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DECREASED INACTIVATION OF PROSTAGLANDIN E_2 IN ISOLATED LUNGS FROM RATS WITH α-NAPHTHYL THIOUREA-INDUCED PULMONARY OEDEMA*

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Abstract—The effect of pulmonary oedema on the pharmacokinetic function of rat lungs was studied using prostaglandin E_2 (PGE_2) as substrate; oedema was induced by α-naphthyl thiourea (ANTU). Male rats were given a single i.p. injection of ANTU (10 mg/kg). Lung wet weight, dry:wet weight ratio and pleural transudate were measured at fixed times up to 50 hr after treatment. Wet weight was increased after 4 hr and remained higher than controls until 50 hr; dry:wet weight ratios were different only at 6 and 16 hr. Survival of PGE_2 (measured by bioassay) was increased at 4 hr, reached a peak value of about six times the control survival at 6 hr and returned to normal by 50 hr. Using ^{14}C-PGE_2 as substrate, survival was maximal at 16 hr and back to normal by 50 hr. The efflux profiles of radioactivity showed an increase in $T_{\frac{1}{2}}$ by 4 hr rising to a maximum at 28 hr and a normal value at 50 hr. Changes in PGE_2 survival precede the period of oedema (assessed by dry:wet ratio) and could be used as an early warning of oedematous states. This altered pharmacokinetic function of lung could also have systemic effects.

Pulmonary oedema is usually manifested in terms of respiratory disturbances—decreased compliance and decreased gas exchange. Since the lung also has important biochemical functions, it is possible that these may also be disturbed by the processes leading to oedema and, further, that such biochemical disturbances may precede or contribute to the accumulation of extravascular fluid.

One method of inducing pulmonary oedema in rats is by the injection of α-naphthyl thiourea (ANTU) [1]. The effects of ANTU have been well characterized morphologically [2, 3] and are dose related in duration and intensity. This model of pulmonary oedema has been used in the work described below to correlate the physical progress of oedema with one biochemical function, the inactivation of prostaglandin E_2 (PGE_2), in perfused isolated lungs from rats.

MATERIALS AND METHODS

Preparation of animals. Male Wistar rats (200–250 g) were injected intraperitoneally with a suspension of ANTU (4 mg/ml) in olive oil (B.P.), at a dose of 10 mg/kg body weight. Sham-treated animals were injected with the same volume of olive-oil only. Rats were then returned to their cages with free access to food and water until they were used. At different times after treatment the rats were anaesthetized with pentobarbitone (60 mg/kg, i.p.) and the lungs removed.

Determination of lung and transudate weights. In a set of animals whose lungs were not used for perfusion studies, the thorax was opened carefully and any fluid present in the pleural cavity sucked out and weighed. The lungs and heart were then excised, the heart and other extraneous tissue trimmed off, before rinsing in Krebs solution and blotting dry. The lungs were weighed (wet weight) and then dried in an oven overnight to give the dry weight.

Preparation of perfused lungs and bioassay. The pulmonary artery was cannulated and perfusion with warmed (37°) and gassed (95% O_2; 5% CO_2) Krebs bicarbonate solution at a constant rate of 8 ml/min carried out as described previously [4]. The Krebs solution contained indomethacin (3 μg/ml) to prevent interference from PGs synthesized by the lung in the bioassay of exogenous PGE_2.

For bioassay of PGE_2, the lung effluent superfused strips of hamster stomach [5]. Inactivation was measured using a bracketing assay [5] with 5–100 ng PGE_2 as calibrating doses and a range of doses injected into the pulmonary flow, from 100 to 750 ng, always including a standard dose of 500 ng.

For bioassay of prostacyclin (PGI_2), different assay tissues were used. The hamster stomach strip does not maintain its contraction to PGI_2 infusions and so the rabbit stomach strip [6] which did maintain contractions, was used in superfusion. As PGI_2 has a limited half life in aqueous media, the volume of PGI_2 solution to be infused was drawn up into the infusion pump tubing immediately before delivery and then pumped out into the pulmonary perfusate at rates of 0.1–0.3 ml/min for 3 min.

Radiochemical assays. $T_{\frac{1}{2}}$. Lung effluent was collected in 4-drop fractions (approximately equivalent to 3 sec) following an injection of ^{14}C-PGE_2 (500 ng; 2×10^4 dpm; 0.1 ml) into the pulmonary arterial flow. To each fraction 10 ml of scintillant A (see below) was added and radioactivity measured in a liquid scintillation counter.

