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Endotoxin-induced plasma exudation in guinea-pig airways *in vivo* and the effect of neutrophil depletion

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ABSTRACT: The contribution of neutrophils to the action of endotoxin on plasma exudation in the airways of anaesthetized guinea-pigs was quantified by measuring the extravasation of Evans blue dye. Endotoxin (*Salmonella enteritidis*) caused a dose-dependent increase in microvascular leakage to Evans blue dye which was maximal after 25 min ($p<0.05$). The minimum dose tested that induced a significant rise in leakage was 1.5 mg·kg^{-1} for "central" intrapulmonary airways (ipa); 4.5 mg·kg^{-1} for trachea and main bronchi and 7.5 mg·kg^{-1} for nasal mucosa, larynx and "peripheral" ipa. Depletion of circulating neutrophil numbers by 97% using an antibody to guinea-pig neutrophils caused no significant diminution of the effects of endotoxin on leakage in any part of the airway. There was no significant influx of neutrophils into the airway interstitium at the time of maximum extravasation of Evans blue. We conclude that endotoxin-induced airway microvascular permeability is dependent upon mechanisms other than circulating neutrophils.

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Increased microvascular permeability and oedema of the airways are important features of asthma and may underlie several of its pathological and physiological features [1]. The precise relationship between viral infection and exacerbation of asthma remains controversial and the effects of bacterial infection upon airway hyperreactivity are a matter of speculation, particularly in children [2]. However, bacterial products such as endotoxin may act as adjuvants in the production of reaginic antibody [3] and airborne endotoxin has been shown to cause bronchoconstriction in man [4] and bronchial hyperresponsiveness in sheep [5].

Intravenous endotoxin has been shown to increase bronchial vascular permeability in the airways of dogs, an effect associated with accumulation of polymorphonuclear leucocytes in pulmonary blood vessels [6]. Airway inflammation is a prominent feature of asthma and neutrophils have been implicated in the mechanism underlying bronchial hyperreactivity induced by ozone [7, 8]. In the current study we investigated the effects of endotoxin on airway microvascular permeability in guinea-pigs and the possible role of circulating neutrophils in the underlying mechanism of action.

Methods

Male Dunkin-Hartley guinea-pigs (300–400 g) were anaesthetized using diazepam (5 mg·kg^{-1}, *i.p.*) and Hypnorm (1 ml, containing 0.315 mg fentanyl citrate and 10 mg fluanisone, *i.m.*). After each dose of endotoxin, administered *via* the jugular vein, in at least 3 animals, blood pressure was monitored throughout using a cannula placed in the left carotid artery, with the pressure trace recorded on a calibrated pen recorder (Ormed Ltd, Welwyn Garden City, Herts., UK). Body temperature was maintained at 37°C using an overhead lamp. Drugs were subsequently injected *via* the jugular veins (*i.v.*) by passing the needle through the pectoralis major to prevent bleeding on withdrawal.

Assessment of microvascular permeability

Changes in vascular permeability were quantified by the extravasation of Evans blue dye using a method modified after LUNDBERG and SARIA [9]. This has been shown in our laboratory to correlate well with measurements of the extravasation of radiolabelled albumin in various parts of the guinea-pig airway after the administration of inflammatory mediators [10]. Evans blue dye (30 mg·ml^{-1} in 0.9% sodium chloride, filtered through a 5.0 μm Millipore filter) 30 mg·kg^{-1} was injected *i.v.* After various time intervals (see below), the thorax was opened and a blunt-ended 13 gauge needle passed through a left ventriculotomy into the aorta. The heart was cross-clamped to seal the ventriculotomy and the right atrium incised to allow outflow of perfusate. The animal

was perfused with 100 ml of 1% paraformaldehyde in phosphate buffered saline, pH 3.5, at 100 mmHg pressure to remove intravascular dye and fix the tissues. The larynx, trachea, main bronchi, lungs, oesophagus, bladder and a portion of nasal mucosa (2.5 mm^2) from the vomer at the base of the vibrissae were removed. The lung parenchyma was stripped from the intrapulmonary airways using a razor blade and separated into "central" (first 3 mm) and "peripheral" components [11]. Wet weights of all tissues were recorded and dye extracted by incubation in 2 ml of 100% formamide overnight at 40°C. The concentration of dye in each 1 ml aliquot was determined by spectrophotometry (SP 1750 spectrophotometer, Pye Unicam, Cambridge, UK) at 620 nm wavelength and expressed as dye $ng \cdot mg^{-1}$ wet weight tissue.

