Br. J. Pharmac. (1978), **64**, 519–525

THE EFFECTS OF PENTOBARBITONE AND URETHANE ON PULMONARY AIRWAY RESISTANCE IN GUINEA-PIGS AND THEIR INTERACTIONS WITH DRUGS

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1 Propranolol increased pulmonary airway resistance (PAR) in the conscious guinea-pig, whereas atropine had no effect, suggesting the existence of a continual sympathetic bronchodilator tone.

2 The direct bronchoconstrictor effects of histamine, acetylcholine and 5-hydroxytryptamine were modified by autonomic reflexes: a bronchodilator one, abolished by propranolol, and a cholinergic bronchoconstrictor one, seen with histamine.

3 Pentobarbitone increased PAR, an effect which was reduced by propranolol but which was unaffected by atropine. The bronchoconstrictor effects of histamine, acetylcholine and 5-hydroxytryptamine were potentiated by pentobarbitone.

4 Pentobarbitone therefore appears to inhibit the adrenergic bronchodilator tone and to depress adrenergic reflexes, these being the preponderant autonomic influences in these experiments.

5 Like pentobarbitone, urethane increased PAR in the conscious guinea-pig and potentiated the bronchoconstrictor effects of the three amines. These actions are similarly attributed to a reduction in adrenergic influences.

Introduction

In the few studies devoted to the effects of general anaesthesia on bronchomotor tone and on drug-induced responses in the guinea-pig, measurements have been made of pulmonary compliance (Dennis & Douglas, 1970; Douglas, Dennis, Ridgway & Bouhuys, 1972). Furthermore, interactions between general anaesthetics and histamine have been studied when histamine was administered intravenously in low doses or as an aerosol. Douglas *et al.* (1972) using urethane in guinea-pigs and Jackson & Richards (1977) using pentobarbitone in dogs, observed a decrease in the effects of histamine.

In contrast, during preliminary investigations in which pulmonary airway resistance was measured, we found that pentobarbitone potentiated the bronchoconstriction caused by large doses of acetylcholine, histamine and 5-hydroxytryptamine.

The purpose of this study was to analyse the effects of pentobarbitone and urethane *per se* on airway resistance and, further, to study their interactions with the above-mentioned mediators.

Methods

Male guinea-pigs weighing 0.4 to 0.55 kg were divided into groups of at least eight animals. They were lightly anaesthetized with ethylether and small polyvinylchloride catheters were inserted into the left jugular vein and carotid artery, exposed by a median anterior incision of the neck. Intrathoracic pressure was measured with a Pezzer probe, one end of which was inserted into the pleural space through the sixth or seventh intercostal space, the other being connected to one port of a differential pressure transducer (Sanborn 268 B).

After awakening, the animals were placed in a body plethysmograph, their heads being kept outside, and

were allowed to breathe spontaneously. The plethysmograph was made airtight by placing a strip of impermeable adhesive tape around the neck. In one of the plethysmograph walls, a Sanborn A 440 pneumotachometer was inserted permitting measurement of air flow. Tidal volume was determined by electronic integration (Sanborn 350-5000 B) of the flow signal. The parameters were recorded continuously on a Sanborn 7700 strip chart recorder.

Pulmonary airway resistance was usually calculated according to Amdur & Mead (1958) or, when studying the action of urethane, pentobarbitone, propranolol and atropine, was measured by means of a Hewlett Packard 8816 A respiratory analyser with which the variations were moderate and not abrupt. In this study, the mean pulmonary airway resistance (PAR) values include upper respiratory, intrathoracic (alveoli to trachea) airway and tissue viscous-resistance components. Mean PAR was expressed as the ratio of the pressure change to flow change occurring at two points of equal volume during inspiration and expiration. Since at these two points of equal lung volume, the elastic component of transpulmonary pressure is the same, this factor does not need to be considered in the calculation of mean airway resistance. This method provides values which represent the average inspiratory and expiratory resistance near peak inspiratory flow. Thus, these values closely approximate to the average resistance during the respiratory cycle (Amdur & Mead, 1958). An interval of 1 to 1.5 h elapsed before any drugs were administered.

