TABLE II. Effect of Estradiol, .75 mg Daily, in a 64-Year-Old Male.

	Sf 10-20	Cholest.	Cholest. esters, %	Phospho-lipids	Ratio C/P*	Total lipids
1/25	43	201	73	8.1	24.9	610
	Medication–started					
2/15	66	178	76	8.3	21.4	550
3/1	36	219	74.5	8.7	25.2	470
3/29	57	235	70	9.7	24.2	510
5/5	59	265	68	10.1	26.2	520
	Medication–stopped					
6/7	55	210	75	9.5	22.1	480

* Ratio of cholesterol to phospholipids.

TABLE III. Effect of 5 mg Estradiol Dipropionate I.M. in a 25-Year-Old Female Castrate.

	Sf 10-20	Cholest.	Phospho-lipids	Ratio C/P*	Total lipids
2/12	36 (inj.)	287	12.4	23.1	700
14	49	260	14.2	18.3	680
16	41	304	12.4	24.5	610
20	29	280	15.4	18.2	630

* Ratio of cholesterol to phospholipids.

To test the influence of larger doses of estrogen on these lipid factors 5.0 mg of estradiol was injected in 4 subjects, one of whom was a young female castrate (Table III).

No dietary nor any other medical management was changed during these experimental trials.

The data obtained are summarized in Table I. Table II shows the values obtained in a 64-year-old man in whom the doses used caused tenderness and hypertrophy of the breasts.

It is readily apparent that the administration of estrogen is followed by no marked nor sustained change in any of the serum lipid factors nor in the cholesterol-phospholipid ratio, nor did analysis of the Sf 12-20 lipoproteins show any consistent trend.

In our hands no evidence has been obtained to indicate that estradiol in either physiological or pharmacological doses influences the serum lipids or the low density lipoproteins.

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Ineffectiveness of 688A (N-Phenoxyisopropyl-N-Benzyl-β-Chloroethylamine Hydrochloride) in Treatment of Essential Hypertension. (19591)

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(Introduced by Irvine H. Page.)

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Certain chloroethylamine derivatives can in varying degree block adrenergic and sympathetic activities. Thus, some patients with essential and malignant hypertension respond to intravenous injection of Dibenamine by more or less prolonged decreases of arterial pressures(1,2). Availability of an orally active(3) drug of this type, 688A prompted observations of its effectiveness in the prolonged treatment of essential hypertension. As this study was completed, Haimovici, Moser and Krakauer(4) reported preliminary studies which indicated that 688A was therapeutically effective in essential hypertension.

Methods. This report is based on data from 8 of 25 patients treated; some observations are omitted or briefly noted because a) the drug was sometimes used in the terminal phases of malignant hypertension (6 patients), b) concurrently with another drug (with

TABLE I. Summary of Effects on Average Arterial Pressure of Administration of 688A in 8 Patients with Essential Hypertension. Dosage indicated is the daily maximum administered and/or tolerated. Arterial pressures are means of control and treatment observations. Differences are indicated as significant (+) when difference between means is greater than 3 times and standard error of the difference.

Treatment, wk	Dose, mg	Means of arterial pressures, mm Hg: Control Supine 1	Treatment Supine 2	Treatment Standing 3	Significance of diff. between 2 and 1 S/D	Significance of diff. between 3 and 1 S/D
25	560	165/116	164/120	148/115	0/0	+/0
21	80	185/121	171/108	140/ 97	0/+	+/+
9	520	200/153	184/142	190/149	0/0	0/0
3	1200	204/130	220/140	169/113	0/0	+/+
4	40	154/112	144/103	147/108	0/0	0/0
26	40	198/110	179/101	172/ 94	+/+	+/+
3	160	197/117	178/113	181/112	+/0	+/0
2	240	187/120	185/122	168/120	0/0	+/0

