Discussion. The present study has shown that human wound tissue has a high histamine forming capacity whereas uninjured skin only exceptionally has any measurable histamine forming capacity. From experimental studies on rats(3) it has been suggested that the histamine forming capacity is an essential factor in initiating and sustaining rapid tissue growth in healing wounds. The present results indicate that the same mechanism may be operative in human wound healing. The present findings are in accordance with those previously reported(4) for histamine forming capacity of wound tissue in man.

In the present experiments normal skin from the groin in man only exceptionally formed ^{14}C-histamine from ^{14}C-histidine *in vitro,* whereas such formation has been demonstrated by other workers(4,7). This apparent discrepancy may be explained by methodological differences, e.g. relative substrate concentration, or may reflect a real difference in the histamine forming capacity of skin in different body regions or experimental conditions.

The present study included determinations on uninjured skin taken 1-11 days after a previous minor operation. This was done because an increased histamine content has been found in uninjured skin after operation in rats(8). The present observations indicate that a corresponding increase in histamine formation does not occur after a minor operation in man.

Summary. The histamine forming capacity of human wound tissue has been studied. It was found that whereas uninjured human skin only rarely showed a measurable histamine forming capacity, human wound tissue regularly showed a high histamine forming capacity.

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Received May 6, 1964. P.S.E.B.M., 1964, v116.

Antiandrogenic Activity of Tetra-N-Butyllead in a Mouse Assay.* (29449)

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Various steroids, a tricyclic compound (2-acetyl-7-oxo-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydrophenanthrene), and 5-fluorouracil(1) have been shown to inhibit the action of testosterone on the seminal vesicles of the castrated mouse(2). This activity has been observed for tetra-n-butyllead and is the subject of this report.

Methods and material. Swiss albino mice were castrated at 21 to 23 days of age. On the day of operation and once daily for a total of 7 consecutive days, testosterone dissolved in 0.1 ml of sesame oil was injected subcutaneously. The total dose of androgen was 0.8 mg. The test material, in an aqueous suspending medium, was injected once daily for 7 days also, starting on the day of operation. This medium consists of sodium chloride (0.9%), polysorbate 80 (0.4%), carboxymethyl cellulose (0.5%) and benzyl alcohol (0.9%). Twenty-four hours after the last injections, the body, prostate, and seminal vesicle weights were determined. The results were expressed as tissue ratios de-

* Supported in part by a grant from International Lead Zinc Research Organization.

TABLE I. Antiandrogenic Activity of Tetra-n-butyllead in a Castrated Mouse Assay.

Exp No.	Test compound Designation	Total dose, mg	Total dose of testosterone, mg	No. of mice	Mean body wt, g	Tissue ratio ± S.E. Prostate	Seminal vesicles
I	0	0	0	8	18	.04 ± .005	.11 ± .01
		0	.8	9	20	.12 ± .02	.99 ± .10
	Progesterone	5	.8	8	20	.19 ± .02	1.23 ± .12
		10	.8	8	19	.16 ± .04	.94 ± .13
		20	.8	8	20	.11 ± .02	.41 ± .04
	Tetra-n-butyllead	1	.8	8	17	.20 ± .03	1.08 ± .15
		2.5	.8	10	17	.21 ± .02	.95 ± .09
		5	.8	7	18	.11 ± .03	.70 ± .11
		10	.8	10	17	.17 ± .02	.68 ± .05
		20	.8	10	16	.12 ± .02	.67 ± .06
II	0	0	0	6	15	.05 ± .01	.20 ± .03
		0	.8	6	15	.22 ± .03	1.20 ± .16
	Progesterone	2.5	.8	9	16	.19 ± .02	.93 ± .08
		5	.8	8	18	.19 ± .01	.88 ± .07
		10	.8	8	17	.20 ± .02	.76 ± .05
		20	.8	9	17	.14 ± .02	.46 ± .04
	Tetra-n-butyllead	20	.8	9	16	.17 ± .02	.75 ± .05
III	0	0	0	8	21	.06 ± .01	.19 ± .03
		0	.8	10	18	.29 ± .02	1.08 ± .07
	Progesterone	20	.8	9	19	.20 ± .01	.48 ± .04
		10	.8	10	18	.24 ± .01	.86 ± .09
		5	.8	10	17	.23 ± .04	.81 ± .13
	Tetra-n-butyllead	.1	.8	10	19	.22 ± .02	.94 ± .10
IV	0	0	0	10	16	.03 ± .01	.20 ± .02
		0	.8	8	17	.22 ± .01	.98 ± .10
	Progesterone	5	.8	10	18	.19 ± .02	1.00 ± .10
		10	.8	9	18	.22 ± .04	.98 ± .13
		20	.8	9	19	.17 ± .02	.75 ± .05
	Tetra-n-butyllead	2.5	.8	8	18	.25 ± .02	1.31 ± .15
		5	.8	9	16	.16 ± .02	.91 ± .07
		10	.8	9	14	.17 ± .01	.77 ± .06

fined as milligrams of tissue per gram of body weight. This method has been described (2,3).

