CIRCULATORY EFFECTS OF NORADRENALINE AND ADRENALINE BEFORE AND AFTER LABETALOL

D.A. RICHARDS, B.N.C. PRICHARD & R. HERNÁNDEZ

Department of Clinical Pharmacology, University College Hospital, London WC1

- 1 Two studies were carried out in the same six normal healthy males to compare the circulatory effects of exogenously infused noradrenaline and adrenaline before and after intravenous labetalol.
- 2 Noradrenaline before and after labetalol produced a similar pattern of circulatory change, namely dose related systolic and diastolic pressor responses accompanied by profound bradycardia and reduced cardiac output.
- 3 Labetalol competitively antagonized both the systolic and diastolic pressor effects of noradrenaline.
- 4 Adrenaline at low doses produced a diastolic depressor response accompanied by increases in heart rate and cardiac output. The highest dose also produced smaller increases in heart rate and cardiac output and diastolic pressure increased slightly. All doses provoked increases in systolic pressure.
- 5 After labetalol all doses of adrenaline provoked a diastolic pressor response which was marked at high doses. The systolic response was attenuated compared with that before labetalol. At all doses, heart rate and cardiac output were reduced.
- 6 Since in the presence of labetalol both noradrenaline and adrenaline profoundly reduce heart rate and cardiac output whilst increasing blood pressure, it may be unwise to use either of these catecholamines alone if attempts are being made to reverse excessive hypotension from labetalol overdose.
- 7 Preliminary observations indicate that labetalol does not increase endogenous plasma catecholamines immediately after intravenous injection. Plasma concentrations of noradrenaline and adrenaline after exogenous infusion were increased after labetalol compared with those levels before labetalol. It appears that labetalol inhibits the clearance of catecholamines from the plasma possibly by inhibiting neuronal uptake mechanisms.

Introduction

In patients with phaeochromocytoma the raised blood pressure and other symptoms result from the liberation of noradrenaline and adrenaline in excessive quantities. It is also thought that the hypertension associated with abrupt withdrawal of clonidine is related to excessively raised catecholamine levels liberated into the plasma (Hansson & Hunyor, 1973). Labetalol has been used successfully to treat patients with hypertension resulting from these conditions (Rosei, Brown, Lever, Robertson, Robertson & Trust, 1976). It is probable that the lowering of blood pressure results from the antagonist effect of labetalol upon α - and β -adrenoceptors. Indeed previous studies have shown that β -adrenoceptor blockade alone with propranolol caused increases in blood pressure in patients with phaeochromocytoma (Prichard & Ross, 1966; Ross, Prichard, Kaufman, Robertson & Haries, 1967). It seemed important therefore to evaluate the pharmacological effects of labetalol upon the

circulatory responses to intravenous noradrenaline and adrenaline. We report here studies in normal healthy males who received noradrenaline and adrenaline by intravenous infusion before and after labetalol.

Methods

Six normal healthy males aged 24–42 years and weighing 66–92 kg body weight, took part. The method was identical in both experiments. Each subject remained in the supine position throughout. Forearm veins were cannulated on both sides and maintained patent with heparinized saline. One side was used for the administration of drugs and in four of the subjects the other for withdrawal of blood for measurement of serum catecholamine levels. An electrocardiogram was running throughout. Electrodes

were also attached for the purpose of measuring cardiac impedance (Kubicek, From, Patterson, Witsoe, Casteneda, Lillehei & Ersek, 1970) and blood pressure was measured with a London School of Hygiene and Tropical Medicine sphygmomanometer (Rose, Holland & Crawlay, 1964).

After a period of rest when heart rate and blood pressure were stable an infusion of noradrenaline was commenced. The initial dose was $4 \mu\text{g}/\text{min}$ followed by $8 \mu\text{g}$ then $16 \mu\text{g}/\text{min}$; each dose level being maintained for 4 min. Blood pressure was measured 1 min intervals whilst at 0, 4, 8 and 12 min, cardiac impedance was also recorded in order to obtain an estimate of stroke output. After a period of 15 min during which the circulation reverted to normal, labetalol $1.0 \text{ mg}/\text{kg}$ was administered intravenously over 1 min. Serial measurements of heart rate, blood pressure and cardiac impedance were made for 10 min after which the noradrenaline infusion procedure was repeated. A similar procedure was followed but on this occasion, noradrenaline in doses of 8, 16 and $32 \mu\text{g}/\text{min}$ were administered in order to produce similar increases in blood pressure as had been recorded before labetalol.

