TABLE II. Chorionic Hormone 750 I. U. Given Each Group on Day 1.

Day 2	No. Animals	Avg body wt, g	Uterus, g	Ovaries, g
Stilbestrol .5 mg	4	45	.099	.038
" 1 "	4	42	.093	.031
Progesterone 5 mg	4	50	.141	.060

ries of .023 and .024 g while they weighed .037 g with sesame oil 0.5 cc, .032 with pregnenolone 5.0 mg and .042 g with cholesterol 25.0 mg (Table I). On the other hand, a marked increase (up to .072 g) in ovarian weight was obtained with high dosages of estrogenic substances, for instance, stilbestrol, estrone (Theelin-Parke Davis), estradiol benzoate (Ovocylin benzoate-Ciba) and estradiol dipropionate (Ovocylin dipropionate-Ciba) (Table I). With progesterone (Proluton-Schering) no enhancement of ovarian weight occurred. In all instances the histologic picture of the ovaries was the same as that found when the chorionic hormone was given alone and showed developing graafian follicles, corpora lutea and hypertrophy of the interstitial cells.

If the order in which the hormones were administered was reversed, namely the chorionic hormone on the first day and stilbestrol on the second, there was no increase in the ovarian weight (Table II). However, a considerable increase was obtained when progesterone was given on the second day (Table II).

Summary. The preliminary administration of high dosages of stilbestrol, estrone, estradiol benzoate and estradiol dipropionate resulted in a marked increase in the ovarian weights of immature rats induced by a chorionic gonadotrophin. The control series were given sesame oil, cottonseed oil, pregnenolone, cholesterol or progesterone. The increase also did not occur if stilbestrol was administered after, instead of before, the chorionic hormone. Although progesterone did not produce increased ovarian weight when given before, a marked enhancement did result when it was administered after, the chorionic hormone.

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Relative Role of Milk Agent and Tissue Sensitivity in Estrogen-Induced Mammary Growth.* (18819)

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The response of the mammary gland to estrogenic stimulation varies in different strains of mice(1,2). Whether or not the presence of the milk agent is correlated with these differences is still a moot question(3-5). The following experiments constitute another attempt to contribute to the solution of this problem.

Material and methods. Ninety-eight sexually immature mice of closely inbred strains were ovariectomized at the age of 4 to 5 weeks and kept on a standard diet of Purina Laboratory Chow and water *ad libitum*. Thirty-one mice of strain Z (C_3H)—15 with the agent (Z) and 16 without it (Zb)—28 mice of strain

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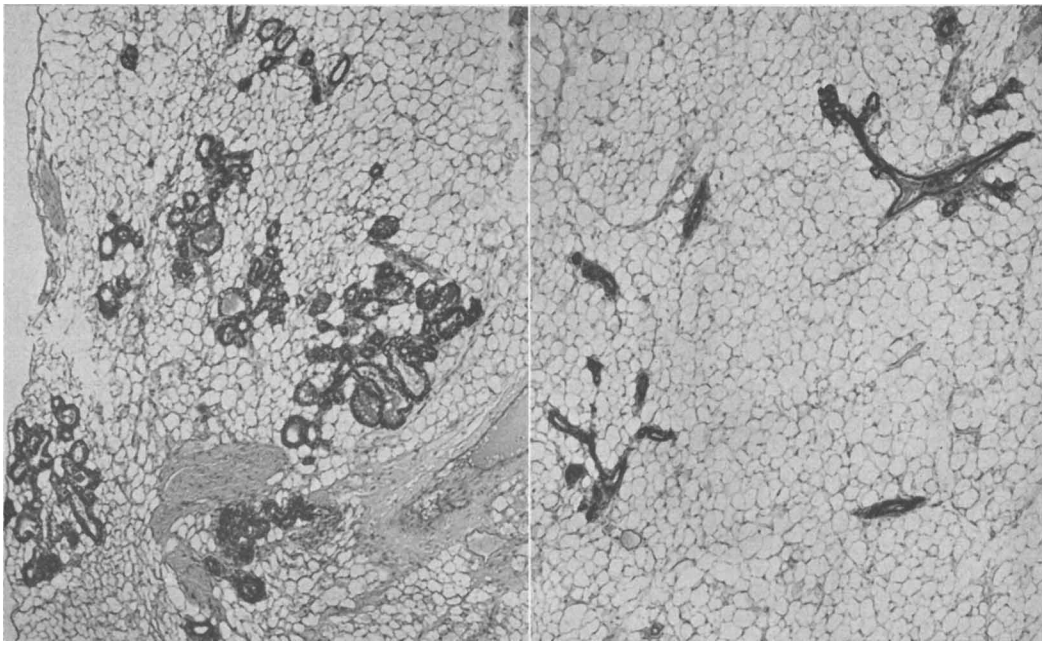
TABLE I. Tabulation of Microscopic Findings in Mammary Glands According to Grades.