Protocols

The dose response to endotoxin was determined by administering *Salmonella enteritidis* in 0.9% NaCl at doses of 1.5 (n=4), 4.5 (n=7), 7.5 (n=6), 15 (n=8) and 30 (n=6) $mg \cdot kg^{-1}$ in 1 ml 1 min after Evans blue dye. Control animals (n=6) were given saline alone. The time course of the effect was studied by injecting endotoxin 15 $mg \cdot kg^{-1}$ and perfusing animals 15 (n=4), 25 (n=6) and 60 (n=4) min later. Control animals were injected with saline and perfused at the same time points (n=3, n=4, n=4, respectively).

Neutrophil depletion and histology

The dependence of endotoxin-induced leakage upon the presence of circulating neutrophils was assessed by pretreating animals (n=7) with an anti-guinea-pig neutrophil antibody (0.4 ml *i.p.*) raised in rabbits, 24 h before experimentation [12]. Control animals were given rabbit serum alone (n=5). Haemoglobin levels, platelet and white cell counts were measured immediately prior to injection of endotoxin.

The temporal association of leakage with infiltration of the airways was assessed by inflating the lungs *via* the trachea with 10% neutral buffered formal-saline (15 ml) until the pleural margins were sharply defined at the time of maximal leak (*i.e.* 25 min) after endotoxin 7.5 $mg \cdot kg^{-1}$ (n=3). Control animals (n=3) were perfused 25 min after the administration of vehicle.

After lung inflation, the trachea was ligated below the larynx to prevent outflow of perfusate. The trachea, main bronchi and whole lungs were removed, fixed in 10% formal-saline and paraffin sections 5 μm thick cut and stained with haematoxylin and eosin. Neutrophils were identified as multi nucleated cells and counted by light microscopy (×400). Neutrophils were counted in one of the main bronchi at 3 sites: epithelium, sub-epithelium and blood vessels and in parenchymal sections in 5 randomly selected areas, each with a graticule area of 175 μm^2.