In a different series of experiments all the above procedures were repeated using intravenously infused adrenaline. Adrenaline was given before and after labetalol in progressively increasing doses of 8, 16 and $32 \mu\text{g}/\text{min}$ for 4 min at each dose level.

Immediately before and at the end of the infusions, a blood sample was obtained in order to measure serum catecholamine levels. Blood samples were also obtained immediately before and three minutes after labetalol administration.

Determination of plasma catecholamines

Samples of venous blood were collected directly into tubes containing $20 \mu\text{l}$ of a solution containing 95 mg EDTA and 60 mg of reduced glutathione/ml. Before use the pH of the solution was adjusted with 6N NaOH to 6–7. The tubes were placed in an ice bath and centrifuged at 4°C to separate the plasma from the cells. The separated plasma was stored at 4°C in a refrigerator prior to analysis which was within 24 h of collection of the sample. Samples of plasma (0.25 ml) were taken for determination of catecholamines. The plasma catecholamines were determined by modification of the radioenzymatic method described by Callingham & Barrand (1976). A partially purified preparation of rat liver catechol-O-methyl transferase (COMT) was used instead of pig liver COMT. In this method the catecholamines are converted to their labelled O-methyl derivatives by COMT in the presence of S-adenosyl- ^3H -methionine. The methylated catecholamines are extracted from the reaction mixture, acetylated with acetic anhydride and the derivatives separated by paper chromatography. The

Figure 1 Changes in blood pressure induced by noradrenaline and adrenaline before (■) and after (▨) labetalol.

acetylated derivatives of methylated COMT are detected by spraying with ammonia and Folin and Ciocalteu reagent. The bands corresponding to noradrenaline, adrenaline and dopamine derivatives are cut out of the paper and combusted in oxygen using the Packard 306 oxidizer. The tritiated water formed is collected in NE260 scintillator and the radioactivity determined with a Packard 3320 liquid scintillator counter using the external standards channels ratio procedure.

Analysis of data

Log dose-response curves were constructed from the mean increases at each dose level of noradrenaline using least squares analysis. These were tested for parallelism. Student's *t*-test for paired samples was used to derive all other probabilities.

Traces of thoracic impedance were used to calculate stroke volume. The traces were analysed using a digitizing board and fed into a Wang 2200T computer which used the formula described by Kubicek *et al.* (1970) for deriving stroke volume.

Results

Effects of noradrenaline

Blood pressure Incremental doses of noradrenaline over 12 min substantially increased systolic, diastolic and mean arterial pressure (Figure 1). The average increase in systolic pressure after the final dose of $16 \mu\text{g}/\text{min}$ was 37 mmHg (+32%), diastolic pressure

33 mmHg (+47%) and mean arterial pressure, 35 mmHg (+42%). The calculated mean peripheral resistance was also increased by 78% over the period (Table 1). The increases in blood pressure and peripheral resistance at each dose level of noradrenaline were statistically significant ($P < 0.001$).

Heart rate and cardiac output As noradrenaline increased the arterial pressure then reductions concurrently occurred in the heart rate (Table 1). There was a significant correlation between these ($r = 0.53$, $P < 0.05$). Overall, heart rate was reduced by an average of 26 beats/min (−35%) and mean cardiac output reduced by 2.3 litres (−22%) (Figure 2). These reductions were statistically significant ($P < 0.001$).

