

## Alpha- and beta-adrenergic receptor blockade in the treatment of hypertension

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*The effects of single and combined selective blockade of the sympathetic alpha- and beta-receptors were examined in patients with severe hypertension (diastolic pressure > 120 mmHg) uncomplicated by cardiac or renal failure. Given intravenously to 12 patients the alpha-receptor antagonist phentolamine and the beta-receptor antagonist oxprenolol together produced a reduction in systemic arterial pressure to normal levels and a reduction in left ventricular end-diastolic pressure without change in the cardiac output; these effects were maintained. Separately, neither drug resulted in such a satisfactory circulatory response. In 6 patients continued oral treatment for 6 months with progressively increased doses of oxprenolol alone up to 480 mg daily, in divided doses, produced a moderate reduction in blood pressure. The addition of oral phentolamine 20 mg t.d.s. resulted in an immediate reduction of blood pressure to normal levels, both at rest and during walking, without postural or other side effects, and without habituation to treatment over a period of 6 months. Arguments are presented that such treatment may have significant advantages over other current medicinal treatments of severe hypertensive vascular disease.*

In uncomplicated essential hypertension the raised blood pressure is accompanied by a normal cardiac output (Taylor, Donald, and Bishop, 1957). The increased peripheral resistance is uniformly distributed throughout all the regional circulations and resides predominantly in the peripheral arterioles (Freis, 1960). These vessels regulate the resistance in many of the regional vascular beds, and particularly in the kidney, through sympathetic alpha-adrenergic receptors (Moran, 1966).

Thus it is reasonable to expect that drugs which possess both vasodilator properties and also the ability to inhibit stimulation of the adrenergic alpha-receptors may offer substantial advantages over other less specific agents in the treatment of hypertensive vascular disease. Phentolamine, an alpha-receptor antagonist with conspicuous vasodilator properties (Taylor *et al.*, 1965a, b; Majid, Sharma, and Taylor, 1971), has been shown to be effective in acutely lowering the blood pressure of hypertensive patients (Taylor *et al.*, 1965a). However, in subjects with intact cardiovascular reflexes the hypotensive effects of the drug are offset by an accompanying increase in cardiac output (Taylor

*et al.*, 1965a; Majid *et al.*, 1971). For this reason it is logical to combine drugs that block both the alpha- and beta-adrenoreceptors so that the reflex increase in sympathetic stimulation of the heart that occurs in response to the fall in blood pressure induced by alpha-receptor blockade is prevented by inhibition of the cardiac beta-receptors.

The following investigation was, therefore, undertaken to test this thesis by acute haemodynamic studies in patients with severe hypertensive disease and to determine the clinical effectiveness of the combination of oral alpha- and beta-receptor antagonists in the longer term treatment of these patients.

### Patients and methods

Twelve patients with severe uncomplicated essential hypertension were studied. Five were men, average age 47 years (range 44 to 50 years) and average weight 89 kg (range 84 to 98 kg); 7 were women average age 41 years (range 34 to 49 years) and average weight 60 kg (range 49 to 83 kg). Seven patients presented with severe headaches which had proved intractable to other anti-hypertensive drugs, singly or in combination. In the remainder a high blood pressure was discovered during routine medical examination for minor illnesses. The lowest diastolic pressure measured in the supine position by doctors in the ward persistently exceeded 120 mmHg (range 120 to 150) in all patients during their hospital

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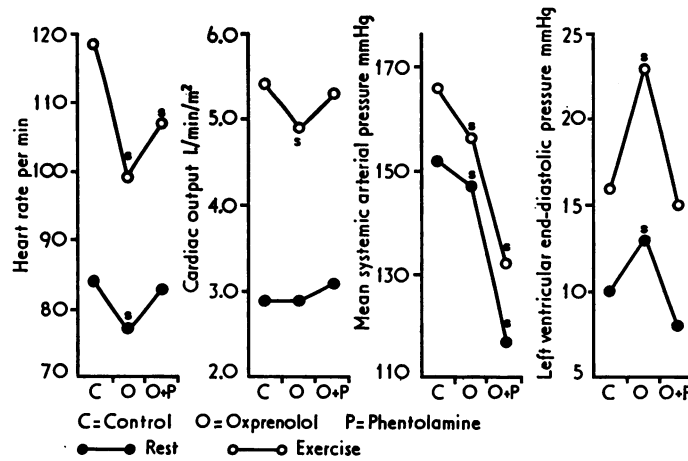