Heart rate and carotid blood pressure were measured continuously by means of a Hewlett Packard 350-3400 cardiotachometer and a Hewlett Packard 267 A transducer respectively.

P_{CO_2}, P_{O_2} and blood pH were measured in arterial blood samples by means of an IL model 113 pH/gas analyzer.

Measurement of drug effects

To study the action of pentobarbitone or urethane *per se*, each animal received a single dose of the anaesthetic administered slowly intravenously, sometimes preceded by either atropine or propranolol intravenously. In other groups of guinea-pigs, each animal was injected intravenously with an appropriate dose of acetylcholine, histamine or 5-hydroxytryptamine on 3 occasions at 4 to 6-min intervals and the mean response was calculated. Then, urethane or pentobarbitone (in the presence or absence of an antagonist) was given and 10 min later the 3 injections of the appropriate bronchoconstrictor agent were repeated and the mean response was again calculated. The results are expressed in $cmH_2O\ ml^{-1}\ s^{-1}$.

The agents used were acetylcholine (ACh), histamine and (±)-propranolol hydrochlorides, atropine sulphate, 5-hydroxytryptamine creatine sulphate (5-HT), sodium pentobarbitone and urethane. All these substances were dissolved in distilled water and injected in volumes of less than 1 ml. The injections were completed in 5 to 10 s for ACh, histamine and 5-HT and in 5 to 10 min for the other drugs. Doses are expressed in terms of the base.

All values quoted in the text are means ± s.e. mean.

Statistical analysis of the results was performed using Student's *t* test for paired data.

Results

Effects of propranolol and atropine

In untreated, conscious guinea-pigs the PAR was generally just below 1 $cmH_2O\ ml^{-1}\ s^{-1}$. A small and statistically non-significant, increase in PAR was produced by 2 mg/kg atropine whereas 1 mg/kg propranolol caused a significant increase of about 45% (Table 1).

Effects of pentobarbitone and urethane

These results are also summarised in Table 1. Pentobarbitone (10 mg/kg) given alone caused a significant increase in PAR of about 60%, a response which was virtually unchanged in the presence of atropine. However, after propranolol which itself increased the PAR, the mean increase in PAR caused by pentobarbitone was smaller (about 35%) and not statistically significant although the change was substantial in 5 out of 24 guinea-pigs, amounting to an increment of more than 0.7 $cmH_2O\ ml^{-1}\ s^{-1}$.

Urethane (1 g/kg) given alone also produced a significant increase in PAR of about 40% which was unaltered by atropine pretreatment but was reduced to statistically insignificant levels after propranol.

The effects of urethane were measured also on several respiratory and cardiovascular parameters (Table 2). Urethane caused moderate depression of ventilation: respiratory rate, tidal volume and minute ventilation were reduced by 9.5, 16 and 21% respectively. Values for blood arterial gases and arterial pH revealed acidosis which was both respiratory and metabolic since the moderate changes in P_{CO_2} and P_{O_2} were insufficient to account for the drop in pH. Lastly, urethane lowered heart rate and blood pressure in guinea-pigs by 14 and 19% respectively.

Interactions of these drugs with bronchoconstrictor agents

Histamine, ACh and 5-HT were used throughout these experiments in doses of 20, 25 and 15 μg/kg

respectively. These drugs invariably produced increases in PAR of between 2.4 and 3.8 $cmH_2O\ ml^{-1}\ s^{-1}$ in untreated guinea-pigs. In every experiment there was virtually no difference in the response to each of the three successive injections of a given drug.