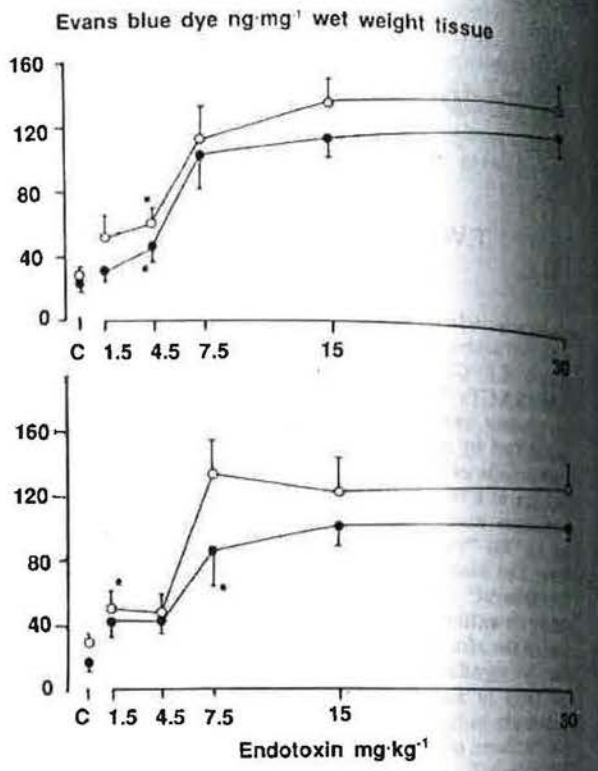

Fig. 1. – Effect of endotoxin 1.5 (n=4), 4.5 (n=7), 7.5 (n=6), 15 (n=8) and 30 (n=6) $mg \cdot kg^{-1}$ on the extravasation of Evans blue dye in (upper panel) trachea (●) and main bronchi (○); and (lower panel) in central (○) and peripheral (●) intrapulmonary airways. Values are mean±SEM. *: minimum dose causing significant increase in extravasation of dye compared with controls (C).

Table 1. – Effect of endotoxin on plasma exudation in non-pulmonary tissue

	Nasal mucosa	Larynx	Bladder	Oesophagus
Saline (n=6)	11.6 (2.4)	14.4 (2.5)	10.2 (1.4)	15.6 (5.1)
Endotoxin $mg \cdot kg^{-1}$				
1.5 (n=4)	6.8 (4.5)	18.2 (2.7)	17.7 (3.2)	12.7 (4.3)
4.5 (n=7)	29.5 (8.9)	22.7 (3.2)	35.1* (11.9)	18.2 (8.3)
7.5 (n=6)	44.0* (12.8)	48.0* (10.1)	75.5 (15.8)	27.3 (4.3)
15 (n=8)	64.8 (10.2)	49.3 (6.5)	80.6 (10.9)	30.4 (8.2)
30 (n=6)	50.8 (7.1)	58.7 (4.6)	97.5 (21.1)	32.7* (3.9)

Values are Evans blue dye $ng \cdot mg^{-1}$ wet weight tissue and are expressed as mean±SEM. *: minimum dose of endotoxin causing a significant increase in leak compared with saline ($p<0.05$).

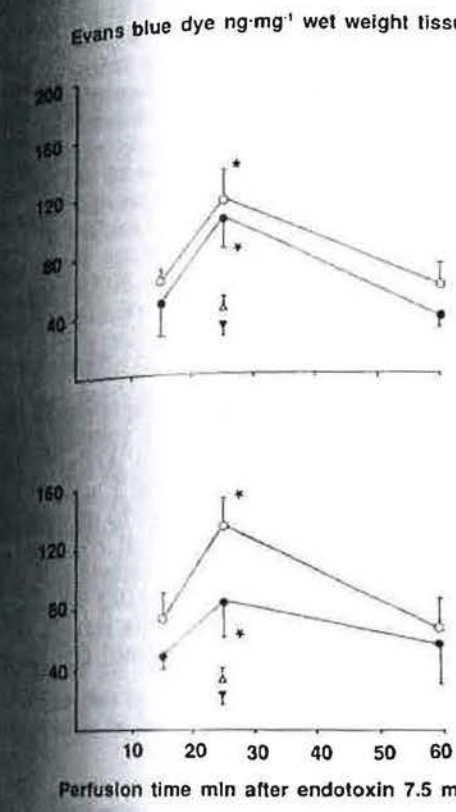

Fig. 2. – Effects of endotoxin (7.5 mg·kg⁻¹) on extravasation of Evans blue dye in (upper panel) trachea (●) and main bronchi (○); and (lower panel) in central (○) and peripheral (●) intrapulmonary airways. Animals were perfused 15 (n=4), 25 (n=6) and 60 (n=4) min after endotoxin administration. (Δ) and (▼) indicate effects of saline control on extravasation of dye (n=4). Values are mean±SEM. *: $p<0.05$ compared with saline control (n=4).