FIG. 1 Haemodynamic effects of intravenous alpha- and beta-receptor antagonists, singly and in combination, at rest and during supine leg exercise, in hypertensive patients. Symbols represent mean values. 'S' indicates significant difference from control value at a probability of 5 per cent or less.

admission. None had papilloedema or fundal haemorrhages or exudates and none had proteinuria. No patient had a history of myocardial infarction, congestive heart failure, or cerebrovascular disease. In 10 patients there was electrocardiographic evidence of left ventricular hypertrophy ( $R_{aVL} > 13$  mm;  $R_{V5-6} > 27$  mm;  $S_{V1} + R_{V5-6} > 35$  mm). In all, the radiographic silhouette suggested concentric left ventricular hypertrophy but in none was the heart dilated (cardiothoracic ratio  $< 55\%$ ). Intravenous pyelography and 24-hour creatine clearance tests were normal in all. Endocrine abnormalities were eliminated by appropriate tests.

The scientific reasons for the study, the proposed programme of investigation, its relation to their individual treatment, and its possible wider therapeutic implications were explained to each patient; the voluntary nature of the co-operation requested was emphasized. All patients freely consented to the study without inducement (Medical Research Council, 1964; Ormrod, 1968).

### Design of investigation

Patients were admitted to hospital for baseline measurements of blood pressure and routine investigations to

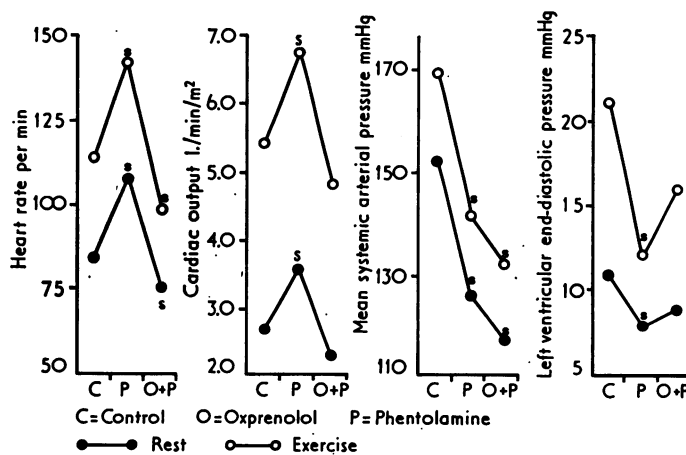


FIG. 2 Haemodynamic effects of intravenous alpha- and beta-receptor antagonists, singly and in combination, at rest and during supine leg exercise, in hypertensive patients. Symbols represent mean values. 'S' indicates significant difference from control value at a probability of 5 per cent or less.

exclude an underlying cause for the raised blood pressure. All were kept active throughout the day to prevent the fall in blood pressure associated with bed rest.

**A) Haemodynamic studies** Patients were familiarized with the laboratory staff and environment and at the same time trained to exercise in the supine position on a bicycle ergometer. A common level of sub-maximal supine leg exercise was selected which all could achieve without discomfort. The bicycle ergometer work load was chosen to give an oxygen uptake similar to that produced by treadmill walking at 2 m.p.h. on a 10° incline, the level of exertion used in the follow-through long-term oral studies. Patients were alternately allocated into one of two groups of six. In group A, the effects of the beta-receptor antagonist oxprenolol (0.2 mg/kg body weight) were studied first before the addition of the alpha-receptor inhibitor phentolamine (0.5-1.0 mg/min). In group B the order of drug administration was reversed. Oxprenolol was given as a bolus injection and phentolamine as a constant infusion through separate lumens of a catheter in the pulmonary artery.