All of the results are shown in Table 3. Atropine (2 mg/kg) caused a significant reduction of the bronchoconstriction to both histamine and ACh but left unaffected the response to 5-HT whilst, in contrast, propranolol (1 mg/kg) potentiated the responses to all three drugs by 206, 86 and 152% for histamine, ACh and 5-HT respectively.

Pentobarbitone (10 mg/kg) also significantly potentiated the responses to these substances, the effect being more prominent on ACh (238%) and 5-HT (340%) than on histamine (185%). Likewise urethane (1 g/kg) increased the bronchoconstriction to histamine, ACh and 5-HT by 133, 194 and 157% respectively.

The effects of the two anaesthetic agents on all three bronchoconstrictor drugs was slightly, though not significantly, increased in the presence of propranolol. However, in some guinea-pigs, pretreatment with propranolol and pentobarbitone resulted in severe bronchospasm and total apnoea following the bronchoconstrictor drugs (three animals in each of the histamine and ACh groups and two in the 5-HT group). When atropine was substituted for propranolol it was found that the anaesthetics still potentiated to a similar extent the bronchoconstriction caused by histamine and 5-HT but in contrast, the response to ACh was now reduced to a size comparable to that recorded before administration of atropine.

Table 1 Effects of pentobarbitone or urethane on pulmonary airway resistance in conscious guinea-pigs in the absence or presence of an antagonist

Pretreatment (mg/kg)	*Number of animals*	*Pulmonary airway resistance ($cm\ H_2O\ ml^{-1}\ s^{-1}$)*		
		Predrug control	*Postdrug*	*Change*
Propranolol alone (1)	50	0.88 ± 0.12	1.27 ± 0.14	+0.39 ± 0.06*
Atropine alone (2)	33	0.87 ± 0.12	0.99 ± 0.13	+0.12 ± 0.09
Pentobarbitone alone (10)	24	0.96 ± 0.27	1.56 ± 0.29	+0.60 ± 0.12*
Pentobarbitone (10) plus propranolol (1)	24	1.23 ± 0.26[a]	1.70 ± 0.32	+0.47 ± 0.24
Pentobarbitone (10) plus atropine (2)	16	0.82 ± 0.21[a]	1.38 ± 0.20	+0.56 ± 0.18†
Urethane alone (1000)	21	1.04 ± 0.13	1.50 ± 0.16	+0.46 ± 0.11*
Urethane (1000) plus propranolol (1)	23	1.27 ± 0.14[a]	1.52 ± 0.22	+0.20 ± 0.09
Urethane (1000) plus atropine	13	0.99 ± 0.17[a]	1.37 ± 0.15	+0.38 ± 0.07*

[a] Control value, after antagonist (propranolol or atropine) and before anaesthetic.
Statistically significant changes are shown as †$P < 0.01$; *$P < 0.001$; (Student's t test).

Table 2 Effects of urethane (1 g/kg i.v.) on ventilation parameters, heart rate and blood pressure in conscious guinea-pigs

	Number of animals	*Before urethane*	*After urethane*	*Change*
Respiratory rate (breaths/min)	12	91.2 ± 5.8	83.1 ± 7.6	−8.1 ± 2.8*
Tidal volume (ml)	12	0.97 ± 0.09	0.80 ± 0.07	−0.17 ± 0.06*
Minute ventilation (ml)	12	88.4 ± 5.6	66.4 ± 5.4	−22.0 ± 5.3†
pH	6	7.42 ± 0.02	7.33 ± 0.03	−0.09 ± 0.02†
Po_2	6	96 ± 11.2	90.75 ± 9.2	−5.25 ± 0.85†
Pco_2	6	41 ± 4	47.5 ± 4.5	+6.5 ± 1.9*
Heart rate (beats/min)	6	280 ± 6.3	240 ± 13.7	−40 ± 13.7*
Blood pressure (mmHg)	6	94 ± 9	76 ± 5	−18 ± 6*

Statistically significant changes are shown as *$P < 0.05$; †$P < 0.01$; (Student's t test).