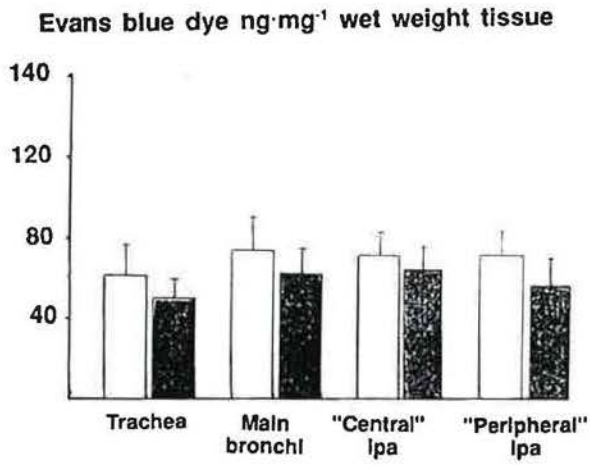

Fig. 3. – Effects of neutrophil depletion (shaded bar, n=7) on microvascular leakage induced by endotoxin 7.5 mg·kg⁻¹ in airway tissues. ipa: intrapulmonary airways.

Drugs and chemicals

The drugs and chemicals used were: Evans blue, formamide, paraformaldehyde and *Salmonella enteritidis* endotoxin from Sigma Chemicals Ltd, St. Louis, Mo.; Diazepam from Roche Pharmaceuticals, Switzerland; Hypnorm from Janssen Pharmaceuticals, Oxford, UK. Anti-neutrophil antibody was kindly supplied by Dr S. Sanjar and M. King of Sandoz Pharmaceuticals (Pre-Clinical Laboratories), Basle, Switzerland.

Table 2. – Mean blood pressure measured at the carotid artery at various time points after the administration of Evans blue dye and endotoxin 0, 1.5, 4.5, 7.5, 15 and 30 mg·kg⁻¹

	Baseline	1 min post EB	Minutes post endotoxin/vehicle 1	5	15	25	60
Endotoxin mg·kg⁻¹							
0	38.0 (1.7)	35.6 (2.3)	35.1 (2.5)	34.4 (3.1)	34.6 (2.2)	33.0 (3.2)	35.1 (4.1)
1.5	35.0 (1.4)	31.6 (2.8)	33.6 (2.7)	35.0 (3.2)	30.3 (3.3)	34.3 (3.0)	32.9 (3.6)
4.5	31.5 (3.1)	29.2 (3.0)	31.2 (3.1)	29.7 (2.6)	31.1 (4.6)	34.7 (3.8)	31.9 (2.7)
7.5	33.6 (2.4)	31.0 (2.0)	25.6* (6.8)	26.2 (3.0)	27.0 (2.4)	36.1 (3.4)	32.4 (5.8)
15.0	37.6 (2.5)	43.0 (2.8)	36.3 (12.8)	49.6 (6.6)	40.0 (3.1)	36.7 (4.1)	33.9 (3.3)
30.0	41.1 (3.6)	38.0 (2.9)	29.0* (4.1)	36.0 (3.6)	37.1 (4.1)	35.8 (3.9)	36.6 (5.7)

n= at least 3 in each group. Values are mean±SEM, mmHg. *: significant fall from baseline; EB: Evans blue dye.

