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.

Received June 4, 1951. P.S.E.B.M., 1951, v77.

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

HENRY HAIMOVICI, MARVIN MOSER, AND HENRY KRAKAUER.
(With the assistance of Sylvan Douglis.)
From the Surgical and Medical Divisions, Montefiore Hospital, New York City.

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,

* This investigation was supported by a grant from the Smith, Kline and French Laboratories.

1. Haimovici, H., and Medinets, H. E., PROC. SOC. EXP. BIOL. AND MED., 1948, v67, 163.

2. Wunsch, R. E., Warnke, R. D., and Myers, G. B., *Ann. Int. Med.*, 1950, v33, 613.

† 688A was kindly supplied by Smith, Kline and French Laboratories.

3. Macko, E., McLean, R. A., Fellows, E. J., (*et al.*), *J. Pharmacol. and Exp. Therap.*, 1951, v101, 24.

4. McLean, R. A., Fendrick, A. J., Macko, E., and Fellows, E. J., *J. Pharm. and Exp. Therap.*, 1951, v101, 26.

‡ 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.

19 were normotensives and 28 were hypertensives. Most of these patients were first hospitalized and a control period of observation before and under 688A treatment was obtained under basal conditions. Electrocardiograms, heart size films, eyeground changes and renal functions were recorded before and during treatment. Sodium amytal, intravenous Dibenamine and benzodioxane tests were done on most of the hypertensive subjects. Cold pressor tests were performed in many cases before, and at regular intervals after, starting the treatment. These patients were allowed to be ambulatory. After a minimum of 2 weeks of hospital observation, the patients were discharged and followed twice weekly as outpatient cases. The blood pressure (B.P.) was measured with a mercury manometer with the patient in both the supine and erect positions after he had rested for at least 15 minutes. The pulse rate (P.R.), counted at the wrist, was also recorded in both the supine and erect positions. At least 3 consecutive readings were made for each measurement. Hourly arterial pressure measurements for 6 to 8 consecutive hours were taken during treatment in many of the hospitalized patients. The average values of the daily readings were recorded and the lowest supine B.P. with its corresponding erect B.P. were used for the analysis of the manometric results.

Results. A. *Effect on the blood pressure in the supine and erect positions.* 1. Nineteen normotensive subjects received 688A for periods varying from 2 to 18 weeks. The average control B.P.s for both supine and erect positions were 124/71 and 124/80, respectively. After the drug administration, the average B.P.s for the 2 positions were 107/62 and 96/64 with a mean change of −17/−9 and −28/−16, respectively. 2. In hypertensive subjects, the degree of fall in B.P. varied with the type of hypertension. a. Eight patients with uncomplicated essential hypertension received the drug for periods varying from 1 to 16 months with an average of 6 months. Their average control B.P.s for both supine and erect positions were 177/112 and 175/118. After treatment with 688A the mean B.P.s were 140/91 and 135/95 with a mean change of −37/−21 and −40/−23, respectively. b. Sixteen patients with malignant hypertension were under observation with 688A for periods varying from 2 weeks to 11 months with an average of 3 months. Their average control B.P.s for both supine and erect positions were 221/125 and 220/131. After treatment the mean B.P.s were 182/105 and 155/99 with a mean change of −39/−20 and −65/−32, respectively. c. Three patients with systolic hypertension were under observation with 688A for periods varying from 1 to 4 weeks. Their average control B.P.s for both supine and erect positions were 199/75 and 199/82. After treatment, the average B.P.s were 173/59 and 165/62, with a mean change of −26/−16 and −34/−20, respectively. d. In one case of pheochromocytoma, the control supine B.P. which fluctuated from 153/95 to 240/150 fell to 95/64 after 75 mg of 688A. 3. The daily range of the average dosage of 688A varied from 40 mg to 230 mg for the entire series. The average effective daily dose of the drug varied with the group of patients as follows: 101 mg for normotensives, 130 mg for benign, 194 mg for malignant, and 67 mg for systolic hypertensives. As a rule the maximum action on the B.P. from a single effective dose of 688A was observed 1 hour to 1½ hours after its administration. The effect was noted on both the supine and erect readings, the latter being usually more pronounced. Within 3 to 5 hours, these effects gradually diminished or disappeared.