Effects of noradrenaline after labetalol

Blood pressure Having administered labetalol (1.0 mg/kg i.v.) it became possible to increase the doses of noradrenaline up to 32 µg/min during the second infusion because labetalol significantly ($P < 0.05$) attenuated the pressor responses induced by noradrenaline (Figure 1). Log dose-response curves of noradrenaline induced increases in systolic pressure (Figure 3) and diastolic pressure (Figure 4) after labetalol were both shifted to the right in a parallel manner compared with those curves before labetalol.

Heart rate and cardiac output Heart rate and cardiac output changed in the same directions as seen prior to labetalol (Figure 2). The same doses of noradrenaline produced similar changes and these were not significantly different from each other. At the highest dose of noradrenaline after labetalol marked reductions occurred in mean heart rate and mean cardiac output (Table 1).

Effects of adrenaline

Blood pressure The 12 min infusion of adrenaline produced a different pattern of change in blood pressure to that seen with noradrenaline (Figure 1). At low doses, adrenaline reduced diastolic blood pressure and only at the end of the infusion was there a small average increase of 2 mmHg (+3%) (Table 2). By contrast, all doses produced significant ($P < 0.001$) systolic pressor responses which at the end of infusion, amounted to an average of 52 mmHg (+46%). The mean arterial pressure was increased finally by 19 mmHg (+22%). Calculated peripheral resistance was initially reduced and finally showed a very small decrease (−3%).

Heart rate and cardiac output In contrast to noradrenaline (Figure 2) adrenaline particularly at the lower doses modestly but not significantly, increased

Table 1 Mean ($\pm$ s.e. mean) circulatory changes induced by noradrenaline before and after labetalol

	Before labetalol				After labetalol			
	Noradrenaline/min				Noradrenaline/min			
	Before noradrenaline	4 µg	8 µg	16 µg	Before noradrenaline	8 µg	16 µg	32 µg [†]
Systolic pressure (mmHg)	113 (2.9)	123 (3.3)	135 (4.1)	150 (6.3)	110 NS (2.9)	120* (3.8)	133* (5.8)	148 (5.9)
Diastolic pressure (mmHg)	70 (1.3)	80 (2.0)	92 (1.7)	103 (3.3)	69 NS (1.3)	85* (3.3)	98 NS (4.6)	111 (4.6)
Mean arterial pressure (mmHg)	84 (1.7)	95 (2.0)	106 (2.0)	119 (4.1)	83 NS (1.7)	96* (3.3)	110* (5.0)	123 (5.0)
Heart rate (beats/min)	75 (5.0)	66 (5.0)	57 (2.9)	49 (2.9)	70 NS (2.0)	56 NS (2.9)	49 NS (3.8)	40 (2.0)
Cardiac output (l/min)	10.4 (0.6)	9.5 (0.7)	9.1 (0.4)	8.1 (0.2)	9.7 NS (0.5)	8.1 NS (0.2)	7.6 NS (0.3)	6.2 (0.2)
Peripheral resistance (PR units)	8.3 (0.5)	10.2 (0.8)	11.8 (0.7)	14.8 (1.0)	8.7 NS (0.6)	12.0 NS (0.6)	14.5 NS (1.1)	20.0 (1.3)

NS Not significantly different from values before labetalol

* $P < 0.05$ difference from same dose before labetalol

[†] Values in this column not compared.

Figure 2 Changes in heart rate, cardiac output and peripheral resistance induced by noradrenaline and adrenaline before (■) and after (□) labetalol.

mean heart rate (5 beats/min) and mean cardiac output (0.2 l/min) (Table 2).

Effects of adrenaline after labetalol

Blood pressure Unlike the pattern of blood pressure change after noradrenaline, the administration of labetalol did not allow any increase in the infused doses of adrenaline. Although labetalol significantly ($P < 0.01$) attenuated the systolic pressure to the highest dose of adrenaline (Figure 1), a significant ($P < 0.001$) increase in diastolic pressure occurred which at maximum was 37 mmHg (+52%). Thus there was an overall increase in mean arterial pressure (Figure 2). Associated with these changes there was a significant ($P < 0.01$) increase of 85% in the calculated peripheral resistance.