Tetra-n-butyllead was prepared by interaction of tri-n-butyllead bromide with n-butylmagnesium bromide similar to the general procedure described by Grünttner and Krause(4). This compound was made available to us by Dr. G. M. van der Want, Institute of Organic Chemistry, T. N. O., Utrecht, The Netherlands.

Results. The comparative antiandrogenic activity of progesterone and tetra-n-butyllead in the testosterone stimulated castrated mouse is described by 4 experiments in Table I. Table II interprets these results by indicating the experiments in which statistically significant inhibition was observed at the various doses of both compounds. Progesterone was highly effective at a total dose of 20 mg and at 10 mg significant inhibition was observed in 3 of 4 trials. At 5 mg the steroid produced inhibition in 2 of 4 trials and in a single trial at 2.5 mg the change was not significant.

Tetra-n-butyllead was inactive at total dose levels from 0.1 to 2.5 mg, but one of 2 trials at 5 mg was active and significant

TABLE II. Summary of Data in Table I.

Compound	Total dose, mg	No. of trials	No. of trials showing significant inhibition
Progesterone	2.5	1	0
	5	4	2
	10	4	3
	20	4	4
Tetra-n-butyllead	.1	1	0
	1	1	0
	2.5	2	0
	5	2	1
	10	2	2
	20	1	1

inhibition was found in each of the 2 trials at 10 mg and in the single trial at 20 mg. On the basis of these data, the antiandrogenic activity of tetra-n-butyllead is judged to be of the order of the reference standard progesterone.

Tetra-n-butyllead was studied for other possible hormonal activities with negative results. The compound, when administered by injection, was not estrogenic at doses up to 100 μg in the immature mouse using the uterus as the endpoint(5). At a total dose of 0.1 μg estrone elicits a highly significant uterine increase. Tetra-n-butyllead was also inactive as an antiestrogen at the 3 mg total dose level in the estrone stimulated immature mouse assay also employing the uterine endpoint(6).

Summary and conclusion. Tetra-n-butyllead exhibited antiandrogenic activity in the testosterone stimulated castrated mouse using the weight of the seminal vesicles as the endpoint. The compound is neither an estrogen nor an antiestrogen under the conditions of the experiments.

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Received May 6, 1964. P.S.E.B.M., 1964, v116.

Evaluation of Protection with Phenoxybenzamine Against Lethal Endotoxin Shock.* (29450)

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The characteristic hypotension encountered in shock has been traditionally treated with vasopressors such as norepinephrine and metaraminol(1,2,3). Paradoxically, microscopic observations of blood vessels *in vivo* during shock have indicated excessive vasomotor activity with decided constriction of arteries and arterioles(4,5). These observations, together with other evidence of adrenergic involvement in shock(2,4,6), have led investigators to employ anti-adrenergic drugs to counteract shock irreversibility.

The most frequently employed anti-adrenergic agent has been phenoxybenzamine (Dibenzyline†). Most studies have reported lengthened survival time using phenoxybenzamine before induction of bacteremic shock (2,7,8), although pretreatment with 6 mg/kg phenoxybenzamine did not protect mice from lethal endotoxin shock(7). Phenoxybenzamine administered after induction of bacteremic shock has been demonstrated to be both beneficial(9,10) and detrimental(1,3). Phenoxybenzamine treatment has had such success in experimental animal shock therapy that it is presently being administered to patients (12,13). This situation emphasizes the need for a critical evaluation of the efficacy of phenoxybenzamine in shock therapy.

The present study was designed to evaluate the effect of pre- and post-treatment with phenoxybenzamine on survival of dogs given lethal injections of endotoxin.

Method. Adult mongrel dogs were maintained in air-conditioned kennels during these experiments. Dogs were divided into groups to test the survival value of pre- and post-treatment with phenoxybenzamine in bacteremic shock. Shock was induced in all groups by administration of 1 to 3 mg/kg *E. coli* endotoxin (Difco) dissolved in 10 cc saline. All injections were initiated through

* Research supported in part by U.S.P.H.S. grant.
† Appreciation is expressed to Smith, Kline and French for a generous supply of Dibenzyline.