Veriloid twice and once with sodium nitroprusside), c) the follow-up was inadequate (7 patients) or very brief. The ages of the 8 patients who suffered from moderately severe or severe essential hypertension ranged from 20 to 60 years. Dosages and duration of treatment appear in Table I. Treatment usually began with the administration of 20 mg twice daily, increased to 4 times daily after a day or two and subsequently adjusted as tolerated. Nasal stuffiness, Horner's syndrome and orthostatic hypotension were taken as criteria of adequate medication; all these tended to remit as treatment was prolonged. *Control observations* consisted in evaluation of the patients' cardiovascular-renal status by methods currently used in the Research Division; 7 of the 8 patients were hospitalized for 2 weeks or more until averages of arterial pressures measured twice daily showed a minimum of variability; in the remaining patient, arterial pressures had been measured at frequent office calls over a period of nearly 2 years. During treatment, pressures continued to be measured twice daily in the supine position and again 3 to 5 minutes after quiet standing. Means of arterial pressures, standard deviations and standard error of differences between means of control supine, treatment supine and treatment orthostatic pressures were calculated by standard methods(5).

A more detailed study of vascular responsiveness carried out by Dr. James McCubbin in one patient is presented in detail below.

Results. 1) *Effect on arterial pressure.* Observations are summarized in Table I. Orthostatic decreases of systolic and diastolic pressures were observed in 3 patients and of systolic pressure only in another 3. Supine systolic and diastolic pressures showed statistically significant, but clinically unimpressive, decreases in 1 patient; 1 patient showed some decrease in supine systolic pressure only and another a decrease in supine diastolic pressure.

2) *Clinical evaluation.* No significant change was observed in the clinical status of any patient.

3) *Side-effects.* The side-effects of which these patients complained were, a) nasal congestion (4 patients), b) giddiness on quiet standing (4 patients), c) increased fatigability (3 patients), d) palpitation on standing (2 patients) and e) "swollen eyes" (1 patient). Epistaxis was not observed in this group, but nasal spotting occurred in some of the patients who were given the drug during the terminal phase of malignant hypertension. The one patient noted above as showing decreases in systolic and diastolic arterial pressures during treatment was especially susceptible to these effects; any increase in dosage over 40 mg daily resulted in disabling orthostatic palpitation and giddiness.

4) *Vascular reactivity.* (patient 4, Table I). This patient's intra-arterial pressure responses to intravenous test doses of adrenaline, noradrenaline and tetraethylammonium chloride (TEAC) were recorded from a Technitrol capacitance manometer. Relevant data are summarized in Table II. Pretreatment tests demonstrated repetitive, marked depressor re-

TABLE II. Vascular Reactivity to Test (Intravenous) Doses of Adrenaline, Noradrenaline and Repetitive Dosage (Sequentially Numbered) of TEAC in a Patient before and at the 7th Day of Treatment with 688A. Responses on 28th day of treatment correspond well with those found in the control period. The stated arterial pressures are levels (systolic/diastolic) measured at the time of the inj.; responses to inj. as indicated as maximum change from this level in mm Hg and decreases in pressure are preceded by a minus (−) sign.

Test drug		Arterial pressure, mm Hg	Response to drug, mm Hg
I. Observations in control period			
Adrenaline		220/118	35/20
			40/25
			20/2
Noradrenaline		230/122	45/12
TEAC	1	265/140	−95/40
	2	250/148	−65/88
	3	242/145	−58/35
	4	230/138	−38/28
	5	240/145	−55/85
	6	240/148	−48/28
II. Observations on 7th day of treatment			
Adrenaline		230/125	−80/40
Noradrenaline		225/125	5/0
TEAC	1	225/118	15/20
	2	220/121	15/24

sponses to TEAC, analogous to those found in dogs with experimental neurogenic (sino-aortic nerve section) hypertension (Page and McCubbin)(6). These animals respond to sympathectomy by a decrease of arterial pressure(7) and demonstrate moderate decreases of arterial pressure during treatment with 688A (McCubbin, unpublished observations). We therefore hoped that this patient might show a sustained favorable effect of treatment. Eighty mg was given 4 times daily on the first day and 120 mg, 4 times daily thereafter. Supine arterial pressure was not affected, although orthostatic hypertension, nasal congestion and Horner's syndrome supervened. Responses to test drugs were redetermined at the end of 1 week. Presence of adrenergic blockade was shown by pure depressor responses to adrenaline and by a damped pressor response to noradrenaline; sympathetic blockade was considered to be present because the responses to TEAC, systematically depressor before treatment, were now repetitively pressor. The dose of the drug was then increased within the limits of tolerance (gauged subjectively and from orthostatic hypertension) to 1200 mg at the end of the third week after discharge. During this time, systolic and diastolic supine arterial pressures had persisted at about control levels. Tests of pressor responsiveness to adrenaline, noradrenaline and TEAC on the 28th day of treatment demonstrated neither adrenergic nor sympathetic blockade.