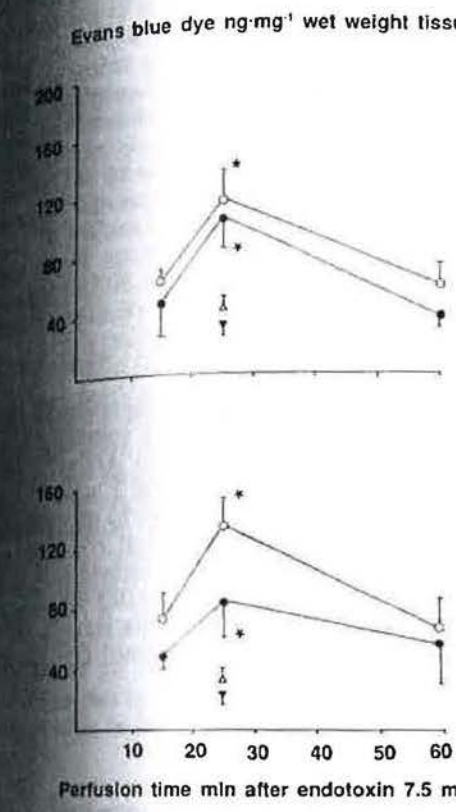

Fig. 2. – Effects of endotoxin (7.5 mg·kg⁻¹) on extravasation of Evans blue dye in (upper panel) trachea (●) and main bronchi (○); and (lower panel) in central (○) and peripheral (●) intrapulmonary airways. Animals were perfused 15 (n=4), 25 (n=6) and 60 (n=4) min after endotoxin administration. (Δ) and (▼) indicate effects of saline control on extravasation of dye (n=4). Values are mean±SEM. *: $p<0.05$ compared with saline control (n=4).

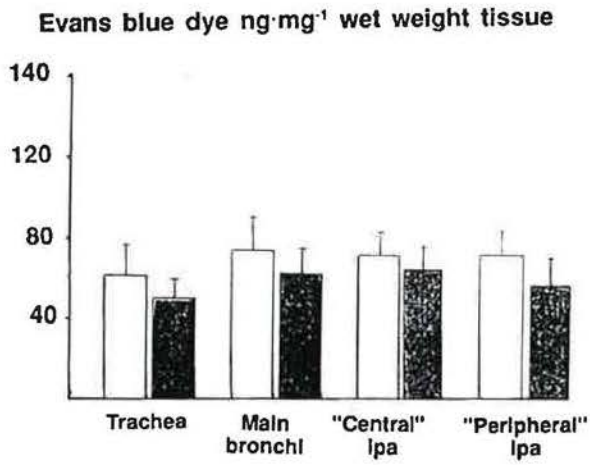

Fig. 3. – Effects of neutrophil depletion (shaded bar, n=7) on microvascular leakage induced by endotoxin 7.5 mg·kg⁻¹ in airway tissues. ipa: intrapulmonary airways.

Drugs and chemicals

The drugs and chemicals used were: Evans blue, formamide, paraformaldehyde and *Salmonella enteritidis* endotoxin from Sigma Chemicals Ltd, St. Louis, Mo.; Diazepam from Roche Pharmaceuticals, Switzerland; Hypnorm from Janssen Pharmaceuticals, Oxford, UK. Anti-neutrophil antibody was kindly supplied by Dr S. Sanjar and M. King of Sandoz Pharmaceuticals (Pre-Clinical Laboratories), Basle, Switzerland.

Table 2. – Mean blood pressure measured at the carotid artery at various time points after the administration of Evans blue dye and endotoxin 0, 1.5, 4.5, 7.5, 15 and 30 mg·kg⁻¹

	Baseline	1 min post EB	Minutes post endotoxin/vehicle 1	5	15	25	60
Endotoxin mg·kg⁻¹							
0	38.0 (1.7)	35.6 (2.3)	35.1 (2.5)	34.4 (3.1)	34.6 (2.2)	33.0 (3.2)	35.1 (4.1)
1.5	35.0 (1.4)	31.6 (2.8)	33.6 (2.7)	35.0 (3.2)	30.3 (3.3)	34.3 (3.0)	32.9 (3.6)
4.5	31.5 (3.1)	29.2 (3.0)	31.2 (3.1)	29.7 (2.6)	31.1 (4.6)	34.7 (3.8)	31.9 (2.7)
7.5	33.6 (2.4)	31.0 (2.0)	25.6* (6.8)	26.2 (3.0)	27.0 (2.4)	36.1 (3.4)	32.4 (5.8)
15.0	37.6 (2.5)	43.0 (2.8)	36.3 (12.8)	49.6 (6.6)	40.0 (3.1)	36.7 (4.1)	33.9 (3.3)
30.0	41.1 (3.6)	38.0 (2.9)	29.0* (4.1)	36.0 (3.6)	37.1 (4.1)	35.8 (3.9)	36.6 (5.7)

n= at least 3 in each group. Values are mean±SEM, mmHg. *: significant fall from baseline; EB: Evans blue dye.