Chromatographic analysis. In another set of experiments, the lung effluent following the injection

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Table 1. Lung weight and transudate formation in rats after treatment with ANTU

	Time after treatment (hr)							
	2	4	6	16	28	50	Sham-treated	Untreated
Lung wet weight (g)	1.21 ± 0.04	1.51 ± 0.07*	1.71 ± 0.07*	1.64 ± 0.03*	1.43 ± 0.07*	1.23 ± 0.06	1.05 ± 0.03*	1.13 ± 0.03
Lung: body weight ratio	556 ± 19*	696 ± 35*	786 ± 35*	716 ± 14*	606 ± 30*	558 ± 23*	436 ± 9*	510 ± 7
Lung dry: wet weight ratio	20.6 ± 0.4	19.5 ± 1.0	17.9 ± 0.4*	19.3 ± 0.6*	20.5 ± 0.5	20.2 ± 0.5	20.0 ± 0.2	21.0 ± 0.3
Weight of pleural transudate (g)	0	0.9 ± 0.4	2.3 ± 0.5	2.8 ± 0.7	0.7 ± 0.2	0	0	0
Number of animals	4	4	4	5	7	4	29	8

* Significantly different from value for untreated animals ($P < 0.05$, unpaired *t*-test).
† These values were calculated for each animal as (lung wet weight ÷ body weight) × 10^5.
‡ These values were calculated as (lung dry weight ÷ wet weight) × 10^2.
The values shown in the table are the means (± S.E.M.) of results obtained from the number of animals used (last row in table). The values for the sham-treated rats, i.e. injected with olive-oil only, have been combined (there were at least 4 at each time). Treated rats received a single injection of ANTU, suspended in olive-oil (10 mg/kg body weight), intraperitoneally and the times shown after this injection were anaesthetized with pentobarbitone and the lungs and exudate removed.

of [^{14}C]-PGE_2 was collected in a single fraction for 5 min. After acidification and extraction with organic solvents [7], the radioactivity was analysed by t.l.c. on silica gel G plates (Merck, 0.2 mm) using the following solvent system—water:acetic acid:iso-octane:ethyl acetate; 10:2:5:11 v/v. After development and drying, the chromatogram was cut into 1 cm strips, each strip extracted with methanol (2 ml) for one hour at room temperature, 8 ml of scintillant B (see below) added and radioactivity measured. The radioactivity co-chromatographing with marker PGE_2 was expressed as a percentage of the total radioactivity on the thin layer chromatogram. All radioactivity measurements were carried out with a Packard liquid scintillation counter. Counting efficiency was calculated from a sample channels ratio and results converted to dpm. The two scintillants used were: A: 5 g PPO, 0.25 g dimethyl POPOP, 1 litre toluene and 0.5 l. Triton X-100; B: 5 g PPO, 0.25 g dimethyl POPOP and 1 litre toluene.

Histological preparation of lungs. Lungs were dissected out and perfused via the pulmonary circulation with 50 ml of Krebs solution to clear blood from the pulmonary vessels. Formalin solution (8% neutral buffered formalin) was then introduced via the tracheal cannula at a pressure of 23 cm H_2O for one hour; the tracheal cannula was then clamped and the whole lung immersed in formalin for 24 hr before sectioning. Sections of 7 μm thickness were cut and stained with haematoxylin and eosin: they were examined by our Veterinary Conservator, Mr. J. E. Cooper MRCVS, without knowledge of the treatment.

Materials. Prostaglandin E_2 was obtained from Sigma and stored in methanolic solution at −5°. Before use, the methanol was evaporated and the PG redissolved in 0.9% (w/v) NaCl solution to the desired concentration. Prostaglandin I_2 was a generous gift from Dr. B. J. R. Whittle of the Wellcome Foundation. The sodium salt of PGI_2 [8] was dissolved (1 mg/ml) when required in 1 M Tris buffer (pH 9.4 at 4°). Radioactive 1-[^{14}C]-PGE_2 (55 mCi/mmole) was obtained from the Radiochemical Centre, Amersham, and diluted with unlabelled PGE, in 0.9% saline to the required concentration.

Statistical methods. In the text, unless otherwise stated, results are given as means ± S.E. mean of measurements from *n* experiments. Each experiment represents a different lung. Difference between means was assessed by an unpaired *t*-test and values of $P < 0.05$ taken as significant.