Table 3 Interactions of pentobarbitone and urethane with bronchoconstrictor agents

	Increases in PAR (cmH_2O ml^{-1} s^{-1})								
	Histamine			*Acetylcholine*			*5-Hydroxytryptamine*		
Pretreatment (mg/kg)	*Predrug control*	*Postdrug*	*Change (%)*	*Predrug control*	*Postdrug*	*Change (%)*	*Predrug control*	*Postdrug*	*Change (%)*
Propranolol alone (1)	3.0 ± 1.0	9.2 ± 1.3**	+206	3.0 ± 0.4	5.6 ± 0.9*	+86	2.3 ± 0.6	5.8 ± 0.9**	+152
Atropine alone (2)	3.6 ± 0.7	1.6 ± 0.5*	−55	2.8 ± 0.8	0.7 ± 0.6*	−75	3.3 ± 1.1	3.6 ± 1.1	+9
Pentobarbitone alone (10)	3.4 ± 1.1	9.7 ± 2.3**	+185	2.6 ± 0.7	8.9 ± 1.5**	+238	2.4 ± 0.6	10.6 ± 2.3**	+340
Pentobarbitone (10) plus propranolol (1)	2.9 ± 1.1	13.6 ± 2.6**	+368	3.0 ± 0.7	12.8 ± 3.1*	+326	2.8 ± 1.4	10.8 ± 2.5*	+278
Pentobarbitone (10) plus atropine (2)	3.7 ± 0.8	9.0 ± 2.8*	+ 143	2.7 ± 0.8	2.3 ± 1.8	−14	3.2 ± 1.4	11.2 ± 3.1*	+250
Urethane alone (1000)	3.7 ± 1.0	8.6 ± 1.8*	+133	3.4 ± 1.4	9.9 ± 1.7*	+194	2.7 ± 0.6	6.9 ± 1.3*	+157
Urethane (1000) plus propranolol (1)	3.8 ± 0.6	9.8 ± 1.6**	+157	2.8 ± 0.5	8.8 ± 2.0*	+214	3.6 ± 1.6	11.0 ± 1.5**	+205
Urethane (1000) plus atropine (2)	3.8 ± 0.7	9.0 ± 2.0*	+136	3.6 ± 0.8	1.4 ± 1.6	−61	2.4 ± 0.8	8.0 ± 2.0*	+233

Statistically significant differences from appropriate controls are shown as: $^*P < 0.05$, $^{**}P < 0.01$.
Guinea-pigs were injected intravenously with histamine (20 μg/kg), acetylcholine (25 μg/kg) or 5-hydroxytryptamine (15 μg/kg) on 3 successive occasions at 4 to 6 min intervals and the mean bronchoconstrictor response recorded. The series of injections was repeated, beginning 10 min after the injection of propranolol (1 mg/kg), atropine (2 mg/kg) pentobarbitone (10 mg/kg) or urethane (1 g/kg) and the mean again recorded. In other experiments, the second series of injections of bronchoconstrictor agents was given after 2 drugs had been administered. All results represent mean increases in pulmonary airway resistance (PAR) ± s.e. mean (8 animals per group).

Discussion

Bronchomotor tone and reflexes in the conscious guinea-pig

The failure of atropine to decrease PAR clearly indicates that there is no continual parasympathetic tone in the unanaesthetized guinea-pig, in accordance with the finding of Douglas, Dennis, Ridgway & Bouhuys (1973), Drazen & Austen (1975), and Marcelle (1976). However, an underlying adrenergically mediated bronchodilatation can be inferred because of the increase in PAR caused by propranolol. It is possible that the propranolol-induced bronchoconstriction may also be due partially to the drug's direct depressant effect on bronchial smooth muscle (Advenier, Boissier & Giudicelli, 1972).