Strain	Injected for wk	# of breasts studied	# of ducts in one low power field 48 mm obj., 10× ocul.	% of mammary glands showing stimulation of growth grade: 0	I	II	III
Z	1	8	17-35	0	50	50	0
	2	8	20-32	0	0	100	0
	4	8	25-35	0	0	0	100
	6	8	14-42	0	12.5	12.5	75
	8	12	21-41	0	0	0	100
	13	8	18-33	0	0	25	75
Zb	1	8	8-20	12.5	87.5	0	0
	2	8	4-25	25	75	0	0
	4	8	8-28	12.5	50	37.5	0
	6	6	18-38	0	33.3	50	16.7
	8	15	21-39	6.7	13.3	33.3	46.7
	13	8	21-37	0	12.5	37.5	50
D2	1	8	8-21	37.5	62.5	0	0
	2	8	8-26	12.5	50	37.5	0
	4	6	8-31	16.7	33.3	50	0
	6	8	10-30	37.5	37.5	25	0
	8	8	12-28	0	25	75	0
	13	8	14-31	0	12.5	50	37.5
D2b	1	8	4-18	62.5	37.5	0	0
	2	8	8-18	75	25	0	0
	4	8	8-30	12.5	62.5	25	0
	6	8	6-22	12.5	75	12.5	0
	8	8	17-39	0	25	75	0
	13	8	14-25	0	50	50	0
A	1	8	14-32	25	75	0	0
	2	8	6-31	12.5	37.5	50	0
	4	8	14-42	0	25	75	0
	6	8	15-41	0	25	25	50
	8	8	14-43	12.5	25	37.5	25
	13	8	12-38	0	0	62.5	37.5
Ax	1	8	9-21	50	50	0	0
	2	8	12-26	12.5	87.5	0	0
	4	8	12-35	0	62.5	37.5	0
	6	8	13-39	0	62.5	37.5	0
	8	8	12-35	25	25	37.5	12.5
	13	8	15-42	0	25	25	50
Axa	1	8	4-23	75	25	0	0
	2	8	12-25	25	37.5	37.5	0
	4	8	14-33	0	50	50	0
	6	7	25-41	14.3	28.6	57.1	0
	8	8	10-43	0	37.5	37.5	25
	13	8	18-33	0	0	62.5	37.5

D2—14 with the agent (D2) and 14 without it (D2b)—and 39 mice of strain A—14 with the agent (A), 11 without (Ax), and 14 (Axa), whose ancestors had been raised without the agent for thirty-two generations and subsequently been refostered to reacquire the agent —were used. In each group, 2 animals served as ovariectomized controls; the remaining ones received subcutaneous injections of 0.03 mg of alpha estradiol† benzoate in sesame oil once a week for 1, 2, 4, 8, or 13 weeks. One week after the last injection, the mice were sacrificed; from each animal, 4 mammary glands, uterus and vagina were removed, fixed in Bouin's solution, embedded in paraffin, and semiserial sections stained with hematoxylin and eosin were prepared for microscopic examination.

Microscopic examination. In each breast of each animal (unless stated otherwise in Table I), the number of ducts in a low power field (48 mm obj., 10x ocul.) were counted, and

† We are indebted to Schering Corp. for generous supply of Progynon-B.