Table 3. – Effects of anti-guinea-pig neutrophil antibody on blood elements in antibody treated animals and controls

	Hb $g \cdot dl^{-1}$	WBC $\times 10^6 \cdot l^{-1}$	Neut $\times 10^6 \cdot l^{-1}$	P $\times 10^9$
Antibody treated (n=7)	12.3 (0.2)	1428.0* (187)	61.1* (22.5)	586.1 (42.4)
Control (n=5)	13.0 (0.7)	3,800.0 (400)	2,378.0 (272)	682 (41.4)

Hb: haemoglobin; WBC: white cell count; Neut: neutrophil count; P: platelet count; *: $p<0.05$ compared with control.

Table 4. – Effects of neutrophil depletion upon endotoxin-(7.5 $mg \cdot kg^{-1}$) induced leakage in other airway tissues

	Nasal mucosa	Larynx	Oesophagus	Bladder
Saline (n=6)	11.6 (2.4)	14.4 (2.5)	10.2 (1.4)	15.6 (5.1)
Endotoxin 7.5 $mg \cdot kg^{-1}$ plus serum (n=5)	54.5* (7.2)	26.1* (3.4)	-	-
Endotoxin 7.5 $mg \cdot kg^{-1}$ plus neutrophil depletion (n=7)	48.6* (9.2)	27.9* (4.7)	-	-

Values are Evans blue dye $ng \cdot mg^{-1}$ wet weight tissue and are expressed as mean±(SEM). *: significant difference when compared with saline.

Data analysis

Changes in blood pressure, comparisons of tissue content of Evans blue dye and neutrophil numbers were made using the Mann-Whitney U-test [13]. Values are expressed as mean±SEM. Values of $p<0.05$ were considered significant.

Results

The effect of endotoxin on the extravasation of Evans blue dye in selected airways is shown in figure 1, and for the remaining tissues in table 1. Endotoxin caused a dose-dependent increase in microvascular leakage in all tissues, with minimum doses required to cause a significant increase in leakage above controls of 1.5 $mg \cdot kg^{-1}$ for "central" intrapulmonary airways, 4.5 $mg \cdot kg^{-1}$ for trachea, main bronchi and bladder, 7.5 $mg \cdot kg^{-1}$ for "peripheral" intrapulmonary airways, nasal mucosa and larynx, and 30 $mg \cdot kg^{-1}$ for oesophagus. Of the time points studied, the maximal effect of endotoxin (7.5 $mg \cdot kg^{-1}$) on microvascular leakage in the airways was at 25 min (fig. 2). There was no significant change in systemic blood pressure from baseline, except for 23 and 28% decreases, respectively, ($p<0.05$) 1 min after the injection of 7.5 and 30 $mg \cdot kg^{-1}$ endotoxin, which returned to baseline levels by 5 min in the case of 30 $mg \cdot kg^{-1}$ and 30 min in the case of 7.5 $mg \cdot kg^{-1}$ (table 2).

Reduction in the number of circulating neutrophils by 97.4% in antibody-pretreated animals compared with controls ($p<0.05$), caused no significant reduction in the effect of endotoxin (fig. 3, tables 3 and 4). No other blood element was affected by the antibody (table 3), the reduction in white cell count being accounted for by the reduction in neutrophil numbers. Total tissue neutrophil counts were 23.0±3 for vehicle treated animals and 8±0.6 for endotoxin animals, suggesting that neutrophils were not recruited into airway tissues following endotoxin.

Discussion

We have shown that endotoxin administered intravenously causes a quantitative and significant increase in microvascular permeability of the airways as assessed by extravasation of circulating Evans blue dye. The effect was dose-dependent, achieved a maximal effect 25 min after administration of endotoxin and was not dependent upon the presence of peripheral systemic neutrophils; nor were more neutrophils detected within airway tissues after endotoxin. Our results are similar to those reported previously, whereby histological observations indicated bronchial venular leakage in dogs during the first hour of endotoxin shock induced by the administration of *E. Coli* lipopolysaccharide [6].