The partial inhibition of the effects of histamine by atropine shows that in addition to the direct action of this mediator on smooth muscle, there is also, in the unanaesthetized guinea-pig, a cholinergic bronchoconstrictor component (Nadel, 1965; Mills & Widdicombe, 1970) possibly originating in the stimulation of irritant receptors in the tracheobronchial tree. Mills & Widdicombe (1970) also described a reflex cholinergic component in the response to histamine which was abolished by bilateral vagotomy. Our results suggest that this cholinergic component is less important with large doses of histamine (20 μg/kg), than with lower doses (1 to 3 μg/kg) such as were used by Drazen & Austen (1975) who demonstrated an essential role of this component in the bronchoconstriction induced by histamine.

We also conclude that a cholinergic reflex bronchoconstrictor component is not involved in the action of 5-HT. It is of interest that Drazen & Austen (1975) also failed to show a reflex component in the initial bronchoconstriction induced by prostaglandin $F_{2\alpha}$.

The potentiation by propranolol of the bronchoconstrictor effects of histamine, ACh and 5-HT clearly demonstrates that in the doses used, there is an associated adrenergic bronchodilator reflex (McCulloch, Proctor & Rand, 1969; Bouhuys, Dennis & Douglas, 1969; Douglas *et al.*, 1972; 1973; Marcelle, 1976) with all three drugs. This reflex probably involves catecholamines released by sympathetic nerve endings in the respiratory tract (De Koch, Nadel, Zwi, Colebatch & Olsen, 1966) and by the adrenal medulla (James, 1967).

Bronchopulmonary effects of pentobarbitone

Another finding in this study was that pentobarbitone in a low dose of 10 mg/kg increased PAR in the guinea-pig. The increase was virtually uninfluenced by pretreatment with atropine but it declined and became statistically non significant when the animals were pretreated with propranolol. Moreover, in our experiments this anaesthetic potentiated the effects of bronchoconstrictor mediators, contrary to the finding of Dennis & Douglas (1970) who used a similar dose (12 mg/kg i.p.). This potentiation was not modified by atropine, except in the case of ACh-induced bronchoconstriction, because of the direct antagonist effect of the alkaloid. It was enhanced in some animals additionally given propranolol but not to any significant extent.

The most likely explanation for these effects of pentobarbitone is a decrease in the autonomic impulses affecting both normal tone and respiratory reflexes. Thus a reduction of the predominant sympathetic tone would explain not only the increase in pulmonary airway resistance caused by pentobarbitone, but also the potentiation by pentobarbitone of the bronchoconstrictor effects of histamine, 5-HT and ACh.

Pentobarbitone has been shown to possess ganglion blocking activity in the dog (10 to 57.5 mg/kg) (Morisson, Walker & Richardson, 1950) and in the cat (4 to 10 mg/kg) (Exley, 1954) and also has a direct depressant effect on secretion of the perfused isolated cow adrenal gland (Holmes & Schneider, 1973). Barbiturates have been reported to inhibit efferent pathways in other circumstances. For example, pentobarbitone (55 mg/kg i.p.) abolished reactional tachycardia to pain in the rat (Barret, 1971) and amobarbitone (80 mg/kg) abolished the reflex bradycardia due to noradrenaline-induced hypertension (Buñag & Mullenix, 1972). However, the ability of pentobarbitone to affect PAR even in the presence of propranolol suggests an additional action. This could be on bronchial secretion, or perhaps inhibition of a reflex involving the nonadrenergic bronchodilator system described in the guinea-pig (Coburn & Tomita, 1973; Coleman & Levy, 1974).

Reports may be found of results contrary to our own. Dennis & Douglas (1970) described an inhibition of the effects of histamine under the influence of pentobarbitone (12 mg/kg i.p.) as did Douglas *et al.* (1973) with urethane. Herxheimer (1956), Bouhuys *et al.* (1969) and Douglas *et al.* (1973) also antagonized the effects of histamine by giving ganglionic blocking agents although McCulloch *et al.* (1967) observed potentiation of the effects of histamine with this latter type of drug.