Sections through the mammary gland of mice of strain Z (Fig. 1) and Zb (Fig. 2), 8 weeks old, ovariectomized at the age of 4 weeks, and having received 4 weekly injections of 0.03 mg of alpha estradiol benzoate. The figures demonstrate the maximum degrees of stimulation observed at this experimental stage. Magnification 55×.

FIG. 1 (left). Stimulation of grade III.

FIG. 2 (right). Stimulation of grade II.

epithelial growth was studied; the findings were graded, as described previously in detail (2b). Briefly, this is the gradation: *Grade O:* Resting ductal epithelium and absence of alveoli. *Stimulation grade I:* Proliferation of ductal epithelium with papillary infolding, elongation of ducts with lateral and terminal budding as the most advanced change. *Stimulation grade II:* Beginning alveolar growth with a few secretory vacuoles in the small acini. *Stimulation grade III:* Multicentric alveolar growth showing dilated acini lined by mitotically proliferating epithelium and containing abundant secretions. Since within the same mouse the 4 breasts were not always equally stimulated, some overlapping of the findings occurred in the various groups. Hence, in order to obtain quantitative data, the degree of stimulation of each mammary gland was recorded separately, and the findings were tabulated on a percentage basis of the total number of breasts studied at each stage in each experimental group. The results are summarized in Table I.

Results. Ovariectomized non-injected mice: All breasts were resting. The number of ducts in a low power field varied from 4 to 16. The epithelium was low and showed no proliferation. Occasionally small amounts of secretions were seen. No differences in the microscopic appearance could be established in mice of the various strains; nor did the presence or absence of the milk agent alter the microscopic picture.

Strain Z. In mice possessing the agent (Z), growth stimulation of grade II was noted in 4 of 8 breasts (50%) after one week, and in all 8 breasts (100%) after 2 weeks' observation; after treatment for 4 weeks, all 8 breasts (100%) disclosed grade III stimulation (Fig. 1). In mice without the agent (Zb), observed up to 2 weeks, mammary growth did not exceed grade I; after 4 weeks, 4 of 8 breasts (50%) disclosed stimulation grade I, and 3 of 8 breasts (37.5%) showed growth of grade II (Fig. 2). Grade III stimulation was not reached until after six weeks' treatment, and then only 1 of 6 breasts (16.7%) had reached

this stage. With prolonged administration of the estrogen, mammary growth became increasingly intensified, and gradually approached conditions seen in the animals possessing the agent. Still, even after 3 months' treatment, the growth response in the breasts of the Zb mice lagged behind that seen in the Z mice.

Strain D2. In mice of this strain, mammary growth was, under the influence of the estrogen, less stimulated than in the Z mice. However, in mice with the agent (D2), the breasts reacted to the estrogen more vigorously than the breasts of mice without the agent (D2b). In the D2 mice, 1 of 8 breasts (12.5%), was resting after 2 weeks of treatment as compared with 6 of 8 breasts (75%) in the D2b mice. Simultaneously, in the D2 mice, 3 of 8 breasts (37.5%) showed grade II stimulation, while in the mice without the agent (D2b) mammary growth did not exceed grade I, and this was seen in 2 of 8 breasts (25%). Grade II stimulation was first noted in 2 of 8 breasts (25%) of the D2b mice after 4 weeks' treatment. After 6 or more weeks of observation, the differences between the growth response in groups D2 and D2b respectively became less distinct. However, none of the mice without the agent developed acini, while of the mice possessing the agent (D2) at least 3 breasts (37.5%) showed grade III stimulation.

Strain A. During the early stages of treatment with the estrogen mammary growth was more accentuated in mice possessing the agent (A) than in those without the agent (Ax). After 2 weeks, 50% of the breasts of the A mice had reached growth of grade II, while those of the Ax mice were not stimulated beyond grade I. After 4 weeks, mammary proliferation of grade II was noted in the Ax group. However, only half as many breasts (37.5%) showed this change as did the corresponding A mice (75%). Again, after 6 weeks, 50% of the breasts of the A mice showed grade III stimulation, while the most advanced growth in the breasts of the Ax mice was still of grade II. After 8 or more weeks, the differences in the growth response of the breasts of the 2 groups began to disappear. In the refostered group (Axa), the reaction of the breasts following the injections of the estrogen was slow. From the second week on, the degree of growth stimulation was intermediate between that of the Ax mice and those who had the agent throughout their entire ancestry (A). The mammary response to estrogen in mice possessing the agent for a varying number of generations may deserve further investigation.