Heart rate and cardiac output After labetalol, mean heart rate and cardiac output changed in the opposite directions to those seen before labetalol administration. The differences were statistically significant ($P < 0.01$) and at the highest dose of adrenaline mean heart rate was reduced by 27 beats/min (-35%) and mean cardiac output by 2.3 l (-23%) (Figure 2).

Plasma catecholamine levels

The administration of labetalol did not produce any significant increases in plasma catecholamine levels immediately after injection. After the administration of noradrenaline by infusion, increases in the plasma concentrations of noradrenaline were shown at the end

Figure 3 Log dose-response curves of increases in systolic pressure induced by noradrenaline before (○) and after (●) labetalol.

of the infusion. This was also the case with plasma adrenaline concentrations. After labetalol administration and after repeating the infusions of noradrenaline and adrenaline, there were marked increases in the plasma concentrations of these amines dependant upon which amine had been infused (Table 3).

Discussion

The observed increases in systolic and diastolic blood pressure after exogenously infused noradrenaline are consistent with its known pharmacological effects which are predominantly those exerted through vascular α -adrenoceptors. The α -adrenoceptor mediated increases in blood pressure then reflexly provoked the marked reduction in heart rate consequent upon increased vagal effects upon the heart. A correlation was found between the increased blood pressure and the reduction in heart rate and indeed the fall in the cardiac output under these circumstances was also largely related to the reduced heart rate. High dose infusions of noradrenaline therefore increased blood pressure which was associated with reflex induced profound reductions in heart rate and cardiac output.

Using traces of thoracic impedance to measure stroke volume provides only an estimate of the absolute values. In a recent study however, in open chest dogs, it was shown that changes in thoracic impedance during systole were dependant upon output from left and right ventricles (Thompson, 1978

Figure 4 Log dose-response curves of increases in diastolic pressure induced by noradrenaline before (O) and after (●) labetalol.

personal communication). The values of stroke output derived from thoracic impedance were similar to those obtained from a flow probe placed around the aortic root. In particular, changes in cardiac output after the administration of propranolol, isoprenaline and noradrenaline indicated that the impedance technique provided reliable values of cardiac output. Furthermore, we have measured in a study in man the circulatory responses to isoprenaline before and after propranolol and labetalol using the thoracic impedance technique (Richards, Prichard & Dobbs, 1978). The changes measured in the cardiac output under these circumstances were similar in degree to those reported in another study in man where the thermodilution technique was used to measure cardiac output (Paley, McDonald, Blumenthal & Mailhot, 1971). In the present study, only changes induced by the catecholamines have been compared and it is likely that these are reliable.

After labetalol administration the pressor responses due to noradrenaline were antagonized in a competitive manner which is similar to previous findings (Richards & Prichard, 1978). These effects are likely to be due to the known α -adrenoceptor blocking effect of labetalol (Richards, 1976). The pattern of change in heart rate and cardiac output

Table 2 Mean ($\pm$ s.e. mean) circulatory changes induced by adrenaline before and after labetalol

	Before labetalol				After labetalol			
	Before adrenaline	Adrenaline/min			Before adrenaline	Adrenaline/min		
		8 μ g	16 μ g	32 μ g		8 μ g	16 μ g	32 μ g
Systolic pressure (mmHg)	113 (2.5)	123 (3.3)	136 (5.0)	165 (8.7)	113 NS (1.6)	123 NS (2.5)	134 NS (3.3)	144** (4.1)
Diastolic pressure (mmHg)	73 (2.0)	65 (2.9)	64 (2.9)	75 (3.7)	71 NS (1.2)	84*** (1.6)	97*** (2.5)	108*** (1.6)
Mean arterial pressure (mmHg)	86 (1.2)	84 (2.0)	88 (2.0)	105 (4.1)	85 NS (1.2)	97* (1.6)	109* (2.5)	120** (2.5)
Heart rate (beats/min)	74 (5.0)	88 (7.5)	87 (7.0)	79 (5.8)	77 NS (3.3)	65*** (4.1)	57*** (1.6)	50*** (2.9)
Cardiac output (l/min)	9.6 (1.0)	11.5 (0.6)	12.9 (0.6)	11.7 (0.9)	10.2 NS (0.8)	9.6 NS (0.9)	8.0** (0.6)	7.9** (0.8)
Peripheral resistance (PR units)	9.5 (1.1)	7.4 (0.4)	6.9 (0.4)	9.2 (0.8)	8.6 NS (0.6)	10.7* (1.1)	14.1** (1.1)	15.9** (1.7)

