The effect of aspirin on the contractile effects of histamine, impromidine and dimaprit on the isolated rat stomach fundus strips. The equipotent concentrations of 3 agonists were selected

Agonist	Percent of maximum response		
	Control	In presence of aspirin (10^{-6} M)	Significance
Histamine (10^{-7} M)	53.0±7.0	48.0±6.5	NS
Impromidine (4.2×10^{-6} M)	45.7±4.5	22.0±2.5	$p < 0.001$
Dimaprit (6.8×10^{-5} M)	43.8±6.5	27.0±3.7	$p < 0.05$

Percent of maximum response; mean ± SE of 10 experiments.

significantly reduced the responses to IMP and DM without altering that on HA (fig.). Incubation of the RSF with ASA (10^{-6} M) for a 20-min period caused a significant decrease in the responses to both IMP and DM without altering that of HA when equipotent concentrations of the agonists used were compared (table). The contractile effects of acetylcholine and 5-HT, on the other hand, were not affected by SC 19220 and ASA. However, a similar inhibition was observed in the responses to agiotensin II in the presence of SC 19220 and ASA when tested on the isolated rat stomach fundus.

Discussion. The results of the present investigation indicate that both IMP and DM produce a contractile response in isolated rat stomach fundus strips[8]. This contraction is unlikely to be mediated via H_1 and H_2-receptors since neither mepyramine nor metiamide was able to alter the effects of these compounds. However, the contractile effect of HA was found to be blocked by mepyramine, supporting our previous observation[2]. Furthermore, the contractions induced by IMP and DM were not changed in the presence of methysergide, 5-HT-D receptor blocker, and atropine, a muscarinic receptor antagonist, indicating that these receptors do not play a part in the contractile response to IMP and DM. However, the PG-receptor blocker SC 19220[6] and PG-biosynthesis inhibitor ASA[7] significantly reduced the contractions produced by the 2 compounds as well as by angiotensin II without altering that of HA. The inhibition by SC 19220 and ASA of the contractile effect of angiotensin II has previously been reported[9]. These findings suggest that the contractions in the RSF produced by IMP and DM are PG-mediated. Another HA H_2-receptor agonist, 4-methyl HA, has been shown to produce a relaxation which can be blocked by metiamide[2]. However, no relaxation was obtained in the RSF strips with IMP and DM, an unexpected effect of these compounds which remains to be eluciated.

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Drug uptake by lung slices from paraquat-pretreated rats

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Summary. Lung slices from male Sprague-Dawley rats pretreated with paraquat (PQ) (100 μmoles · kg^{-1}, i.v.) 16 h before sacrifice, accumulated less PQ in vitro than lung slices from saline-treated controls. Neither lung slices from PQ-pretreated nor saline control animals released (effluxed) PQ accumulated in vitro. The accumulation and efflux of imipramine and 5-hydroxytryptamine by lung slices was unaffected by prior in vivo administration of PQ.

The pulmonary absorption of a variety of drugs and chemicals is increased during experimental silicosis[2], papain-induced emphysema[3] and α-napthylthiourea-induced pulmonary oedema[4], possibly due to changes in membrane permeability within the lung. Paraquat is a potent pneumotoxin producing pulmonary oedema, haemorrhage, and ultimately lethal interstitial and interalveolar fibrosis. It might therefore be expected that the paraquat poisoned lung may exhibit altered accumulation and metabolism of various drugs. Indeed in the rat, pulmonary absorption of p-aminohippuric acid and procainamide is increased during paraquat toxicity, reaching a peak 3–5 days after oral administration of the herbicide[5]. However, the changes in pulmonary absorption of organic anions occur in the presence of gross pathological changes in the lung, as judged by increased lung weight and water content. Relatively little is known about pulmonary drug accumulation during the early stages of paraquat-induced toxicity, despite the fact that drug interactions within the lung have been employed in experimental and clinical situations in attempts to ameliorate the course of paraquat toxicity[6–9]. The aim of the investigation described in this communication was to determine the extent to which pulmonary drug accumulation may be altered soon after paraquat administration. Lung slices from control and paraquat-treated rats were used to determine the in vitro pulmonary uptake and efflux of imipramine (IP), paraquat (PQ) and 5-hydroxytryptamine (5HT). These drugs were chosen because the lung accumulates them via different mechanisms[10–14] and hence PQ pneumotoxicity might produce differential effects on the relative rates of uptake and efflux of the compounds.