B. *Effect on the pulse rate.* The P.R. changes following 688A varied with the group of patients. The average changes in the supine position were: + 8 for normotensives, none for benign, −2 for malignant and −1 for systolic hypertensives. The average changes in the erect position were: + 20 for normotensives, + 12 for both benign and malignant, and + 7 for systolic hypertensives.

C. *Effect on symptoms.* Evaluation of symptomatic improvement following any medication in hypertension is notoriously difficult. Effect of placebos and comparison with symptoms before treatment with 688A

were used as criteria for this evaluation. Headaches, dizziness, palpitations and dypsnea were common complaints in 22 of the 27 hypertensive subjects. The remaining 5 subjects were completely asymptomatic. The degree of symptomatic improvement in the 22 patients was as follows: good in 9, moderate in 7, poor in 6. The relation between manometric response to the drug and symptomatic improvement was apparent in most cases but not in all.

D. *Other effects.* A total of 51 cold pressor tests performed on 14 subjects before and during treatment usually showed partial inhibition and seldom complete blockade. Time relationship to the administration and dose of the drug appeared to influence the degree of the inhibition to the cold stimuli. Miosis was noted in most cases. Dilatation of the pupil with neosynephrine appeared impossible during drug administration. The results of 688A on the heart size, EKG and fundi were studied in 8 patients with long-term treatment. Heart size changes were not significant, while improvement in both the EKG pattern and fundi were present in 2 patients. Effect of 688A on pain and peripheral blood flow were also studied and will be reported elsewhere.

E. *Side effects.* Side reactions to 688A were few and minor. Dryness of the mouth and stuffiness of the nose were not infrequent. Drowsiness and fatigue or weakness occurred in a few cases and were rather disabling at times. Toxic effects such as nausea and vomiting were rarely noted and were usually accounted for by overdosage. Dizziness and palpitation were observed in several patients especially on rapid change of position. Most of the side effects were observed during the first few days of treatment. With proper adjustment of the dosage the patients displayed little of the above symptoms.

F. *Tolerance to the drug.* The effectiveness of the drug appeared to diminish somewhat in most cases after 2 to 3 months of administration. Increased dosage of the drug became necessary to restore its effectiveness. Tolerance to the drug, however, developed in a few patients receiving 688A over long periods of time. This was studied in 14 patients observed on the drug for periods ranging between 2 and 16 months with an average of 6 months. In 2 cases the B.P. returned to its initial level after 5 and 7 months and was not influenced by further increase in the dosage. In 5 cases tolerance to the drug was partial, while in the remaining 7 cases no tolerance was apparent as long as 11 months later. The effectiveness of the drug varied in the hospitalized and ambulatory patients. The latter usually required higher dosage than the former.

Summary and conclusions. 1. The foregoing results indicate that 688A, a new adrenergic blocking agent, is an effective oral drug. It induces a fall in both supine and erect blood pressures in all subjects. The degree of the manometric effect depends on the dosage used and on the group of patients. The duration of the decrease in B.P. following a single dose is variable and usually lasts 3 to 5 hours. Symptomatic improvement occurred in 16 of 22 patients with hypertension. Improvement was noted in a few cases even in the absence of appreciable fall in B.P. As noted above, evaluation of symptomatic improvement may be difficult, since in a few cases the effects of placebo were equally good, for at least several weeks. Cold pressor tests showed that 688A in the dosage used, usually induced partial inhibition. It is possible that by its specific sympatholytic action 688A, besides its hypotensive effect, also prevents sudden rises in B.P. as indicated by the cold pressor tests. 2. Side effects of this drug were remarkably few and minor. Occasional drowsiness and sensation of fatigue were among the most disabling reactions noted in some patients. Proper dose adjustment seemed to be an important factor in preventing side effects. It should be noted that these side effects actually represent clinical criteria of adequate adrenergic blockade. Toxic symptoms such as nausea, vomiting and possibly fatigue were rarely encountered. Tolerance to the drug was noted in a few cases and may represent a shortcoming in a long-term treatment. 3. While individual responses to the drug were variable, the overall results in the entire