These discrepancies might be due to differences in the doses of histamine; in our experiments we gave 20 μg/kg rapidly intravenously, whilst in the others the drug was administered either by aerosol in doses giving a threshold variation of bronchomotor tone (Herxheimer, 1956; Bouhuys *et al.*, 1969), or by intravenous perfusion in a dose of 39.5 ng/s for 20 s (Douglas *et al.*, 1972). In this connection, Drazen & Austen (1975) showed that for low doses of histamine

(up to 3 μg/kg i.v.), most of the bronchoconstriction was reflex whereas for high doses (20 μg/kg), the reflex component was reduced in comparison to the direct effect.

Thus, if pentobarbitone inhibits the reflexes triggered by the administration of histamine, the bronchoconstrictor effects of low doses of this substance would be reduced by blockade of the cholinergic reflex that produces the bronchoconstriction whilst the effects of high doses of histamine would be potentiated since the direct effect predominates and the bronchodilator adrenergic reflex assumes greatest importance.

The discrepancies might also result from differences in methodology. Bouhuys *et al.* (1969) and Douglas *et al.* (1972) studied bronchomotor tone in guinea-pigs by measuring variations in dynamic pulmonary compliance. This parameter reflects PAR but only the resistance of the distal airways is measured by this technique (Macklem & Mead, 1967; Douglas *et al.*, 1972; Drazen & Austen, 1975). The PAR measured in our experiments is essentially a reflection of the permeability of the airways for which adrenergic innervation appears to be preponderant (O'Donnell & Saar, 1973; Foster & O'Donnell, 1975). Under these conditions, it is perhaps possible to analyse more accurately phenomena that involve adrenergically mediated reflexes.

Bronchopulmonary effects of urethane

Urethane enhanced the baseline PAR in guinea-pigs by approximately 50%. A significant increase was also observed when animals were pretreated with atropine but the increase was not statistically significant following pretreatment with propranolol, thereby resembling the effects of pentobarbitone. Moreover, like pentobarbitone, urethane also potentiated the bronchoconstrictor responses to histamine, ACh and 5-HT.

This increase in PAR appears paradoxical at first sight in view of reports that urethane induces release of adrenal medulla catecholamines and elevation of circulating adrenaline levels in the cat (Aub, Bright & Forman, 1922), the rabbit (Hökfelt & MacLean, 1950) and the rat (Spriggs, 1965). Thus a decrease in PAR might have been expected. In our experiments urethane decreased heart rate and arterial blood pressure also contrary to what might be anticipated. However, results consistent with our own were reported by Buñag & Mullenix (1972) and Buñag & Eferakeya (1973) who observed a fall in resting heart rate and blood pressure in urethane-treated rats and Giles, Quiroz & Burch (1969) who showed that this anaesthetic depressed myocardial contractility in the dog.

Presupposing that urethane reduced the sympathetic respiratory component, its mechanism of action is not clear at the moment. It is unlikely that acidosis was responsible in view of the small drop in arterial pH induced by urethane in our experiments. The ventilatory depression which we observed was less severe than that reported by Douglas *et al.* (1972) who found a 42.5% decrease in minute ventilation in their animals, although they did use a higher dose of urethane (1.5 g/kg).

However, it is possible that urethane could interrupt the adrenergic reflex at the central nervous system or peripheral synapse level. In support of this contention it has been shown that, in the rat, urethane raises the threshold of electrical stimulation of the hypothalamus required to reduce heart rate or increase blood pressure (Buñag & Eferakeya, 1973), and, in the dog, inhibits reflex hypertension triggered by stimulation of saphenous nerve fibres (Baïsset, Laporte & Montastruc, 1959). This hypothesis remains open to question, however, insofar as other investigators have obtained conflicting results; urethane did not modify tachycardia in response to painful stimuli (Barrett, 1971) nor did it affect the hypertension resulting from stimulation of the extremity of the splanchnic nerve or carotid compression (Baïsset *et al.*, 1959).

