on the third day of effective debrisoquine treatment and this was repeated on the third day after debrisoquine had been withdrawn.

Blood pressures measured during the first phenylephrine experiment were significantly higher, and their elevation more prolonged in three of the four subjects than in the

TABLE 1. *Changes (△B.P.) in blood pressure (mmHg) in four normal subjects, induced by oral phenylephrine before and during debrisoquine treatment. All results are means±S.E. of 3 readings. C represents results within 95% confidence limits for the control means. Parentheses enclose single readings*

		Control observations—phenylephrine alone				First phenylephrine experiment, with debrisoquine			
		Supine		Tilted		Supine		Tilted	
Subject	△ B.P.	Peak effect	At 90 min	Peak effect	At 90 min	Peak effect	At 90 min	Peak effect	At 90 min
A.S.	△ Syst.	14±6	C	20±3	C	24±2	17±1	44±4	44±4
	△ Dias.	15±0·3	C	19±1	C	35±4	25±2	34±0·3	34±0'3
C.D.	△ Syst.	25±3	C	16±3	C	(62)	17±2	46±4	25±1
	△ Dias.	22±4	C	9±5	C	(30)	6±5	43±10	16±4
T.B.	△ Syst.	6·6±3	C	8·7±6	C	18·3±8	—	35±5	—
	△ Dias.	3·2±1	C	9·7±3	C	24±2	—	29±1	—
W.A.	△ Syst.	12±3	C	15±4	C	7±2	C	16±4	C
	△ Dias.	8±4	C	10±5	C	15±3	C	11±1	C

control observations made before debrisoquine (Table 1). In one subject phentolamine was given when blood pressure exceeded the prearranged limit of 180/120 mmHg. The effect was not seen in the experiment after debrisoquine withdrawal.

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The pharmacology of human isolated pulmonary vascular tissue

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The pharmacological actions of human isolated pulmonary arterial and venous tissues have been studied. Spirals of muscle were cut from vessels dissected after lobectomy or

TABLE 1. *Responses of human isolated pulmonary vascular tissues to some pharmacological agonists*

Agonist	n	Artery Response	n	Vein Response	Dose range
Acetylcholine	17	+/−/0 (6) (7) (4)	25	+/0 (19) (6)	100 ng/ml– 10 μg/ml
Noradrenaline	50	+++ (50)	40	+++ (40)	5 ng/ml– 2 μg/ml
Adrenaline	2	+++ (2)	4	+++ (4)	50 ng/ml–400 ng/ml
Phenylephrine	2	+ (2)	2	+ (2)	50 ng/ml–800 ng/ml
Isoprenaline	22	++/−/0/biphasic* (4) (13) (3) (2)	29	++/−/0 (7) (15) (7)	50 ng/ml– 32 μg/ml
Histamine	15	+++ (13)	13	+++ (13)	0·5 μg/ml–128 μg/ml
5-Hydroxytryptamine	10	+++ (10)	9	+++ (9)	250 ng/ml– 1 μg/ml
Nicotine	14	+ (8)	14	+ (11)	1 μg/ml– 50 μg/ml

0=No response to agonist although tissue shown to be alive in response to other agonists.
+Contraction, −Relaxation } Numbers of symbols for each agonist give an approximate comparison of height of maximal contraction between agonists.
n=Number of tissues.
*In these two tissues initial relaxation (slight) was followed by contraction at higher doses.

pneumonectomy for carcinoma or bronchiectasis. Isometric and isotonic recordings were made on a Devices 2M instrument, during which the tissues were kept under tension (artery 1·5–2·5 g and vein 0·5–1·5 g). Reactions were generally slow, some strips taking 6 min to reach their maximum height and 45 min to recover to the original baseline after a single dose of agonist. Large branches of both pulmonary artery and vein reacted more slowly than smaller side branches. Spontaneous myogenic activity was seen in many strips, more marked in artery than vein. The results are shown in Table 1.

Tachyphylaxis developed easily to both histamine and 5-hydroxytryptamine, and even at low doses an interval of 1 h or more between doses was required to obtain constant responses. The contractile response to nicotine was probably due to the release of noradrenaline from postganglionic nerve endings. Some quantitative work with antagonists has been possible and pA_2 values of thymoxamine against noradrenaline (6·6), atropine against acetylcholine (9·6), and mepyramine against histamine (7·9) have been calculated.

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The α-adrenoceptor blocking activity of desacetylthymoxamine on human isolated smooth muscle

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Desacetylthymoxamine is a hydrolysis product of thymoxamine hydrochloride, and is formed by the substitution of a hydroxyl group in place of the acetoxy group in the phenyl ring of the parent compound. Arbab & Turner (1971a & b) found that thymoxamine and desacetylthymoxamine fluoresce at the same wavelengths, and therefore the extraction method from plasma which they described measured the desacetylated metabolite as well as its parent compound. For this reason, it was of interest to determine if desacetylthymoxamine possessed α-adrenoceptor blocking activity. pA_2 determinations (Schild, 1957) against noradrenaline were performed on strips of human smooth muscle from surgical specimens of colon, ileum and saphenous vein. The mean pA_2 value of desacetylthymoxamine was 6·25, which compares with a value of 6·9 for thyxomamine (Coupar & Turner, 1970). Values on individual tissues and the mean values of the slope of the log (dose ratio—1) versus negative log molar concentration of

TABLE 1.

Tissue	n	pA_2 (mean and range)	Slope of log (dose ratio − 1) versus −ve log molar concentration of antagonist plot (mean and range)
Longitudinal colon	3	6·51 (6·37–6·69)	1·1 (0·9–1·4)
Longitudinal ileum	1	6·1	1·0
Saphenous vein	1	6·1	0·66

desacetylthymoxamine plot are shown in Table 1. Desacetylthymoxamine appeared to be acting as a competitive antagonist on specimens of colon and ileum, but as a non-competitive antagonist on one specimen of vein. However, on three specimens of vein it depressed the maximal contractile response to noradrenaline and appeared to be acting as a non-competitive antagonist. Moreover, the heights of the maximal responses were suppressed on human saphenous vein, providing further evidence for the non-competitive nature of the antagonism.

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