The definitive studies were carried out in the morning, two hours after a light meal without premedication.

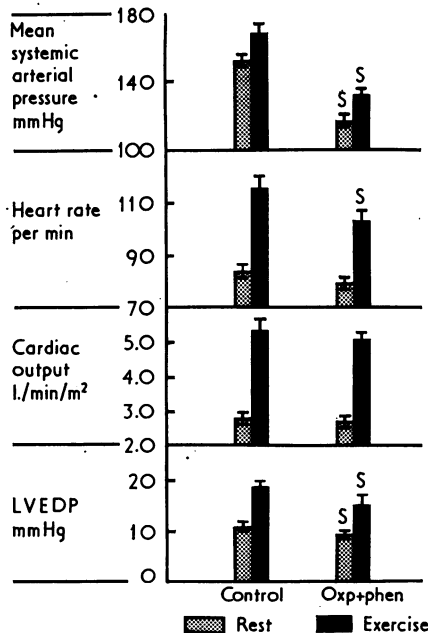


FIG. 3 Haemodynamic effects of intravenous alpha- and beta-receptor antagonists at rest and during supine leg exercise in hypertensive patients. Histograms represent mean values at  $\pm$  S.E.M. 'S' indicates significant difference from control value at a probability of 5 per cent or less. Oxp = oxprenolol. Phen = phentolamine.

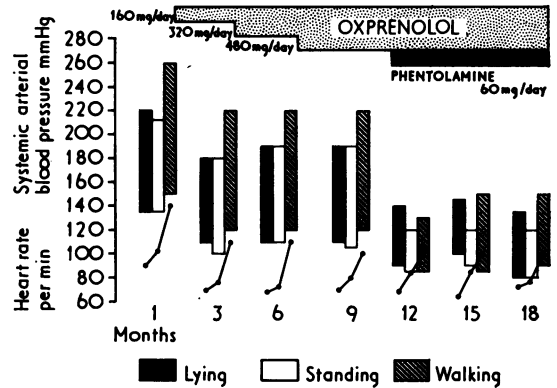


FIG. 4 Effects of oral alpha- and beta-receptor antagonists, singly and in combination, during long-term treatment of a hypertensive patient.

Observations began 30 minutes after introducing a multilumen catheter into the pulmonary artery and nylon catheters (75 x 0.1 cm) into the aorta and left ventricle.

In group A, the programme of investigation started with 6 minutes of supine leg exercise followed by 20 minutes of rest. Oxprenolol was then injected and 15 minutes later the rest and exercise studies were repeated in reverse order. At the end of the second 6-minute period of exercise, phentolamine infusion was started and the rate adjusted to lower the mean systemic arterial pressure to 20 to 30 mmHg. Twenty minutes later the rest and exercise studies were repeated for the third time. In group B the order of drug administration was reversed; the infusion of phentolamine was temporarily discontinued during the second post-exercise recovery period in this group so that patients in both groups received approximately the same total amount of phentolamine (20-40 mg). The times and doses of phentolamine and oxprenolol used were decided after pilot studies in ourselves had confirmed the effectiveness of each drug in producing a conspicuous degree of alpha- or beta-receptor blockade over the time scale of the intended investigation. Cardiac output was measured by the direct oxygen Fick method during the last four minutes of each rest period and during the final two minutes of each exercise period. Intravascular pressures and electrocardiogram were displayed and recorded continuously throughout.

**B) Clinical studies** An oral preparation of phentolamine was supplied at our special request by Ciba Laboratories, Horsham, after initial studies had confirmed the antihypertensive effectiveness of the intravenous preparation in combination with oxprenolol. Thus, only the last six patients were able to be treated on a direct follow-through basis from the intravenous studies, without the intervention of other antihypertensive treatment.