Potentiation of the effects of the three bronchoconstrictor amines studied was not observed by Douglas *et al.* (1972) who found, on the contrary, that the effects of histamine were inhibited by urethane (1.5 g/kg i.p.) in 13 of a series of 17 guinea-pigs. The explanation for this apparent discrepancy may lie, as in the case of pentobarbitone, in differences of doses and methodology. Whatever the explanations, these results show that pentobarbitone and urethane are capable of inducing significant modifications in the bronchial reactivity of guinea-pigs and that drug interactions in the presence of these agents should be interpreted with caution.

This investigation was supported by a grant from the Conseil Scientifique de la Faculté de Médecine Necker-Enfants-Malades. The authors wish to thank Professor P. Macklem for his interest in this study during his sabbatical year in Paris. Thanks are also extended to Miss M. C. Santais for her excellent technical assistance.

References

ADVENIER, C., BOISSIER, J.R. & GIUDICELLI, J.F. (1972). Comparative study of six β-adrenoceptive antagonists on airway resistance and heart rate in the guinea-pig. *Br. J. Pharmac.*, **44**, 642–650.

AMDUR, M.O. & MEAD, J. (1958). Mechanics of respiration in unanaesthetized guinea-pigs. *Am. J. Physiol.*, **129**, 364–368.

AUB, J.C., BRIGHT, E.M. & FORMAN, J. (1922). The metabolic effect of adrenalectomy upon the urethanized cat. *Am. J. Physiol.*, **61**, 349–368.

BAISSET, A., LAPORTE, Y. & MONTASTRUC, P. (1959). Contribution expérimentale à l'étude des effets de l'urethane sur les réflexes circulatoires généraux. *Thérapie*, **14**, 1053–1067.

BARRET, A.M. (1971). The effects of some autonomic blocking agents on the heart rate of anaesthetized and pithed rats. *Eur. J. Pharmac.*, **15**, 267–273.

BOUHUYS, A., DENNIS M.W. & DOUGLAS, J.S. (1969). Histamine-induced bronchoconstriction in man and guinea-pig. *J. Physiol.*, **200**, 64–65.

BUÑAG, R.D. & EFERAKEYA, J.E. (1973). Reduced cardiovascular responsiveness to hypothalamic stimulation during urethane and amobarbital anaesthesia. *Pharmacology*, **10**, 143–151.

BUÑAG, R.D. & MULLENIX, P. (1972). Augmentation of drug-induced blood pressure increases in rats by amobarbital. *Br. J. Pharmac.*, **46**, 511–513.

COBURN, R.F. & TOMITA, T. (1973). Evidence for noradrenergic inhibitory nerves in the guinea-pig trachealis muscle. *Am. J. Physiol.*, **224**, 1072–1080.

COLEMAN, R.A. & LEVY, G.P. (1974). Nonadrenergic inhibitory nervous pathway in guinea-pig trachea. *Br. J. Pharmac.*, **52**, 167–174.

DENNIS, M.W. & DOUGLAS, J.S. (1970). Control of bronchomotor tone in spontaneously breathing unanaesthetized guinea-pigs. In *Airway-Dynamics, Physiology and Pharmacology*, ed. Bouhuys, A. & Charles, C. pp. 253–262. Springfield, Ill. Thomas.

DE KOCH, M.A., NADEL, J.A., ZWI, S., COLEBATCH, H.J.H. & OLSEN, C.R. (1966). New method for perfusing bronchial arteries: histamine bronchoconstriction and apnea. *J. appl. Physiol.*, **21**, 185–194.

DOUGLAS, J.S., DENNIS, M.W., RIDGWAY, P. & BOUHUYS, A. (1972). Airway dilatation and constriction in spontaneously breathing guinea-pigs. *J. Pharmac. exp. Ther.*, **180**, 98–109.