RESULTS

Lung weight and transudate

At the dose of ANTU used (10 mg/kg, i.p.), the rats showed no obvious signs of distress and only four animals out of the whole series died before they were used. Some quantitative measures of the effect of ANTU on the physical state of the lung are presented in Table 1. Compared with the untreated rats, lung wet weight increased after 4 hr to a peak between 6 and 16 hr and then returned to normal by 50 hr after the injection of ANTU. The lung: body weight ratio was higher throughout the period of study although it reached a peak at 6 hr. The dry: wet

Table 2. Effect of ANTU treatment on PGE_2 metabolism in rat isolated lungs

	Time after treatment (hr)						Sham-treated	Untreated
	2	4	6	16	28	50		
Survival of PGE_2 (%)								
a. Bioassay	2 ± 0.4 (6)	4 ± 0.6* (7)	13 ± 1* (4)	8 ± 1* (5)	8 ± 1* (4)	2 ± 0.5 (4)	2 ± 0.3 (18)	2 ± 0.3 (8)
b. Radiochemical assay		10.4 ± 0.8* (3)	20.2 ± 2.2* (3)	33.5 ± 2.6* (3)	20.0 ± 2.2* (3)	8.3 ± 1.1† (3)	5.6 ± 0.6 (13)	7.6 ± 0.7 (7)
Efflux of radioactivity—$T\frac{1}{2}$ (sec)	36 ± 2 (3)	47 ± 2* (3)	51 ± 2* (3)	76 ± 9* (4)	92 ± 10* (5)	37 ± 2 (3)	34 ± 1 (13)	35 ± 2 (7)

The values shown are the means ± S.E.M. of results obtained from the number of lungs shown in brackets.
* Significantly different from value for untreated rats ($P < 0.05$).
† Significantly different from value for sham-treated rats ($P < 0.05$).

weight ratio was significantly different only 6 and 16 hr after treatment and pleural exudate showed a pattern similar to that of lung weight, small amounts being present at 4 and 28 hr with a peak at 16 hr.

The sham-treated rats, injected with olive-oil only, maintained lung weights, lung: body weight ratios and lung dry: wet weight ratios at a constant level throughout this time. The first two variables were slightly but significantly less than those of normal, untreated, rats.

In some cases lungs from ANTU- and sham-treated and untreated rats (two each) were fixed for histological investigation by intratracheal perfusion with formalin. Examination of the sections of ANTU-treated rat lungs shows perivascular and peribronchiolar oedema more obvious after 6 hr and most marked at 28 hr. At this time (28 hr) there was also some leukocyte infiltration in the oedematous areas. These changes were absent from the lungs of sham-treated rats at any time and from normal lungs.

Inactivation of prostaglandin E_2

Bioassay. The inactivation of PGE_2 has been expressed as percent survival at a single dose (500 ng; Table 2). Treatment with ANTU decreased inactivation and thus increased survival. As shown in Table 2, PGE_2 survival was increased as early as 4 hr, reached its maximum at 6 hr and then declined slowly to attain normal levels between 28 and 50 hr after injection.

The experimental traces in Fig. 1 illustrate another feature of PGE_2 inactivation in ANTU-affected lungs. The survival values in Table 2 are calculated from the peak heights of the contractions without any allowance for the "area under the curve" of the bioassay response. As the traces show, the shape of the contraction due to PGE_2 surviving passage through the lung (the second response in each set) became wider 6 hr after treatment and this wider response persisted until 28 hr. By 50 hr the response was similar in shape to that at 2 hr and was equivalent in shape to that in normal untreated animals or in sham-treated animals at any time after injection of olive-oil. The responses of the assay tissues to direct calibrating doses of PGE_2 (the two outer responses in each set) were not similarly affected. No attempt was made to quantitate the wider response but it was seen in each lung tested at 6, 16 and 28 hr after ANTU treatment.

Radiochemical assays

The efflux of radioactivity from lung following injection of [^{14}C]-PGE_2 was rapid in untreated and sham-treated lungs (Fig. 2 and Table 2). The efflux profiles from four lungs are illustrated in Fig. 2. The sham-treated lung was taken at 28 hr after treatment and showed a $T\frac{1}{2}$ value of 33 sec. This was not different from the $T\frac{1}{2}$ of untreated lungs (Table 2) and the profile contrasts with that obtained in ANTU-treated lung at the same time displaying a much lower maximum and a 'tail' of radioactivity that persisted up to the 40th fraction. The other profiles shown in this figure demonstrate that as early as 4 hr a change in efflux was noticeable ($T\frac{1}{2}$ increased to 46 sec) but by 50 hr the efflux was returning to normal with a $T\frac{1}{2}$ of 37 sec.