NS Not significantly different from values before labetalol

* $P < 0.05$

** $P < 0.01$ all differences from same dose before labetalol

*** $P < 0.001$.

reduced by noradrenaline after labetalol was broadly similar to that seen with noradrenaline alone. At the same doses of noradrenaline before and after labetalol the reductions in heart rate and cardiac output were similar. At doses of noradrenaline which produced similar increases in blood pressure the reductions in heart rate and cardiac output after labetalol were somewhat greater but the differences were not statistically significant. From these data it is clear that if noradrenaline were to be used alone to reverse marked hypotension which might follow from excessive dosage of labetalol, the profound reductions in heart rate and cardiac output which are also likely to occur would probably outweigh the benefit of increasing the blood pressure.

Exogenously administered adrenaline produced effects upon the blood pressure which varied according to the dose used. Low doses produced reductions in diastolic pressure which are likely to have resulted from its agonist effect at vascular β_2 -adrenoceptors. Increasing the dose up to 32 $\mu\text{g}/\text{min}$ caused any vasodilator effect to be overcome by the increasing vasoconstrictor effect. At all doses adrenaline provoked systolic pressor effects which probably result from its combined α -vasoconstrictor and the cardiac β -agonist properties. The modest effects of adrenaline upon heart rate and cardiac output are also consistent with these pharmacological properties.

The pattern of change which adrenaline produced after labetalol administration was quite different from that produced by adrenaline alone. The diastolic depressor effect of adrenaline was converted into a marked pressor effect. It has been shown previously (Prichard & Ross, 1966; Johnson, 1975; Herwaarden,

Fennis, Binkhorst & Laar, 1977) that propranolol produces a similar effect. Indeed it has been observed that the administration of propranolol to patients who had a phaeochromocytoma caused an increase in blood pressure (Prichard & Ross, 1966; Ross *et al.*, 1967). It would follow therefore that since propranolol and labetalol block vascular β_2 -adrenoceptors, then both are likely to antagonize the vasodilator effects of adrenaline. The net results would be an increase in diastolic pressure due to the now predominating α -vasoconstrictor effect of adrenaline as we observed in the present study of labetalol. The changes which occurred in systolic pressure after labetalol and adrenaline were not the same as those reported by Herwaarden *et al.* (1977) with propranolol and adrenaline. Using 8 $\mu\text{g}/\text{min}$ of adrenaline for 6 min, they showed that propranolol enhanced the systolic and diastolic pressor effects of adrenaline and this is in agreement with the earlier experiment (Prichard & Ross, 1966). We found that labetalol modified the systolic pressor effect of adrenaline particularly at the higher doses. This was not unexpected since we have previously shown that the systolic pressor response after noradrenaline infusion is competitively antagonized by the alpha blocking drug phentolamine as well as by labetalol (Richards, Woodings & Prichard, 1978; Richards & Prichard, 1978). The pattern of change in heart rate and cardiac output induced by adrenaline after labetalol which resulted in a bradycardia and reduced cardiac output was broadly similar to the pattern induced by noradrenaline after labetalol.