group of patients indicate that 688A is effective in lowering B.P. and alleviating hypertensive symptoms. 4. These preliminary results obtained with 688A appear encouraging. The potentialities of this drug in arterial hypertension and peripheral vascular diseases are under further investigation. Detailed studies will be published elsewhere.

The authors wish to express their appreciation to Dr. Louis Leiter, Chief of the Medical Division, and to Dr. Samuel Silbert, Attending Surgeon for Peripheral Vascular Diseases, for their active interest in this investigation.

Received June 4, 1951. P.S.E.B.M., 1951, v77.

Selective Inhibition of Adrenal and Thyroid Stimulating Effect of Amphenone B* by Cortisone and Thyroxine. (18821)

ROY HERTZ, WILLIAM W. TULLNER, AND MILTON J. ALLEN.

From the National Cancer Institute,† Bethesda, Md.

We have previously reported that the oral administration of Amphenone "B"(1-2) in the rat induces a marked adrenal and thyroid hypertrophy(3). The adrenal stimulation was lacking in the hypophysectomized animal and was prevented by cortisone administration in the intact rat.

This report presents data which show that thyroxine will prevent the Amphenone-induced thyroid hypertrophy without altering the adrenal response. Conversely, cortisone will prevent the adrenal enlargement without materially depressing the thyroid hypertrophy.

Materials and Methods. Female rats of the Holtzman strain were ovariectomized at 24 days of age and were started on these experiments at 57 days of age. A stock pellet ration was fed *ad libitum*. Amphenone B, Cortisone, and Thyroxine were administered daily as indicated in Table I. The animals were autopsied 24 hours after the last injection. The adrenal thyroid and thymus glands were dissected out and weighed to the nearest milligram.

Results and Discussion. Data from a representative series are presented in Table I. It will be seen that when Amphenone "B" is administered for 14 days it induces a marked adrenal and thyroid hypertrophy. The simultaneous administration of thyroxin and Amphenone "B" reduces the thyroid weight from an expected mean of 50 ± 6 to 9 ± 1. However, the adrenal response is not reduced by thyroxine administration. Moreover, the simultaneous administration of cortisone and Amphenone "B" reduces the adrenal weight from an expected mean of 112 ± 18 to 32 ± 8, but the thyroids in this same group of animals remain enlarged. This selective inhibition of the thyrotropic and adrenotropic action by thyroxin and cortisone respectively indicates that the pituitary is capable of simultaneously increasing its thyrotropic activity and reducing its adrenotropic effect or vice versa. It also indicates that there must be two distinct and separate endpoints in the pituitary through which Amphenone "B" exerts its distinctive effects upon the thyroid and adrenal.

The thymus weights indicate that although the adrenal of the Amphenone "B" treated rat is producing some corticoid, its hormone production is not at all in keeping with the increased size of the adrenal. Thus the control thymus weight of 827 ± 62 mg is reduced to 51 ± 11 mg by Amphenone "B" plus cortisone, but only to 408 ± 177 mg by Amphenone "B" alone. This evidence of limited

* 1,2 bis-(p-aminophenyl)-2-methylpropanone-1 dihydrochloride.

† National Institutes of Health, Public Health Service, Federal Security Agency.

1. Allen, Milton J., U. S. Patent 2,539,388 (1951).

2. Allen, Milton J., and Corwin, A. H., *J.A.C.S.*, 1951, v72, 117.

3. Hertz, R., Allen, M. J., and Tullner Wm. W., PROC. SOC. EXP. BIOL. AND MED., 1950, v75, 627.