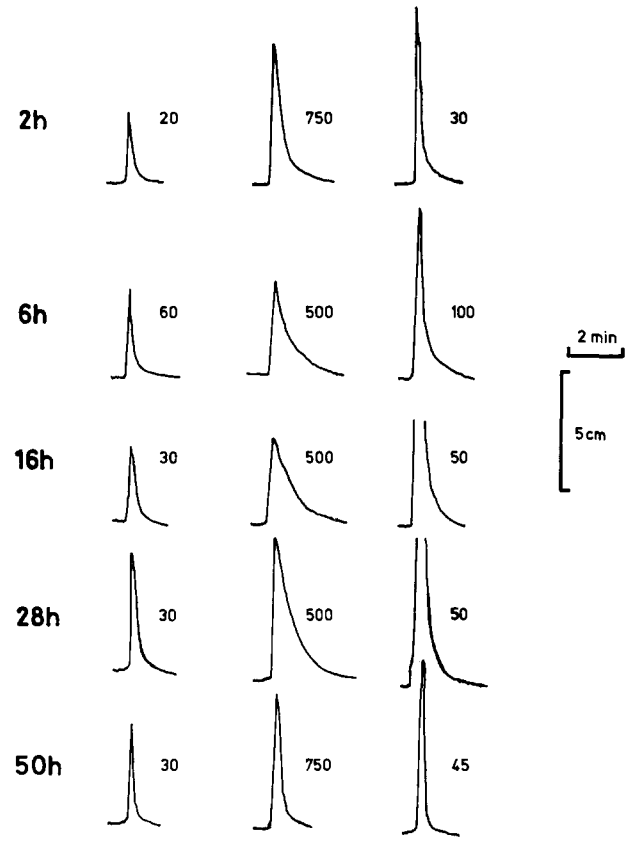

Fig. 1. Bioassay of PGE_2 inactivation in isolated rat lungs. The responses shown are of a hamster stomach strip (RSS) superfused with effluent from lungs taken from rats treated with ANTU. At the left hand edge is shown the time after the injection of ANTU. Each set of three responses is taken from the same experiment and consists of two responses to PGE_2 given directly over the tissue as bracketing doses—the first and third responses. The central response is to PGE_2 injected into the Krebs perfusate entering the lung and thus represents PGE_2 activity surviving passage through the pulmonary circulation. The numbers to the right of each response represent the doses of PGE_2 in nanograms.

Survival of PGE_2 was calculated from the peak height of the central responses but these traces also show that the width, i.e. duration, of these responses was greater at 6, 16 and 28 hr after ANTU injection than at 2 or 50 hr. Note that the bracketing responses did not change, suggesting a delayed efflux of PGE_2 activity at 6, 16 and 28 hr. Responses for the bioassay using sham-treated and untreated lungs are not shown but they were the same as those for the 2 and 50 hr treated lungs.

The summary of the efflux profiles presented in Table 2 shows that no significant changes occurred before 4 hr after treatment. At this time and at 6 hr the $T_{\frac{1}{2}}$ had increased by 30–40% of the sham- or untreated values. At 16 hr the $T_{\frac{1}{2}}$ further increased to double the sham values and, although at 28 hr the mean value was again increased (to nearly 3 times normal), the variability of results at this point did not allow statistical significance to be attained over the 16 hr value. By 50 hr after injection, the mean $T_{\frac{1}{2}}$ had fallen to that of the sham animals. For this variable ($T_{\frac{1}{2}}$), sham treatment with olive-oil only did not change $T_{\frac{1}{2}}$ at any time from that observed in lungs from untreated animals.

Chromatographic analysis of the radioactivity in the effluent (see Table 2) showed that sham treatment caused a relatively slight but significant decrease in the proportion of [^{14}C]-PGE_2 surviving compared with that in untreated lungs. However, this decrease was not related to the time after treatment. In the ANTU-treated lungs, [^{14}C]-PGE_2 survival was increased by 4 hr to almost double the sham values (Table 2), continued to increase up to 16 hr (about six times sham) and then fell to a level at 50 hr which was higher than the sham value but not significantly higher than that in untreated lungs. Authentic 15-oxo-PGE_2 and 13,14-dihydro-15-oxo-PGE_2 were not routinely used as markers on the chromatogram. Preliminary experiments had established that these metabolites were not resolved from each other in the solvent system used but they were clearly resolved from the parent PGE_2 and had chromatographic mobility matching that of the faster moving radioactive peak (see Fig. 3).

