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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Comparison of the potencies of edrophonium, neostigmine and eserine with a new anticholinesterase drug RX 67668 on human tissues

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RX 67668 (cis-2-phenyl-1-(N-pyrrolidinyl) cyclohexane hydrochloride) is a novel anticholinesterase compound which appeared in animal studies (Doxey, Metcalf, Smith & Whittle, 1972) to have greater affinity for nicotinic receptors at the neuromuscular junction than for muscarinic receptors, although human studies have not confirmed this (Gillett, Hedges, Metcalf, Richens & Royds, 1972). Anticholinesterase activities of established compounds have been compared with that of RX 67668 on isolated human tissues and blood. pP_2 determinations (Edge, 1967) were performed on strips of human smooth muscle from surgical specimens of stomach, ileum and colon, and biochemical estimations of anticholinesterase activity on human blood using a modification (Glegg & Turner, 1971) of the method of Fleisher & Pope (1954).

The mean pP_2 of RX 67668 was 6·82 which compared closely with edrophonium, 6·76. Neostigmine, 7·35, was ten times more potent than RX 67668. In Table 1 the

TABLE 1. *Mean ID50 values for anticholinesterase activity of RX 67668, neostigmine, edrophonium and eserine estimated biochemically on human blood and mean pP_2 values reduced to their molar equivalents measured on isolated human smooth muscle*

Drug	Mean ID50	Mean pP_2 (moles)
RX 67668	$2{\cdot}65 \times 10^{-7}$	$1{\cdot}54 \times 10^{-7}$
Neostigmine	$5{\cdot}81 \times 10^{-8}$	$4{\cdot}57 \times 10^{-8}$
Edrophonium	$5{\cdot}32 \times 10^{-5}$	$1{\cdot}76 \times 10^{-7}$
Eserine	$2{\cdot}50 \times 10^{-10}$	$8{\cdot}0 \times 10^{-11}$

mean anticholinesterase ID50 for the compounds using the biochemical method are compared with their pP_2 values reduced to their molar equivalent in moles, obtained from the isolated tissue studies. Although the ID50 and pP_2 values are comparable for RX 67668, neostigmine and eserine, the values for edrophonium did not correlate so closely. This might be due to variation in stability of the complex formed between edrophonium and the anionic site of the cholinesterase enzyme.

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