DOUGLAS, J.S., DENNIS, M.W., RIDGWAY, P. & BOUHUYS, A. (1973). Airway constriction in guinea-pigs. Interactions of histamine and autonomic drugs. *J. Pharmac. exp. Ther.*, **184**, 169–179.

DRAZEN, J.M. & AUSTEN, K.F. (1975). Atropine modification of the pulmonary effects of chemical mediators in the guinea-pig. *J. appl. Physiol.*, **38**, 834–838.

EXLEY, K.A. (1954). Depression of autonomic ganglia by barbiturates. *Br. J. Pharmac. Chemother.*, **9**, 170–181.

FOSTER, R.W. & O'DONNELL, S.R. (1975). Evidence that adrenergic nerves are responsible for the active uptake of noradrenaline in the guinea-pig isolated trachea. *Br. J. Pharmac.*, **53**, 109–112.

GILES, T.D., QUIROZ, A.C. & BURCH, G.E. (1969). Hemodynamic alterations produced by prolonged urethane anesthesia in the intact dog. *Am. Heart J.*, **78**, 281–282.

HERXHEIMER, H. (1956). Bronchoconstrictor agents and their antagonists in the guinea-pig. *Archs int. Pharmacodyn.*, **106**, 371–380.

HÖKFELT, B. & McLEAN, J. (1950). The adrenalin and noradrenalin content of the suprarenal glands of the rabbit under normal conditions and after various forms of stimulation. *Acta physiol. scand.*, **21**, 258–270.

HOLMES, J.C. & SCHNEIDER, F.H. (1973). Pentobarbitone inhibition of catecholamine secretion. *Br. J. Pharmac.*, **49**, 205–213.

JACKSON, D.M. & RICHARDS, I.M. (1977). The effects of pentobarbitone and chloralose on the vagal component of bronchoconstriction produced by histamine aerosol in the anaesthetized dog. *Br. J. Pharmac.*, **61**, 251–256.

JAMES, G.W.L. (1967). The role of the adrenal glands and of α- and β-adrenergic receptors in bronchodilatation of guinea-pig lungs *in vivo*. *J. Pharm. Pharmac.*, **19**, 797–802.

MACKLEM, P.T. & MEAD, J. (1967). Resistance of central and peripheral airways measured by a retrograde catheter. *J. appl. Physiol.*, **22**, 395–401.

MARCELLE, R. (1976). La Maladie Asthmatique, son Déterminisme Adrenergique. p. 204. Masson Ed., Paris.

McCULLOCH, M. W., PROCTOR, C. & RAND, M.J. (1967). Evidence for an adrenergic homeostatic bronchodilator reflex mechanism. *Eur. J. Pharmac.*, **2**, 214–223.

MILLS, J. & WIDDICOMBE, J.G. (1970). Role of the vagus nerves in anaphylaxis and histamine-induced bronchoconstriction in guinea-pig. *Br. J. Pharmac.*, **39**, 724–731.

MORISSON, J.L., WALKER, H.A. & RICHARDSON, A. P. (1950). The effect of pentobarbital on the response of cardiovascular system of dogs to epinephrine, acetylcholine and tilting. *Archs. int. Pharmacodyn.*, **82**, 53–62.

NADEL, J.A. (1965). Structure relationships in the airways: bronchoconstriction mediated via vagus nerves on bronchial arterial peripheral lung constriction mediated via pulmonary arteries. *Med. Thorac.*, **22**, 231–242.

O'DONNELL, S.R. & SAAR, N. (1973). A histochemical study of extraneuronal accumulation of noradrenaline in the guinea-pig trachea. *Br. J. Pharmac.*, **49**, 267–278.

SPRIGGS, T.L.B. (1965). The effects of anaesthesia induced by urethane or phenobarbitone upon the distribution of peripheral catecholamines in the rat. *Br. J. Pharmac. Chemother.*, **24**, 752–758.

(Received January 5, 1978. Revised June 20, 1978.)