Inactivation of prostacyclin (PGI_2)

The inactivation of PGI_2 was measured by bioassay in three sets of lungs; untreated and at 16 and 28 hr after treatment with ANTU. The results (Table 3) show that for 3 concentrations of PGI_2, treatment with ANTU did not change the inactivation of PGI_2 at either 16 or 28 hr when compared with the

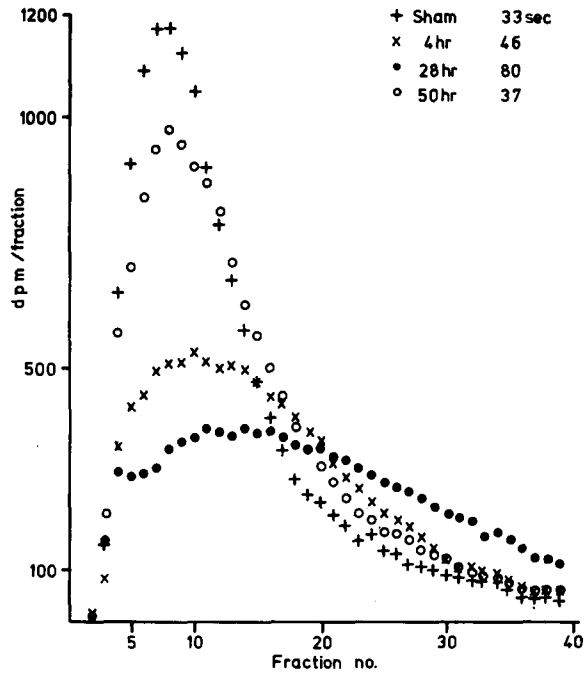

Fig. 2. Efflux of radioactivity from isolated lung following injection of [^{14}C]-PGE_2. Lung effluent was collected in 4 drop fractions (approx. 3 sec) for 2 min after the injection of [^{14}C]-PGE_2 (2×10^4 dpm) and the total radioactivity in each fraction measured. The profiles of efflux vs fraction shown are for ANTU-treated lungs at 4, 28 and 50 hr after treatment and a sham-treated lung at 28 hr after treatment. The profile changed as early as 4 hr and at 28 hr the efflux was at its slowest. By 50 hr the profile is similar to that of the sham-treated lung. Untreated lungs provided efflux profiles identical to the sham-treated lung shown. At the right hand side of the figure, are given the actual values of $T\frac{1}{2}$ (time for 50% of injected radioactivity to appear in effluent) for the efflux profiles shown.

untreated lungs. Although the mean survival at 20 ng PGI_2/ml in the 28 hr lungs was the lowest observed (about 75%), survivals at 10 or 40 ng/ml were 85 and 83%, respectively, very close to the control values of 83 and 90%.

DISCUSSION

The intention of these experiments was to correlate changes in PGE_2 inactivation with the physical changes associated with the development of oedema in isolated lungs of rats. It was important to induce a reversible, i.e. non-fatal oedema so that both onset and recovery stages could be monitored.

Although the histological examinations were not exhaustive and the changes observed were not quantitated, they were valuable in confirming that the rats in the present experiments were responding as expected [2, 3]. Our histological experience did not allow us to make any comments on the extent of interstitial oedema but, qualitatively, the incidence and intensity of peribronchial and perivascular oedema correlated well with the gross changes in lung weight and lung: body weight ratios. Both these two variables reached maximal values at 6 hr after treatment and by 16 hr a slow return towards normal values had started. A transudate started to form in the thorax by 4 hr, peaking between 6 and 16 hr and had been totally resorbed by 50 hr when lung: body weight ratios were still above normal. The amount

Table 3. Effect of ANTU on survival of PGI_2 in rat isolated lungs

Infused concentration (ng/ml)	Concentration surviving (ng/ml) Untreated	Treated 16 hr	28 hr
10	8.3 ± 0.8	8.9 ± 0.4	8.5 ± 1.2
20	20.0 ± 1.0	18.7 ± 4.5	15.1 ± 2.5
40	36.7 ± 2.7	33.6 ± 2.8	33.4 ± 1.6

The values in the table are the means ± S.E.M. of results from 3 lungs in each set of experiments. None of the values in treated lungs, 16 and 28 hr after i.p. injection of ANTU (10 mg/kg), are different from those obtained with lungs from untreated rats.

