone. Though the oral activity of SC-12790 approaches that of methyltestosterone, it should be pointed out that the latter compound is only one-tenth as active as an androgen when administered orally as when it is given by a parenteral route(15). Therefore we feel that in clinical trials SC-12790 should not show undesirable androgenic side effects.

From the hormonal properties of SC-12790 the question arises whether it may not be exhibiting lipid effects akin to those of methyltestosterone rather than androsterone since Abel and Mosbach(16) have recently shown methyltestosterone to be an effective hypocholesterolemic agent in the rat. A preliminary study of this compound with our assay has shown methyltestosterone to exhibit a dose response curve with a much steeper slope than either SC-12790 or androsterone. The methyltestosterone-induced reduction of serum cholesterol levels to 46% of control values that was observed by Abel and Mosbach at a dose of 0.05% in the diet (our calculation: about 30 mg/kg/day) after 21 days of treatment is not unlike our value of 33% reduction in serum cholesterol concentration achieved during our standard 10 day treatment with orally administered methyltestosterone at a dose of 30 mg/kg. This differs considerably from the responses seen with SC-12790 and androsterone in Fig. 1. Therefore, we believe that the hypocholesterolemic effect of SC-12790 or androsterone may differ in some fundamental respect from that of methyltestosterone.

Summary. An assay was devised in which the hypocholesterolemic action of parenterally administered androsterone could be demonstrated in rats given a low dose of propylthiouracil. Using this procedure an analogue of androsterone, 3α-methoxy-17α-methyl-5α-androstan-17-ol (SC-12790), was found to have an oral hypocholesterolemic activity similar to that of parenterally administered androsterone. Endocrine assays indicated the new steroid to be a weak androgen of the same order of potency as androsterone.

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