From the study of adrenaline alone it can be concluded that its circulatory effects are provoked by both its β - and its α -agonist properties; the precise

Table 3 Plasma concentrations of noradrenaline and adrenaline before and after infusions of noradrenaline and adrenaline

	Noradrenaline (ng/ml)		Adrenaline (ng/ml)			Noradrenaline (ng/ml)		Adrenaline (ng/ml)	
	Subject 1	Subject 2	Subject 1	Subject 2		Subject 5	Subject 6	Subject 5	Subject 6
Before noradrenaline	0.98	0.26	0.72	0.28	Before adrenaline	0.05	0.02	0.36	—
After infused noradrenaline	2.59	0.42	0.96	0.10	After infused adrenaline	—	0.13	0.67	1.8
Before labetalol	0.87	0.11	0.68	0.12	Before labetalol	—	0.25	—	0.26
3 min after labetalol	1.11	0.24	0.89	0.42	3 min after labetalol	0.09	0.35	0.44	0.22
Before noradrenaline	1.95	0.19	1.25	0.46	Before adrenaline	0.23	0.64	0.02	0.54
After infused noradrenaline	6.14	2.39	1.10	0.21	After infused adrenaline	0.56	0.32	6.42	10.84

— below level of detection.

pattern of change being dose dependant. After the administration of labetalol however, the pattern of circulatory response to adrenaline is conspicuously altered. As the α -adrenoceptor blocking effect of labetalol is less potent than its β -adrenoceptor antagonist effect, the former would be more readily overcome by the α -agonist effect of exogenous adrenaline. This would explain why adrenaline after labetalol acts in a similar manner to exogenous noradrenaline i.e. predominantly as an α -agonist.

From our preliminary findings on plasma catecholamine levels, it seems that intravenous labetalol does not significantly increase the levels immediately after intravenous injection; the apparent small increases being within the error of the method of detection (Callingham, 1978, personal communication). Other data from hypertensive patients receiving oral labetalol confirm our observation (Reid, 1978, personal communication). When noradrenaline was infused after labetalol, the plasma concentrations appeared to be elevated particularly in comparison with those levels prior to labetalol. During the second noradrenaline infusion however, the total dose was doubled and if anything, our data only suggest a trend in favour of increased levels. There is much less doubt over the plasma adrenaline concentrations since repeat infusions after labetalol show marked elevations compared with those levels of adrenaline before labetalol without the dose of adrenaline being altered. From this it seems that labetalol reduces the clearance of catecholamines from the plasma after their infusion. Noradrenaline and adrenaline are rapidly inactivated by neuronal and extra-neuronal uptake mechanisms on their passage through peripheral vascular beds (Vane, 1969). It may be therefore that the effect of labetalol upon the clearance of exogenous catecholamines was related to an effect upon uptake mechanisms. There is

evidence to show that in animal preparations labetalol can block neuronal uptake (i.e. uptake₁) (Blakeley & Summers, 1977; Summers & Tillman, 1977; Drew, Hilditch & Levy, 1978). There are as yet no data on the effect of labetalol upon extra-neuronal uptake. It does seem therefore that labetalol may be inhibiting the clearance of catecholamines from the plasma by blocking their uptake. This would be consistent with our previous observations that the pressor responses of infused noradrenaline were inhibited to a lesser extent than those of phenylephrine in the same normal men (Richards & Prichard, 1978). It is clear however that the pharmacodynamic data presented here are also consistent with other previous observations which indicate that labetalol competitively antagonizes the α -adrenoceptor agonist effects of endogenous and exogenous catecholamines (Richards, 1976). In particular, labetalol antagonizes the pharmacological effects of exogenous catecholamines despite apparently inhibiting their clearance from the plasma. Distinction must be drawn between our data derived from conditions where catecholamines were deliberately introduced into the circulation and those conditions, such as in phaeochromocytoma where endogenous levels of catechols are grossly elevated. In such cases it has already been shown that labetalol administration satisfactorily reverses the untoward effects of increased endogenous catecholamines (Rosei *et al.*, 1976). It does seem therefore that our findings of raised plasma catecholamines in the context in which they occurred are of little or no practical significance in the treatment of patients.

Reprint requests should be addressed to D.A.R., Medical Division, Glaxo Allenburys Research (Ware) Ltd, Ware, Herts.

