Thus urinary retrieval was highest from small particles, while mouthwash retrieval was highest from large particles. Exhaled material was unimportant. Material untraced was presumed to have been swallowed and excreted in faeces, and/or absorbed and excreted in bile. The small particles will have penetrated most easily to the most distant parts of the bronchial tree, so this study and those quoted earlier, give added weight to the belief that the action, and transfer of DSCG across the pulmonary epithelium into the blood stream, both occur most favourably in the smallest airways. Additionally, it can be concluded the DSCG would be best administered as small particles, since large particles were deposited to a great extent in the mouth.

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The effects of some prostaglandins on respiration in the rabbit

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Certain prostaglandins have been shown to stimulate respiration in various animal species; the dog, calf, rat, guinea-pig, and man (Maxwell, 1967; Lewis & Eyre, 1972; McQueen, 1972, 1973 and references cited therein). Excluding man, all studies involved animals anaesthetised with pentobarbitone sodium.

This report records our findings during preliminary investigations into the influence of some naturally occurring prostaglandins and their derivatives on both the normal and depressed respiration of New Zealand White rabbits. From three to six rabbits were used for each study. Animals (adult, of either sex and body weight 3·5–4·0 kg) were anaesthetized with halothane and used as such, or dosed with a solution of one of 19 barbiturates (up to 400 mg), including thiopentone and Brietal sodium, 7 narcotic analgesics (up to 5·5 mg), urethane (up to 2·5 g), chloralose, or glutethimide (both up to 500 mg), until a standard number of respirations min^{-1} was obtained, and the mean femoral arterial blood pressure allowed to regain a steady value. The drug solutions were administered by slow infusion via a marginal ear vein during which time the anaesthetic was increasingly diluted until totally replaced by room air. Insulation and spot lamps were used to maintain the normal body temperature of the rabbits to within $\pm 1°$. Prostaglandins (PGs) were administered i.v. or i.a. via femoral or marginal ear vein, or common carotid artery, in normal saline or in dimethylacetamide (DMA) diluted 0·3:100 with normal saline, and respiration, tidal volume, blood pressure and ecg monitored. DMA alone in normal saline (up to 10% v/v) did not influence any of the parameters monitored.

All PGs excluding 16, 16-diMe$PGF_2\alpha$ elicited an increase of up to 10× the resting respiratory rate and respiratory minute volume in animals dosed with pentobarbitone sodium. PGE_1, PGE_2 and $PGF_2\alpha$ also elicited a rise in respiratory rate in the animals receiving other barbiturates, and $PGF_2\alpha$ elicited a comparable rise in all other animals except those receiving dihydrocodeine, diamorphine and glutethimide. Respiratory stimulation was enhanced most by 15(S)15-MePGE_2Me ester, followed in order of decreasing potency by 15(S)15-Me$PGF_2\alpha$Me ester, 15(S)15-Me$PGF_2\alpha$, PGE_1, 8-iso PGE_2,PGE_2, $PGF_2\beta$ $PGF_2\alpha$, $PGF_1\beta$, PGA_1, PGA_2, $PGF_1\alpha$, PGB_1, PGB_2, 5,6-trans $PGF_2\alpha$, 20-Et$PGF_2\alpha$, 8-iso $PGF_2\alpha$. Doses, equivalent in effect, ranged from 5 nanomoles for 15(S)15-MePGE_2Me ester to 1 micromole for 8-iso $PGF_2\alpha$. The tidal volume was not significantly influenced by any prostaglandin. Compared with the other prostaglandins tested, the F series was as much as 5× longer (1·25 to 2 min) in effecting a maximum response. Defaecation was observed

about 10 min after injection of PGE_1, PGE_2, 8-iso PGE_2, 15(S)15-MePGE_2Me ester and $PGF_2\alpha$.

The respiratory response was not influenced by bilateral cutting of the sinus nerves or bilateral vagotomy. Reduction of mean arterial blood pressure (up to 40 mmHg) by amyl nitrite did not influence the respiratory rate. Reponse to PGs was not affected when noradrenaline (20 μg ml^{-1}) was co-administered to maintain blood pressure

In conclusion, structural modifications among the prostaglandins dramatically influence their effect on respiration, and promotion of defaecation in the rabbit. Their action does not appear to involve directly the chemoreceptors or baroreceptors of the carotid body and sinus. Their effects are not simple reflex actions to blood pressure fluctuations.

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The effect of amantadine on the turnover of catecholamines in the rat brain

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The anti-Parkinsonian drug amantadine probably acts on dopaminergic mechanisms in the striatum. Direct stimulation of dopamine receptors, (Papeschi, 1974), blockade of neuronal uptake, (Fletcher & Redfern, 1970; Heimans, Rand & Fennessy, 1972; Baldessarini, Lipinski & Chace, 1972), catecholamine release, (Scatton, Cheramy & others, 1970; Von Voigtlander & Moore, 1971; Stromberg & Svensson, 1971; Farnebo, Fuxe & others, 1971) and increased synthesis, (Scatton & others, 1970), have all been suggested as being responsible for the clinical effectiveness of the drug. We have attempted to investigate this problem by examining the effect of amantadine on the turnover of catecholamines in the brain following α-methyl-*p*-tyrosine administration.

Groups of 10 male Sprague Dawley rats were injected i.p. with either saline or α-methyl-*p*-tyrosine methyl ester HCl, (α-MPT), 250 mg kg^{-1}. After 4 h the animals were killed and the brains rapidly dissected and homogenized in 0·4 N perchloric acid. Noradrenaline (NA) and dopamine (DA) were isolated on alumina and assayed fluorimetrically (Shellenberger & Gordon, 1971).

The rates of decline in NA and DA concentrations after MPT were taken as an indication of the rates of turnover of the amines. Blockade of dopamine receptors with either haloperidol, 1 mg kg^{-1}, or pimozide, 1 mg kg^{-1} injected i.p. 30 min before α MPT, significantly increased the rate of decline of DA, ($P<0{\cdot}001$) presumably by a process of negative feedback. On the other hand apomorphine 2 × 2 mg kg^{-1}, and ET 495 (1,-[2″ pyrimidyl-4-piperonyl-piperazine] 25 mg kg^{-1} both of which are believed to stimulate dopamine receptors (Corrodi, Farnebo & others, 1972), significantly decreased the rate of decline of DA ($P<0{\cdot}001$). The rate of change of NA concentrations was unaffected by haloperidol, pimozide or apomorphine but was reduced by ET 495 ($P<0{\cdot}02$).

Amantadine HCl 80 mg kg^{-1} i.p. did not significantly affect DA turnover, but produced a slight but significant increase in the rate of decline of NA concentrations. Rates of decline of both NA and DA concentrations in the brains of rats treated for 9 days with amantadine in the drinking water, (mean daily dose 63 mg kg^{-1}) were not significantly different from those in the brains of control animals.

The lack of effect of amantadine in this experimental situation, when compared to the effectiveness of other drugs, all of which are believed to stimulate or block dopamine receptors, suggests that amantadine does not owe its anti-Parkinsonian properties to a post-synaptic action at dopaminergic synapses in the c.n.s.