Materials and methods. Male Sprague Dawley rats (200–250 g) which had been allowed food and water ad libitum were injected i.v. with either saline (5 ml · kg^{-1}) or paraquat (100 μmoles · kg^{-1}) (Sigma Chemical Co.). 16 h later, animals were sacrificed by exsanguination by the severing of the abdominal aorta while under pentobarbital anesthe-

sia (60 mg · kg^{-1}, i.p.). The lungs were quickly removed and rinsed in saline, lung slices (20–50 mg) were cut free-hand from the right lobe and only slices with 2 cut surfaces and of a uniform thickness (1–2 mm) were used. Drug uptake by and efflux from lung slices was determined essentially as previously described[6,15]. Briefly, lung slices were equilibrated for 20 min in gassed (5% CO_2–95% O_2) Krebs-Ringer bicarbonate solution at 37 °C, transferred to fresh media containing radiolabelled drug (0.2–0.6 μCi/slice) IP (10 μM), PQ (10 μM) or 5HT (5 μM) and incubated with agitation to determine drug uptake. Lung slices used for determining 5HT uptake were equilibrated in the presence of pargyline (1 mM), a monoamine oxidase inhibitor. After 2 h incubation, lung slices were removed, briefly rinsed and transferred to fresh, drug free media for efflux studies, and further incubated for 2 h. Slices and media were sampled after various times and their radioactivity estimated. The effect of paraquat on lung water content was determined by heating lung samples, obtained immediately after in situ removal, to a constant weight at 70 °C under vacuum. Lung slice inulin and sucrose spaces were determined by incubating slices in media containing 50 μCi ^{14}C-inulin or ^{14}C-sucrose for 60 min and determining the radioactivity of the slices after rinsing and blotting dry.

Sources of materials: ^{14}C-IP hydrochloride (98 mCi · $mmole^{-1}$), ^{14}C-PQ dichloride (33 mCi · $mmole^{-1}$), ^{14}C-5HT creatinine sulphate (54 mCi · $mmole^{-1}$), ^{14}C-inulin (10.9 mCi · $mmole^{-1}$) and ^{14}C-sucrose (381 mCi · $mmole^{-1}$) were purchased from Amersham Radiochemical Centre. Unlabelled compounds were purchased from Sigma Chemical Co.

Results. The uptake and efflux of IP, PQ and 5HT by lung slices from rats previously treated with i.v. paraquat is shown in the figure. The accumulation of IP by lung slices from treated rats was the same as for slices from control rats; tissue/medium (T/M) ratios were 29 and 31 respectively. The efflux of previously accumulated IP was also unaltered by paraquat pretreatment; both groups of lung slices retained 51–53% of their initial IP content after 2 h incubation under efflux conditions. Similarly, accumulation and efflux of 5HT was the same for lung slices from saline and paraquat pretreated animals. T/M ratios after 2 h incubation with ^{14}C-5HT were 10 and 9.6 for control and paraquat treated slices, and 19–25% of the accumulated 5HT was retained. In sharp contrast to the IP and 5HT results, there was a marked difference in PQ uptake by lung slices from saline and paraquat pretreated animals. Paraquat pretreatment significantly depressed the subsequent in vitro pulmonary accumulation of PQ by 60% (T/M ratios were 5.1 for control and 2.0 for paraquat pretreatment). Although PQ uptake was decreased, efflux was not affected, and both groups of lung slices retained the greater part of their previously accumulated PQ.