Discussion. Injections of equal amounts of alpha estradiol benzoate into ovariectomized mice of various strains caused more vigorous mammary growth in individuals possessing the milk agent than in mice of the same strains free of the agent. These differences were most conspicuous during the early stages of hormonal stimulation. Thus, the milk agent seems to determine at least partly the response of the breast to estrogen. The failure of previous experiments(3,4) to demonstrate these variations may be due to differences in the methods employed: Whole mount specimens will not reveal the early proliferation of the ductal epithelium, particularly if infolding rather than elongation of ducts occurs. Besides dosage, the time factor may play a role in the mammary response so that investigations of one single stage following administration of the estrogen may not disclose the complete picture. In addition to the differences in the mammary response attributable to the milk agent (strains Z, D2, A, Axa) strain differences in the mammary response to the hormone continued to exist also in the absence of the milk agent. These differences manifest themselves if corresponding stages in strains Zb, D2b, Ax, and C57 black (2a) are compared. These findings are thought to be related to the different genetic constitution of various strains. Strain differences exist in the response of the adrenals and the hypophyses to castration(5-8). The estrogen injected, however, should obviate such castration effects and therewith strain differences in the latter. Apparently then the sensitivity of the target tissue plays a major role in the mammary

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response to hormonal stimulation. The nature of factors determining the tissue susceptibility is under further investigation.

Summary. The mammary glands of ovariectomized mice of strains Z, D2 and A possessing the milk agent were more susceptible to estrogenic stimulation than the breasts of mice of the same strains raised for many generations without the milk agent. However, strain differences in the mammary response to the estrogen continued to exist also in the absence of the milk agent. These variations are considered to be due to strain differences in the susceptibility of the target tissue to hormonal stimulation.

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Effect of Oral 688A (N-Phenoxyisopropyl-N-Benzyl-β-Chloroethylamine Hydrochloride) on Blood Pressure in Normotensive and Hypertensive Subjects.* (18820)

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Previous investigations have shown that Dibenamine, administered intravenously in man, closely approximates the effects of a surgical sympathectomy(1,2). However, its clinical usefulness proved to be of limited value because of its mode of administration and its side effects. These shortcomings of Dibenamine have stimulated the search for an orally effective adrenergic blocking agent, devoid of side effects. A compound, designated 688A, recently developed, seems to meet the requirements for an orally active drug.

In the present report, we wish to summarize the preliminary clinical results obtained with this compound, used since February 1950, in patients with arterial hypertension and peripheral vascular diseases.

Methods and material. 688A (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride) is a new synthetic adrenergic blocking agent.† Chemically it is a derivative of Dibenamine (N,N-dibenzyl-β-chloroethylamine hydrochloride). Pharmacologic studies in animals showed that its adrenergic blocking potency is greater than that of Dibenamine, and that it is active parenterally as well as orally(3,4). 688A was used in enteric coated tablets, supplied in dosages of 10, 20, and 40 mg. The drug was administered 3 times daily with meals. The dosage used varied with the patient and ranged between 30 mg and 560 mg daily. Each patient was first tested carefully for his sensitivity to the drug by starting with a small dose and then increasing it progressively. The optimum daily dose was determined by the therapeutic effectiveness without, or with only minimal, side reactions. Observations were made during treatment with 688A and during administration of placebo. The size and color of the latter were identical to those of the active drug. The subjects were mostly patients admitted to the wards of the Montefiore Hospital.‡ Of a total of 47 subjects used in this investigation,

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‡ Two patients, included in this series, were hospitalized at the V. A. Hospital, Bronx, N. Y. We are indebted to Dr. Abraham Azulay, Senior Resident in Cardiology, for the data obtained in these two cases with essential hypertension.