During their initial hospital admission 6 patients were walked daily on a motor-driven treadmill at 2 m.p.h. on a 10° incline for 10 minutes, a level of exercise that was well within the usual range of their normal everyday exertion. Sphygmomanometric blood pressure and electrocardiographically determined heart rate were measured in duplicate after lying supine for 10 minutes, after standing for 3 minutes, and at minute intervals during treadmill walking for 10 minutes; values used for analysis were the average of measurements taken at the 8th, 9th, and 10th minute of walking. Control values were furnished by six daily studies on each patient before the haemodynamic investigation. Treatment was started the day after the circulatory studies with oxprenolol 40 mg q.d.s. (160 mg daily). Patients were discharged from hospital a few days later and followed up at fortnightly intervals. At each follow-up blood pressure and heart rate were measured lying, standing, and at the same speed of treadmill walking as during the control studies. The dose of oxprenolol was increased at 2-monthly intervals up to a maximum of 160 mg t.d.s. (480 mg daily) where it was held for 3 months to measure any habituation effects. This dose of oxprenolol was chosen as the final dose as previous studies in this laboratory had shown that 160 mg oxprenolol induces a substantial suppression of the circulatory response to exercise for up to 8 hours (Taylor *et al.*, 1974). Phentolamine 20 mg t.d.s. (60 mg daily) was then added to this regimen and out-patient observations continued. This dose of phentolamine was used as preliminary observations conducted throughout the day showed that 20 mg produced its maximal antihypertensive effect within one hour with an effective duration of 3 to 6 hours (Fig. 5). Similar hour-by-hour studies were carried out in each patient at monthly intervals after the addition of phentolamine to determine the magnitude and duration of its antihypertensive activity in these circumstances. At each out-patient clinic, bodyweight, serum, sodium, potassium, chloride, and urea, and electrocardiogram

were also examined; standard chest radiographs were taken at monthly intervals.

### Laboratory techniques, measurements, and statistics

The haemodynamic methods of investigation used in this study have been reported in detail previously (Majid *et al.*, 1971; Sharma *et al.*, 1972). In this laboratory, using such methods under similar conditions of study, duplicate measurements of oxygen uptake, cardiac output, intravascular pressures, and left ventricular end-diastolic pressure agreed within 5, 7, 3, and 8 per cent, respectively. To avoid observer bias during the oral treatment period, brachial arterial blood pressure was measured with a sphygmomanometer incorporating a randomly offset zero (Hawksley-Gelman), (Garrow, 1963; Evans and Prior, 1970; Wright and Dore, 1970). Pressure measurements were made in duplicate and read to the nearest 2 mmHg. For clarity of tabulation (Table 2) measurements were averaged throughout each period in each subject. The probability of statistical significance of changes compared to the control observations was calculated by Student's 't' test for paired data.

## Results

### Haemodynamic studies

No symptomatic side effects followed the intravenous administration of either drug alone or in combination in any patient. The electrocardiogram was continuously monitored and did not reveal any dysrhythmia or any other change during or after the injection of either phentolamine or oxprenolol.

**Group A (Fig. 1, Table 1)** Oxprenolol alone produced a reduction in heart rate and mean systemic arterial pressure and rise in left ventricular

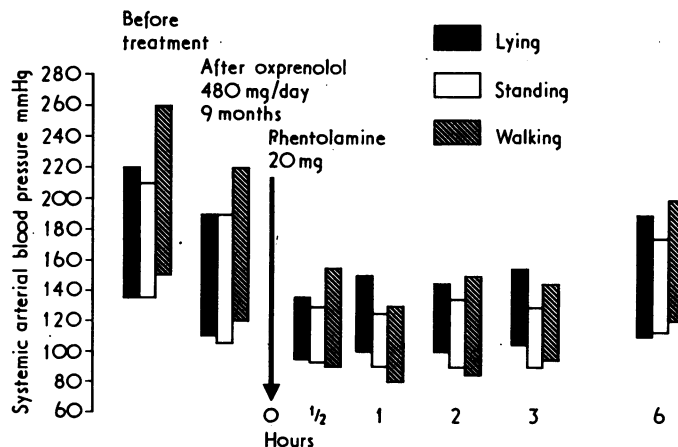


FIG. 5 Magnitude and duration of action of a single oral dose of 20 mg phentolamine on the blood pressure of a hypertensive patient pretreated with 480 mg oral oxprenolol daily.