It is becoming increasingly clear that plasma exudation plays an important role in the mechanisms underlying asthma, leading to impaired mucociliary transport, mucus plug formation and small airway narrowing [1]. Infection of the upper respiratory tract is perhaps the commonest cause of acute exacerbations of asthma [14]. It therefore seems likely that endotoxin released during bacterial infections and inhaled from the atmosphere may partially exert its deleterious effects on airway function through increased bronchial vascular permeability and airway oedema formation. However, as the effect of endotoxin was not attenuated by a mean reduction in circulating neutrophil count of 97%, it seems unlikely that neutrophils are essential for the development of endotoxin-induced microvascular leakage in the airways of guinea-pigs. In dogs the accumulation of polymorphonuclear leucocytes in lung capillaries, small arteries and veins has been observed following the

jection of endotoxin and is accompanied by histologi-
al evidence of increased endothelial permeability, but
we observed, if anything, a reduction in neutrophil
umbers within airway tissues at the time of maximal
Evans blue extravasation. Other workers have found that
neutrophil depletion abolishes endotoxin-induced changes
in pulmonary (*i.e.* rather than bronchial) vascular per-
meability in the rabbit [15]. Furthermore, the pulmonary
vascular sequestration of neutrophils that is known to
occur in endotoxaemia has been shown in rabbits to be
dependent upon a direct effect of endotoxin on
neutrophils [16]. Nevertheless, in dogs endotoxin causes
leakage exclusively from bronchial vessels [6]. It is,
therefore, possible that neutrophils are necessary for
endotoxin-mediated pulmonary vascular injury, but not
bronchial permeability changes.

The role of neutrophils in several forms of lung injury
remains controversial. Neutrophil depletion has been
shown to inhibit changes in pulmonary vascular
permeability in sheep [17] and rats [8], but not goats
[18]. However, the increase in airway microvascular
permeability induced by substance P in the rat also occurs
in the absence of neutrophils or other circulating
cells [19]. If, as has been suggested [1], the airway
hyperreactivity that characterizes asthma is linked to
oedema of the bronchial wall, the presence of neutro-
phils may not be essential in the development of either
abnormality as far as the guinea-pig is concerned [20].

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Exsudation plasmatique induite par les endo-toxines dans les voies aériennes de cobayes in vivo, *et effet de la déplétion neutrophilique. T.W. Evans, D.F. Rogers, M.G. Belvisi, J.A.L. Rohde, K.F. Chung, P.J. Barnes.*

RÉSUMÉ: La contribution des neutrophiles à l'action de l'endo-toxine sur l'exsudation plasmatique dans les voies aériennes de cobayes anesthésiés, a été quantifiée par mesure de l'extravasation du colorant bleu Evans. L'endo-toxine (*Salmonella enteritidis*) a provoqué une augmentation dose-dépendante de la fuite microvasculaire du colorant bleu Evans, qui a atteint son maximum après 25 min ($p<0.05$). Les doses minimales testées qui induisent une augmentation significative de la fuite, furent de 1.5 $mg \cdot kg^{-1}$ pour les voies aériennes "centrales" (ipa); 4.5 $mg \cdot kg^{-1}$ pour la trachée et les bronches principales; et 7.5 $mg \cdot kg^{-1}$ pour la muqueuse nasale, le larynx et les ipa "périphériques". La déplétion du nombre de neutrophiles circulants jusqu'à 97%, obtenue par l'utilisation d'un anticorps pour les neutrophiles de cobayes, ne provoque pas de diminution significative des effets de l'endotoxine sur la fuite dans aucune des parties de la voie aérienne. Il n'y a pas d'afflux neutrophilique significatif dans l'interstitium des voies aériennes au moment de l'extravasation maximale du bleu Evans. Nous concluons que la perméabilité microvasculaire des voies aériennes induite par l'endo-toxine dépend de mécanismes autres que la présence de neutrophiles circulants.
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