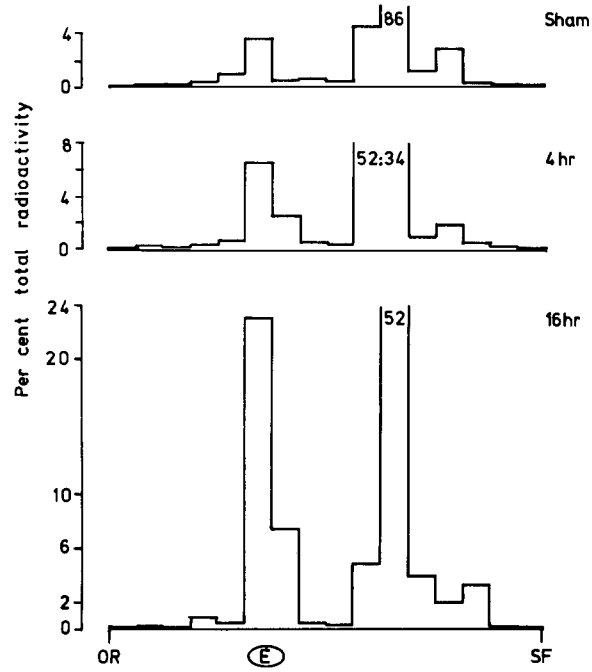

Fig. 3. Chromatographic analysis of effluent following injection of [^{14}C]-PGE_2 through rat isolated lung. The effluent was collected in a single fraction for 5 min after injection of [^{14}C]-PGE_2 and, after extraction, the radioactivity was analysed by t.l.c. on silica gel. The position of marker PGE_2 is shown at the bottom of the figure (marked as E) as is the origin (OR) and solvent front (SF). The radioactivity in each 1 cm zone along the chromatogram has been expressed as a percentage of the total radioactivity on the chromatogram and the scales have been chosen to show primarily the increase in radioactivity associated with unchanged PGE_2 (R_F 0.3). The numbers in the peak with R_f 0.6 represent the percentage radioactivity associated with those zones (metabolites of PGE_2).

At the top of the figure, in effluent from a sham-treated lung (at 16 hr), about 5% of the total radioactivity was associated with unchanged PGE_2. This proportion was greater in effluent from ANTU-treated lungs at 4 hr (the second example), almost 10%, and was greatest at 16 hr after treatment (the third example), about 34% of the total.

of transudate was much more variable than the lung weight and it would seem to be a less reliable measure of oedema. The usual measure of oedema is the dry/wet weight ratio and this suggested that oedema was only present 6 and 16 hr after treatment, a much shorter period of abnormality than indicated by the other measures. The discrepancy was particularly noticeable at 28 hr where the histological condition of the lung was clearly abnormal and the wet weight was also increased but the dry:wet weight ratio was equally clearly normal.

Oedema caused by an increased permeability to plasma protein would suggest an increased permeability to, and distribution of, PGE_2 throughout the extravascular spaces of the lung. This could lead to an increase in exposure of sub-endothelial cells to PGE_2 and a consequent increase in its inactivation, as it seems from the presently available evidence that it is not endothelial cells which exhibit PG-inactivating properties [9, 10]. The suggested lack of PGDH in endothelial cells would also mean that destruction of these cells by ANTU [3] should not affect the overall metabolic fate of PGE_2. Furthermore, the increased extravascular volume available to the bolus of injected PGE_2 would also be expected to cause a greater dilution of this bolus, and, hence, a lower peak concentration of PGE_2 and a lower peak contraction of the bioassay tissue. In spite of these predictions, the pulmonary oedema caused by ANTU led to a decreased inactivation of PGE_2. This decreased inactivation was evident 4 hr after treatment, was most marked by bioassay at 6 hr and slowly returned to normal levels by 50 hr after treatment, a pattern correlated closely with the increase in lung weight over the same period.