TABLE I Haemodynamic effects of adrenergic alpha- and beta-receptor antagonists singly and combined in hypertensive patients

Variable	State	Group A (6)			Group B (6)	
		Control	Oxprenolol	Oxprenolol + phentolamine	Control	Phentolamine
Oxygen uptake (ml/min per m <sup>2</sup> )	R	140 ± 12	152 ± 9	162 ± 11	142 ± 11	154 ± 7
	Ex	436 ± 26	432 ± 17	420 ± 35	461 ± 44	576 ± 35
Cardiac output l./min per m <sup>2</sup>	R	2.9 ± 0.2	2.8 ± 0.2	3.1 ± 0.1	2.7 ± 0.2	3.6 ± 0.3*
	Ex	5.4 ± 0.3	4.8 ± 0.2*	5.3 ± 0.2	5.4 ± 0.3	6.7 ± 0.3‡
Heart rate/min	R	84 ± 5	77 ± 4*	83 ± 5	85 ± 4	108 ± 10*
	Ex	119 ± 7	99 ± 5‡	107 ± 6†	114 ± 8	142 ± 13‡
Mean systemic arterial pressure (mmHg)	R	152 ± 7	147 ± 7*	117 ± 6§	152 ± 7	126 ± 8†
	Ex	166 ± 8	156 ± 7‡	132 ± 7§	169 ± 8	141 ± 7*
Left ventricular end-diastolic pressure (mmHg)	R	10 ± 1	13 ± 2*	8 ± 1	11 ± 1	8 ± 1*
	Ex	16 ± 2	24 ± 3‡	15 ± 3	21 ± 3	12 ± 2‡

Number of patients in each group in parentheses. Data expressed as mean ± standard error of mean. R, rest; Ex, exercise. Probabilities relate to the significance of difference between paired data as compared to the control:  $P < 0.05^*$ ;  $P < 0.02^\dagger$ ;  $P < 0.01^\ddagger$ ;  $P < 0.001^\S$ .

end-diastolic pressure both at rest and during exercise; cardiac output was unchanged at rest but reduced during exercise. The addition of phentolamine produced a more substantial decrease in mean systemic arterial pressure: this was accompanied by a reduction in the left ventricular end-diastolic pressure to control levels and an increase in the heart rate both at rest and during exercise. Cardiac output was unchanged from control values.

**Group B (Fig. 2, Table 1)** Phentolamine alone induced a conspicuous fall in mean systemic arterial pressure both at rest and during exercise. This was accompanied by an increased heart rate and cardiac output and a reduction in left ventricular end-diastolic pressure. The addition of oxprenolol reduced the heart rate and cardiac output to near control values, reduced the mean systolic arterial pressure still further, and increased the left ventricular end-diastolic pressure towards control volumes.

**Combined results (Fig. 3, Table 1)** The net result of oxprenolol and phentolamine together in all 12 patients was a reduction in systemic arterial pressure to normal levels both at rest and during exercise. This was achieved without any change in the normal resting cardiac output or in the output response to exercise. There was a significant reduction in the left ventricular end-diastolic pressure both at rest and during exertion.

#### Clinical studies (Fig. 4, Table 2)

There was a gradual reduction in systemic pressure both lying and standing at rest and also during

exercise as the dose of oxprenolol was increased. But in only 2 of the 6 patients was there a further fall in blood pressure when the dose was increased from 320 to 480 mg daily. No further fall in blood pressure was observed in any patient when 480 mg oxprenolol alone daily was continued for three months. No postural effects on the blood pressure were observed. There was a conspicuous reduction in the heart rate lying, standing, at rest, and during walking in all patients. On this regimen the only complaint was that of tiredness of the legs when climbing stairs or hurrying.