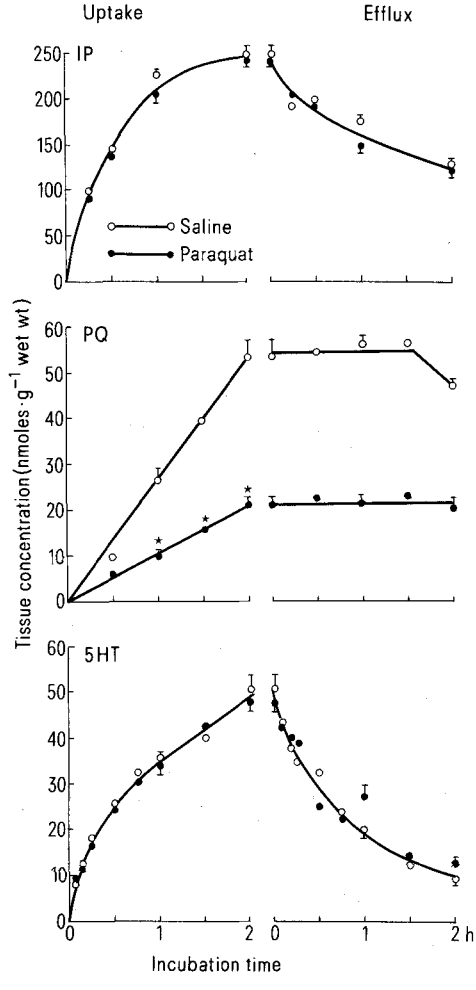
Total lung weight was slightly increased by PQ pretreatment but was not significantly different from that in saline-treated animals; similarly, pulmonary water content and sucrose space were not significantly changed (table). The apparent inulin space, however, was significantly increased by 20%.

Effect of paraquat on rat lung weight, water content and sucrose and inulin spaces[a]

	Saline-treated	Paraquat-treated
Lung weight (g)	1.48 ± 0.04	1.78 ± 0.15
Lung weight (g/kg b.wt)	4.72 ± 0.27	5.67 ± 0.58
Water content (ml/g)	0.79 ± 0.03	0.81 ± 0.09
Sucrose space (%)	44.9 ± 0.2	46.8 ± 1.5
Inulin space (%)	26.7 ± 1.0	32.2 ± 1.4*

[a] Male rats received paraquat (100 μmoles · kg^{-1}, i.v.) or saline (5 ml · kg^{-1}, i.v.) 16 h before sacrifice. Results are the mean values ± SEM of each parameter for 6–7 animals. An asterisk indicates a significant difference from saline controls ($p < 0.05$, Student's t-test).

Discussion. Smith et al.[14] have previously shown that 2–16 h after a small i.v. dose of PQ the initial uptake of 5HT by rat lung slices was unaffected, but between 8–16 h the in vitro uptake of PQ by lung slices was significantly reduced. We have confirmed and extended these observations in the present investigation to include additional drugs and both uptake and efflux data. Smith et al.[14] estimated the initial uptake of 5HT by lung slices over a 15-min incubation period. During this time the 5HT concentration had not achieved equilibrium with the media concentration, and hence it was possible that PQ-induced changes in the uptake of 5HT over longer incubation times may have been missed by these authors. However, the figure shows that neither the accumulation nor the efflux of 5HT was affected by PQ given 16 h earlier. Similarly, the uptake and efflux of IP over 2-h incubation periods was unchanged. On the other hand, PQ uptake was significantly depressed at a



Accumulation and efflux of imipramine (IP), paraquat (PQ) and 5-hydroxytryptamine (5HT) by lung slices from male rats treated with saline (5 ml · kg^{-1}, i.v.) or paraquat (100 μmoles · kg^{-1}, i.v.) 16 h previously. Lung slices were incubated in Krebs-Ringer bicarbonate solution containing radiolabelled IP (10 μM), PQ (10 μM) or 5HT (5 μM) for 2 h and then transferred to fresh, drug free media. Each point represents the mean drug content of 6–8 slices and for clarity the SEM has only been included for the 1- and 2-h time points. An asterisk indicates a significant difference from saline treated controls ($p < 0.01$, Student's t-test).

time when the lung was not oedematous (table) and yet efflux of PQ was unaffected. It therefore appears that during the early stages of PQ toxicity the pulmonary uptake of PQ is selectively affected.