However, the change in the shape of the bioassay response with time suggested that the assessment of PGE_2 survival simply from the peak height of the response was not an adequate measure, because more PGE_2 than was indicated by the peak height was emerging, delayed in some way in its passage through the lung. This suggestion was supported by the increase in $T\frac{1}{2}$ and the increase in survival of [^{14}C]-PGE_2. Thus, at 16 or 28 hr when the survival by bioassay appeared to be falling, the protracted response of the tissue and the increased $T\frac{1}{2}$ were indicators of the increased survival of [^{14}C]-PGE_2 as measured by the chromatographic analysis of effluent, which gave a measure of the 'area under the curve', i.e. total PGE_2 surviving.

Both $T\frac{1}{2}$ and [^{14}C]-PGE_2 survival reached their maximum values later than 6 hr, the time of maximum lung weight. If lung weight can be taken as a measure of increased permeability, then it appears

that the delay (increased $T\frac{1}{2}$) and increased survival are not simply related to an increased volume of distribution for PGE_2 in lung. Neither is increased survival associated with a decrease in contact time with lung cells, as seen, for instance, in the presence of some chemicals [11, 12]. The results presented here may be explained if, in addition to the increased permeability, there was a decrease in the efficiency of the enzymic step in PG inactivation but not in the uptake step. Such conditions would allow PGE_2 to be removed from the vascular space by cellular uptake—appearing as a reduction in peak height of the bioassay, but the subsequent attack by PGDH would be less efficient than usual, allowing unchanged PGE_2 to leak out of the cells and reappear in the vascular perfusate—giving a longer $T\frac{1}{2}$, longer lasting contraction of the bioassay tissue and a greater total survival of [^{14}C]-PGE_2.

There are least two ways in which these conditions might be produced: firstly, if the activity of lung PGDH were directly affected; Nakano and Prancan [13] reported a loss of PG inactivating enzymes in rat lungs after endotoxin injection, a procedure also known to produce pulmonary oedema. The changes in the shape of the bioassay response to PGE_2 surviving transit through the lung described here have also been observed in lungs from rats exposed to 95% oxygen [14] and was attributed by those authors to inactivation of PGDH by oxygen [15, 16]. The second possibility is that, as a result of the oedema, another "compartment" not containing PGDH is available to PGE_2. This compartment does not simply comprise lung fluid but may also represent a population of cells which take up PGE_2 but lack PGDH.

The experiments with PGI_2 show that the normal survival of this PG is not due to its restricted access to the metabolizing cells, by being confined to the vascular space for instance, as, when vascular permeability was higher than normal (16 and 28 hr) and PGE_2 survival was markedly affected, survival of PGI_2 was unchanged. These results also demonstrate that increased vascular permeability was not accompanied by increased cellular permeability which might allow the normally excluded PGI_2 [17, 18] to enter cells and be oxidised by PGDH [19].

The purpose of the temporal correlation of physical changes in lung with a biochemical change (PGE_2 inactivation) was to assess whether this biochemical variable preceded or followed the physical changes. At this does of ANTU, changes in PGE_2 survival seemed to follow changes in lung weight with a later onset and an earlier return to normal values. However, if changes in the dry : wet weight ratio are taken as the indicator of oedema, then changes in PGE_2 survival precede and exceed the period of oedema. The last mentioned result is comparable with that of Block and Schoen [20] who found a decreased metabolism of 5-hydroxytryptamine in lungs of rats treated with ANTU before changes in dry : wet ratio had occurred. These authors did not study the immediate recovery period but by 14 days after treatment physical and biochemical properties were normal. The present results like those of Block and Schoen [20] suggest that it may be possible to use a pharmacokinetic property to give an early warning of pulmonary oedema. It may even be possible to rely simply on the transit time of PGE_2 through the pulmonary circulation since $T\frac{1}{2}$ changed as early as survival.

Furthermore, the increased survival of PGE_2 and, particularly, the suggestion of decreased PGDH activity, show that at least in this model of pulmonary oedema, the lung loses its important protective function of PG inactivation. Thus, blood-borne PGs will survive to a greater extent their pulmonary transit and enter the systemic arterial circulation in larger amounts. Furthermore, PGs generated within the lung may also, by surviving longer, have increased effects on lung cells and a greater chance of 'spilling over' into the pulmonary blood. Whether such changes could be considered as beneficial or harmful would depend on the actual PG or thromboxane substrate involved. Nevertheless, this study has demonstrated that there are important biochemical consequences of this form of pulmonary oedema which could also have important systemic effects.

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