The addition of phentolamine produced a further substantial reduction in systemic blood pressure to normal levels both at rest and during exercise without symptomatic postural effects. The magnitude and duration of the antihypertensive activity of oral phentolamine in these circumstances is illustrated in Fig. 5. The reduction in systolic and diastolic pressures after the addition of phentolamine to oxprenolol was statistically significant lying (systolic:  $P < 0.001$ ; diastolic:  $P < 0.01$ ), standing (systolic:  $P < 0.01$ ; diastolic:  $P < 0.001$ ), and walking (systolic:  $P < 0.01$ ; diastolic:  $P < 0.05$ ) compared to the values with oxprenolol alone. The effect on the blood pressure of the combination of oxprenolol and phentolamine persisted unchanged for more than 6 months, the minimum length of study in all subjects.

No side effects of the combined oral treatment were observed except in one patient who complained of slight nausea on first taking phentolamine; this symptom disappeared when the tablets were taken with food. Throughout the year of follow-up in each of these patients, no changes were

TABLE I (Cont'd)

Groups A and B (12)		
Phentolamine + oxprenolol	Control	Phentolamine + oxprenolol
141 ± 8	141 ± 8	151 ± 7
442 ± 37	449 ± 25	431 ± 25
2.4 ± 0.1	2.8 ± 0.2	2.7 ± 0.2
4.9 ± 0.4	5.4 ± 0.3	5.1 ± 0.2
76 ± 4*	84 ± 3	79 ± 3
99 ± 5‡	116 ± 5	103 ± 4§
117 ± 6‡	152 ± 4	117 ± 4§
132 ± 5‡	168 ± 6	132 ± 4§
9 ± 1	11 ± 1	8 ± 1‡
16 ± 3	19 ± 1	15 ± 2‡

observed in body weight, blood electrolytes, standard liver function tests, electrocardiogram, or chest radiograph. Four of the six patients complained of severe headaches before treatment; all are now symptom free.

Discussion

The rationale for the use of vasodilator drugs in combination with beta-receptor antagonists in the treatment of essential hypertension was outlined in the introduction to this report. The results of the haemodynamic studies support the thesis that partial blockade of the cardiac beta-receptors augments the blood pressure lowering effects of the vasodilator and alpha-receptor antagonist phentolamine by reducing the sympathetic stimulation of the heart that occurs in response to the fall in blood pressure. The blockade of the cardiac beta-receptors can also be expected to counteract the cardiac stimulation that results from the release of endogenous catecholamines by phentolamine (Gould, Zahir, and Ettinger, 1969). Oxprenolol and phentolamine in combination produced a more conspicuous reduction in blood pressure than either drug alone. Furthermore, the increase in left ventricular end-diastolic pressure due to beta-blockade alone was nullified by the addition of phentolamine, and conversely the disadvantageous tachycardia and increase in cardiac output with phentolamine alone was completely counteracted by the addition of oxprenolol. In these haemodynamic terms, the

TABLE 2 Results of oral treatment of hypertensive patients with alpha- and beta-receptor antagonists

Case No.	Sex, age (yr), wt (kg)	Variable	Control			Oxprenolol			Oxprenolol and phentolamine		
			Lying	Standing	Walking	Lying	Standing	Walking	Lying	Standing	Walking
1	F	Systolic	221	212	258	192	188	220	138	130	145
		Diastolic	133	135	148	112	108	117	88	82	91
		HR	88	98	137	72	78	112	76	81	114
2	F	Systolic	218	213	231	166	162	183	146	138	148
		Diastolic	121	124	127	118	121	129	94	90	95
		HR	81	96	122	69	72	98	72	85	106
3	F	Systolic	188	189	221	172	173	188	158	145	160
		Diastolic	122	121	129	109	112	115	98	95	98
		HR	80	99	135	68	76	113	78	90	116
4	M	Systolic	219	215	245	187	192	223	145	140	156
		Diastolic	120	120	141	104	109	116	95	90	94
		HR	70	84	112	60	67	106	68	82	108
5	M	Systolic	202	201	274	168	169	179	136	125	132
		Diastolic	122	125	148	118	121	124	91	89	96
		HR	78	83	127	73	75	108	75	81	112
6	M	Systolic	219	220	231	170	163	192	148	145	159
		Diastolic	128	130	143	109	109	116	89	86	90
		HR	73	80	123	67	70	105	70	80	110
Mean		Systolic	210 ± 5	208 ± 5	240 ± 8	175 ± 5‡	175 ± 6‡	197 ± 9†	143 ± 4‡	137 ± 5§	150 ± 6§
±		Diastolic	124 ± 3	126 ± 3	139 ± 4	112 ± 3‡	113 ± 3‡	119 ± 5‡	90 ± 3‡	89 ± 3‡	94 ± 3§
SEM		HR	78 ± 3	90 ± 4	126 ± 6	68 ± 4†	73 ± 4‡	107 ± 5†	73 ± 4*	83 ± 4†	111 ± 3§