Discussion. Our observations contrast with those of Haimovici, Moser and Krakauer(4), who noted symptomatic improvement in 16 of 22 hypertensive patients given 688A and what were considered to be significant decreases in supine arterial pressures of the group although dosage and general plan of study were similar. We were especially disappointed in the patient whose pretreatment responses to TEAC suggested that sympathetic nervous mechanisms actively participated in his arterial hypertension. Subsequent persistence of hypertension in the supine position at a time when adrenergic mechanisms had been blocked suggests that at this time, at least, the mechanisms which sustained arterial pressure were not those considered as characteristic of the activity of sympathetic nerves.

Wunch, Warnke and Myers(2) have shown that remissions of the course of malignant hypertension can sometimes be secured by intravenous infusions of Dibenamine; the similar properties of 688A suggest that it should be as effective. However, as noted above, no remarkable effect occurred in 6 patients who received the drug in the terminal phase of malignant hypertension. Thus, in our hands, 688A has not proven of value in the prolonged treatment of hypertensive vascular disease. The limited scope of the study does not exclude the possibility that favorable responses may not sometimes occur nor do our observations bear on the effectiveness of 688A in the treatment of peripheral vascular diseases, or in causalgia(8). Our data suggest that such treatment might advantageously be discontinuous if the effects are to be sustained.

Summary. Oral administration of 688A, an agent which causes adrenergic and sympathetic blockade, did not ameliorate the condition of 8 patients with essential hypertension

when administered over a period of from 2 to 26 weeks. A statistically significant, but clinically unimpressive decrease of supine systolic and diastolic pressures occurred in only 1 of these patients; in another, supine arterial pressures were maintained in the presence of "blockade" and tolerance to a daily dosage of 1200 mg was established at the end of 4 weeks.

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Some Observations on Effect of Gamma Radiation on the Biochemistry of the Rat Thymus.* (19592)

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The marked sensitivity of thymus to both internal and external radiation has been well established. Morphologic changes(1) can be detected within a few hours after exposure. On the other hand, Barron reported that 4 hours after exposure to x-ray (500 r) the respiratory and glycolytic activities of rat thymus were normal(2); marked changes in respiration and glycolysis were not evident until at least 24 hours after exposure.

It was thus of interest to establish whether various respiratory enzymes of thymus homogenates maintained their activities in spite of extensive cellular damage as evidenced by changes in nucleic acid concentrations.

Methods. In most experiments, 2- to 3-month-old Sprague-Dawley female rats, weighing between 150 and 200 g, were used. It was frequently necessary to pool the thymuses from 3 or more rats in order to obtain sufficient amounts of tissue. Rats were given a dose of 800 r of gamma radiation from a 4 curie point source of Co^{60}. This dose is slightly above the LD_{50}. Succinic dehydrogenase, malic dehydrogenase, cytochrome oxidase, and adenosine triphosphatase were assayed by the methods of Potter and coworkers(3-5). The capacity of thymus homogenatees to esterify inorganic phosphate was studied using a system based on that of Potter(6), except that succinate and pyruvate, both at a final concentration of 0.004 M, were used together as substrates. Neither substrate by itself was adequate for esterification. Attempts were made to prepare mitochondria from thymus by differential centrifugation of tissue homogenized in 0.25 M sucrose(7). The principal difficulty seemed to be in obtaining sufficiently complete separation of nuclei from cytoplasmic elements; up to 40% of the succinic dehydrogenase activity of the thymus

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