The lack of efflux of PQ form lung slices[6,7] indicates that the PQ molecule is unable easily to retraverse the cellular membrane once it is in the intracellular environment, owing either to tight tissue binding or to its being ionized intracellularly or requiring a transport process for removal that may have been destroyed upon entry. However, it has been suggested that the pulmonary uptake and retention of PQ may not be related to any binding process[16]. Both PQ and 5HT are accumulated by the lung via active, energy dependent processes[11-14]. Since 5HT uptake was unaffected, it is unlikely that the reduction in PQ uptake represents a general inhibition of energy producing processes. However, 5HT is accumulated by pulmonary endothelial cells[11,12] whereas it is speculated that PQ uptake occurs in type I and type II alveolar cells[14], as it is these cells which are first damaged in vivo by PQ. 16 h after 100 μmoles PQ kg^{-1}, i.v., rat lung contains 10–15 nmoles PQ/g tissue (unpublished observations). This is approximately 20–30% of the amount of PQ accumulated in vitro in 2 h by untreated lung slices, and 50–75% of that accumulated by lung slices from PQ-treated rats. Thus, by virtue of there being substantial amounts of PQ in the lung 16 h after in vivo administration, and since this is presumably localized in those cells possessing the necessary PQ transport mechanism, it is possible that PQ may selectively inhibit its own active transport. This could occur by selective cellular damage or competitive inhibition of ^{14}C-PQ uptake by the residual pool of unlabelled PQ in the lung. Unlike PQ and 5HT, IP is accumulated by mammalian lungs by diffusion and tissue binding[10]. When lung slices from untreated rats are incubated in the presence of both IP and PQ, more IP is accumulated than if the slices were incubated with IP alone (unpublished observations). Similarly, the active uptake of phenol red by lung slices is increased in the presence of paraquat[17] and the in vitro binding of chlorphentamine to rat lung 15,000 × g subcellular fraction is increased by PQ[18]. It was, therefore, surprising that in vivo PQ pretreatment did not alter pulmonary IP accumulation.

The results presented in this communication suggest that the failure of drugs[6-8], possessing the potential of displacing PQ from the lung, to ameliorate PQ-induced pneumotoxicity is unlikely to be due to altered pulmonary uptake of the displacing drug.

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Effect of suloctidil on blood viscosity in healthy volunteers after forearm occlusion

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Summary. The effect of suloctidil (1-(4-isopropylthiophenyl)-2-n-octylaminopropanol) on increased blood viscosity was studied in healthy volunteers after forearm occlusion. A significant reduction of blood viscosity was observed in subjects treated 1 day before, or immediately before, the ischaemic trial. It is concluded that the drug may preserve the deformability of erythrocytes during an ischaemic episode.

Vascular diseases of the legs are, in many cases, accompanied by abnormally high blood viscosity[1,2]. In patients with claudicatio intermittens, hyperviscosity appears to carry a worse prognosis[1]. The high blood viscosity is commonly associated with an increased tendency of the red cells to aggregate and with an increase in total fibrinogen levels. The ability of the erythrocytes to change form seems to be impaired[3], as well.

In the present study we have verified that ischaemic obstruction of the forearm leads to an increase of blood viscosity in healthy normolipidaemic volunteers. Moreover, we studied under these conditions the effect of suloctidil (1-(4-isopropylthiophenyl)-2-n-octylaminopropanol), a new drug found to be able to reduce blood hyperviscosity[4-6], used also for the treatment of claudicatio intermittens[7].

Materials and methods. The study was performed on 12 healthy normolipidaemic volunteers (6 males and 6 females, 18–32 years old). Selection criteria were a minimal 2-month drug-free period before the present study, and no smoking habit. Experimental ischaemia was induced as described previously by De Clerck et al.[8] by occlusion of the upper arm with a blood pressure cuff at a pressure above 200 mm Hg, followed immediately by compressing a rubber bulb in the hand at a standard rhythm, until ischaemic pain precluded further exercise. Plasma and