References

- BLAKELEY, A.G.H. & SUMMERS, R.J. (1977). The effects of labetalol (AH 5158) on adrenergic transmission in the cat spleen. *Br. J. Pharmac.*, **59**, 643–650.
- CALLINGHAM, B.A. & BARRAND, MARGERY, A. (1976). Catecholamines in blood. *J. Pharm. Pharmac.*, **28**, 356–460.
- DREW, G.M., HILDITCH, A. & LEVY, G.P. (1978). Effect of labetalol on the uptake of (³H)-(-)-noradrenaline into the isolated vas deferens of the rat. *Br. J. Pharmac.*, **63**, 471–474.
- HANSSON, L. & HUNYOR, S.N. (1973). Blood pressure overshoot due to acute clonidine (catapres) withdrawal. Studies on arterial and urinary catecholamines and suggestions for management of the crisis. *Clin. Sci. Mol. Med.*, **45**, Suppl. 1, 181–183.
- HERWAARDEN, C.L.A., FENNIS, J.F.M., BINKHORST, R.A., LAAR, A., Van't. (1977). Haemodynamic effects of adrenaline during treatment of hypertensive patients with propranolol and metoprolol. *Eur. J. clin. Pharmac.*, **12**, 397–402.
- JOHNSON, G. (1975). Influence of metoprolol and propranolol on haemodynamic effects induced by adrenaline and physical work. *Acta Pharmac. Tox.*, **36**, Suppl. V., 59–68.
- KUBICEK, W.G., FROM, A.H.L., PATTERSON, R.P., WITSOE, D.A., CASTENEDA, A., LILLEHEI, R.C. & ERSEK, R. (1970). Impedance cardiography as a non-invasive means to monitor cardiac function. *J. Ass. Adv. Med. Instrum.*, **1**, 79–81.
- PALEY, H.W., McDONALD, I.G., BLUMENTHAL, J. & MAILHOT, H. (1971). The effects of posture and isoproterenol on the velocity of left ventricular contraction in man. *J. clin. Invest.*, **50**, 2283–2294.
- PRICHARD, B.N.C. & ROSS, E.J. (1966). Use of propranolol in conjunction with alpha receptor blocking drugs in phaeochromocytoma. *Am. J. Cardiol.*, **18**, 394–398.
- RICHARDS, D.A. (1976). Pharmacological effects of labetalol in man. *Br. J. clin. Pharmac.*, **3**, 721–723.
- RICHARDS, D.A. & PRICHARD, B.N.C. (1978). Concurrent antagonism of isoprenaline and noradrenaline after

- labetalol. *Clin. Pharmac. Ther.*, **23**, 253–258.
- RICHARDS, D.A., PRICHARD, B.N.C. & DOBBS, R.J. (1978). Adrenoceptor blockade of the circulatory responses to intravenous isoprenaline. *Clin. Pharmac. Ther.*, **24**, 264–273.
- RICHARDS, D.A., WOODINGS, E.P. & PRICHARD, B.N.C. (1978). Circulatory and α -adrenoceptor blocking effects of phentolamine. *Br. J. clin. Pharmac.*, **5**, 507–513.
- ROSS, E.J., PRICHARD, B.N.C., KAUFMAN, L., ROBERTSON, A.I. & HARRIS, B.J. (1967). Pre-operative and operative management of patients with phaeochromocytoma. *Br. med. J.*, **1**, 191–198.
- ROSE, G.A., HOLLAND, W.W. & CRAWLAY, E.A. (1974). A sphygmomanometer for epidemiologists. *Lancet*, **i**, 296–300.
- ROSEI, E.A., BROWN, J.J., LEVER, A.F., ROBERTSON, A.S., ROBERTSON, J.I.S. & TRUST, P.M. (1976). Treatment with phaeochromocytoma and of clonidine withdrawal hypertension with labetalol. *Br. J. clin. Pharmac.*, **3**, 809–815.
- SUMMERS, R.J. & TILLMAN, JANET. (1977). The effects of labetalol (AH 5158) on metabolism of ^3H (-)-Noradrenaline released from the cat spleen by nerve stimulation. *Biochem. Pharmac.*, **26**, 2137–2143.
- VANE, J.R. (1969). The release and fate of vaso-active hormones in the circulation. *Br. J. Pharmac.*, **35**, 209–242.

(Received May 19, 1978)