Data given relate to averages of measurements in each period. Probabilities relate to the significance of difference of the paired data from the control value. P < 0.05\*; P < 0.02‡; P < 0.01‡; P < 0.001§.

circulation of these severely hypertensive patients could not be distinguished from that of normal subjects after this combination of drugs. Such beneficial circulatory results have rarely been achieved by other antihypertensive drugs in common use singly or in combination.

The clinical follow-up studies with oral treatment of these patients with this combination of drugs were equally promising. Though oxprenolol alone produced a moderate reduction in the arterial pressure in the majority of the patients, in none was the blood pressure of these severely hypertensive patients reduced to clinically satisfactory levels. The addition of a relatively small dose of oral phentolamine to this regimen produced a further conspicuous reduction in blood pressure, in every patient to normal levels without postural hypotension and with a normal response (small increase) to exercise. This antihypertensive activity of oral phentolamine was observed for 3 to 6 hours after each oral dose and its effectiveness was maintained in all patients for longer than six months without habituation. The combination of oxprenolol (480 mg daily) and phentolamine (60 mg daily) during this time was unaccompanied by any symptomatic side-effects or any untoward change in body weight, heart size, electrocardiogram, renal, or liver function.

However, the study can be criticized from a number of aspects. The rigid criteria employed for their selection almost certainly resulted in a cohort of patients infrequently seen in routine clinical practice. Though this must necessarily limit the wider clinical application of these results, clinical homogeneity of the patient group is essential if the results of such studies are to be therapeutically valid. It must also be pointed out that no attempt was made to equate the relative degree of either alpha- or beta-receptor blockade achieved either in the haemodynamic or in the clinical studies in these patients. The doses of both drugs used in both situations were empirically chosen and no attempt was made to determine the dose-response relation for either drug singly or in combination. In fact, the complete response of all patients in this group of severely hypertensive patients suggests that smaller doses of these drugs, particularly that of the beta-receptor antagonist, may have achieved equally beneficial results; the effects of small doses should certainly be explored in any future trial of alpha- and beta-blockers in hypertension. Finally, it must be emphasized that though every effort was made to remove measurement bias, as by the use of a random-zero sphygmomanometer, the clinical studies were not double-blind in design. Though these provisos relegate the significance of these results to those of a promising preliminary report, we consider that the

objective nature of the measurements furnish sufficient evidence to encourage further investigation of this treatment in severe hypertension.

Vasodilator drugs with alpha-receptor blocking activity in combination with beta-receptor antagonists have two distinct advantages over the use of beta-receptor inhibitors alone in the treatment of hypertension. The reduction in blood pressure produced by vasodilator drugs results in a lowering of impedance to ejection of blood from the ventricle, thus reducing left ventricular pressure work. The beta-receptor antagonists reduce blood pressure largely by reducing cardiac output, peripheral resistance remaining unchanged or even increasing (Majid *et al.*, 1970). The effects on the heart of these two methods of achieving blood pressure reduction were clearly contrasted in the present study. Phentolamine resulted in a reduction in blood pressure and a decrease in left ventricular end-diastolic pressure. Beta-receptor blockade alone resulted in a lesser reduction in blood pressure at the expense of an increase in left ventricular end-diastolic pressure. In combination the antihypertensive effects of the two drugs were summated and associated with a reduction in left ventricular end-diastolic pressure. The other major advantage of the drugs that block vasoconstrictive alpha-receptors in the treatment of hypertensive disease depends on their ability to inhibit the renal vascular effects of sympathetic stimuli. The alpha-receptors play a key role in the regulation of the circulation through the kidney (Handley and Moyer, 1954). An increase in sympathetic activity whether due to emotion, excitement, exercise, trauma, or the incidental fall in blood pressure that occurs after beta-receptor antagonists alone, results in vasoconstriction of the renal vessels due to alpha-receptor activity. Blockade of these receptors by preventing or reducing such frequent shutdown of the renal vessels may retard or even prevent the progression of renal vascular disease, which is still one of the major causes of death in hypertension (Smirk and Hodge, 1963).

A number of studies involving selective blockade of the sympathetic alpha- and beta-receptors alone or in combination have been reported. Alone, the alpha-receptor antagonists never achieved popularity in the treatment of hypertension. Though phentolamine was specifically introduced for this purpose (Moyer and Caplovitz, 1953), doses up to 900 mg daily were necessary to achieve a satisfactory reduction in blood pressure; these doses frequently induced gastrointestinal disturbances. Phenoxybenzamine, another alpha-receptor antagonist likewise never found wide favour in the treatment of hypertension, probably because of its

pronounced cumulative effects (Nickerson, 1962). Hydralazine, a vasodilator drug with weak alpha-receptor blocking activity achieved a temporary popularity (Freis, 1962), but the high doses necessary to achieve satisfactory control of the blood pressure with this drug alone often gave rise to unpleasant side effects and its use was quickly curtailed. Beta-receptor antagonists alone have also been advanced in the treatment of hypertension (Prichard and Gillam, 1969; Zacharias and Cowen, 1970). However, the large doses (e.g. 1000 mg propranolol daily or more) often necessary to achieve a satisfactory reduction in the blood pressure of severely hypertensive patients, the frequency of inadequate blood pressure control despite such large doses, and the possible long-term deleterious effects of such high doses on left ventricular function (Majid *et al.*, 1970), have resulted in some waning of interest in the use of these drugs alone in the treatment of severe hypertensive disease. This has led to the consideration that both types of drug together may be more effective than either alone, and recently several claims have been made for the antihypertensive effectiveness of combined selective sympathetic blockade. Consistent control of the blood pressure in hypertensive patients has been achieved with vasodilator drugs in combination with beta-receptor antagonists in acute intravenous studies (Santerstedt *et al.*, 1971), in short-term oral studies (Gilmore, Weil, and Chidsey, 1970; Katila and Frick, 1970; Hansson *et al.*, 1971; Santerstedt *et al.*, 1972; Zacest, Gilmore, and Koch-Wesser, 1972), and during single-blind trials (Aenishänslin *et al.*, 1972). The absence of potentiation or the development of side effects with such combined treatment reported in previous open (Hansson *et al.*, 1971), single-blind (Aenishänslin *et al.*, 1972) or double-blind (Beilin and Juel-Jenson, 1972) trials is probably explicable on the basis that in the majority of instances the vasodilator drugs used had only weak alpha-blocking activity, e.g. hydralazine, or cumulative side effects, e.g. phenoxybenzamine, or that the trial incorporated a fixed dose regimen. Comparison of these reported results with those of the present study indicates the clinical importance of the choice of drugs used and the necessity of titration of their dosage against the blood pressure in each individual patient. In hypertension, in which the sympathetic component of the blood pressure is so variable, fixed-dose drug schedules probably have no place in the treatment of the individual patient. Though we found that the combination of phentolamine 20 mg and oxprenolol 160 mg each thrice daily was effective in all the patients we studied, the group was small and selected only to include patients with par-

ticular severe disease; smaller doses of both drugs may be equally efficacious in patients with less severe hypertension.

We consider that these studies provide sufficient physiological and clinical evidence to warrant further clinical trials in the use of combined alpha- and beta-receptor blockade in the treatment of severe hypertension.

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