0.7 ± 0.02 $cmH_2O\ l^{-1}\ s^{-1}$ $n=6$). A 'Vaponefrin inhalajet' nebulizer modified to produce an aerosol containing particles of 10 μm mean diameter produced much greater changes in R_L (e.g. 4 inhalations of an aerosol generated from a 0.5% w/v solution histamine produced increases in R_L of 6.5 ± 1.4 $cmH_2O\ l^{-1}\ s^{-1}$ $n=6$). However, the bronchoconstriction resulting from using histamine aerosols generated from either nebulizer was not inhibited by bilateral vagal cooling.

A further series of experiments was performed to compare the effects of histamine aerosol of 10 μm mean particle size on R_L and Cdyn in dogs anaesthetized with pentobarbitone sodium with those anaesthetized with chloralose (80 mg/kg i.v. followed by 10–15 mg every 15 minutes). Histamine aerosols of 10 μm now produced marked increases in R_L even when comparatively low concentrations of histamine solution were used to generate the aerosol (e.g. 4 inhalations of a 10 μm aerosol generated from a 0.125% w/v solution of histamine produced increases in R_L of 12.7 ± 1.9 $cmH_2O\ l^{-1}\ s^{-1}$ $n=6$, in dogs anaesthetized with chloralose compared with 1.6 ± 0.8 $cmH_2O\ l^{-1}\ s^{-1}$ in dogs anaesthetized with pentobarbitone sodium). In dogs anaesthetized with chloralose the increase in R_L was significantly inhibited by vagal cooling, while the falls in Cdyn were largely unaffected.

The effects of direct electrical stimulation of the efferent vagal nerves were also noted in these experiments. Stimulation of the vagus nerves in dogs anaesthetized with pentobarbitone sodium produced a mean increase in R_L of 1.2 ± 0.4 $cmH_2O\ l^{-1}\ s^{-1}$, while vagal stimulation in dogs anaesthetized with chloralose produced a much greater increase in R_L of 12.4 ± 1.8 $cmH_2O\ l^{-1}\ s^{-1}$. (Stimulation parameters: 20 Hz 1.ms at supramaximal voltage.) It was further noted that i.v. administration of pentobarbitone sodium to the chloralose anaesthetized dog significantly reduced the response to direct-efferent vagus nerve stimulation (5 mg/kg by 49.4% and 10 mg/kg by 69.5%).

These experiments indicate the importance of selecting the right experimental conditions to obtain a reflex bronchoconstriction to histamine aerosol in the anaesthetized dog. Our results show that using chloralose anaesthesia and an aerosol of mean particle size 10 μm a large reflex bronchoconstriction is produced. If, however, pentobarbitone sodium is used as the anaesthetic and an aerosol of mean particle size of 0.5 μm is used, the response is almost entirely direct.

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Studies on the mechanism of action by which 5H-[1]-benzopyrano-[2,3-b]-pyridin-5-ol (AH 6696) inhibits gastric acid secretion

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Peptic ulceration in man can be treated by inhibiting the secretion of acid into the stomach. Interest in 5H-[1]-benzopyrano-[2,3-b]-pyridin-5-ol (AH 6696) arose because it is a potent inhibitor of gastric acid secretion in the rat and dog. The mechanism by which AH 6696 inhibits gastric acid secretion has been investigated.

In the urethane anaesthetized rat (Ghosh & Schild, 1958) AH 6696 (1, 3 or 10 mg/kg i.v.) caused a dose-dependent reduction of submaximal gastric acid secretion. Five female rats (80–110 g) were used per dose level and the ED_{50} values for AH 6696 to inhibit gastric acid secretion induced by histamine, pentagastrin or bethanechol were 1.6, 2.8 and 2.4 mg/kg respectively.

On the guinea-pig ileum preparation (Krebs-Henseleit solution at 32°C gassed with 95% O_2:5% CO_2) the EC_{50} values (μg/ml) for AH 6696 to inhibit contractions induced by barium chloride, acetylcholine, histamine and 5-hydroxytryptamine were [mean ± s.e. mean, $n=10$] 354 ± 48, 338 ± 40, 86 ± 25 and 28 ± 6 respectively. On the isolated right atrium preparation of the guinea-pig (Krebs-Henseleit solution at 37°C gassed with 95% O_2:5% CO_2) AH 6696 (10–100 μg/ml) failed to antagonize histamine-induced tachycardia (H_2-effect). Cardiovascular actions were investigated in 4 female

cats (2.4–2.9 kg) anaesthetized with chloralose (90 mg/kg i.v.) AH 6696 (10–30 mg/kg i.v.) produced transient depressor responses of 40–80 mmHg (1 mmHg ≈ 133 Pa) but did not affect the vasodepressor responses to either acetylcholine or histamine. Clearly, AH 6696 has no anticholinergic, H_2-blocking and little or no H_1-blocking activity.

In conscious dogs with Heidenhain pouches AH 6696 (15–25 mg/kg orally) caused a dose-dependent inhibition (39–100%) of submaximal gastric acid secretion induced by pentagastrin, bethanechol or histamine. This effect was accompanied by an increase in the ratio of gastric mucosal blood flow to gastric acid secretion (Curwain & Holton, 1973) indicating that inhibition of secretion was not due to a primary decrease in blood flow.

Inhibition of metabolic processes in the parietal cell could reduce gastic secretion. AH 6696 (2.5 mM) had no significant effect on the rate of oxygen uptake by rabbit parietal cells (McDougal & De Cosse, 1970). Furthermore, AH 6696 (10 mM) neither inhibited nor uncoupled oxidation from phosphorylation using rat liver mitochondria with succinate or β-hydroxybutyrate as substrate. Rat stomach carbonic anhydrase (Roughton & Booth, 1946; Waygood, 1955) was not inhibited by AH 6696, 2.5 mM, whereas acetazolamide (2.5 mM) completely inhibited the enzyme. However, AH 6696 (6.5 mM) did inhibit HCO_3^--stimulated ATPase from rabbit gastric mucosa (Kaskebar & Durbin, 1965; Blum, Shah, St. Pierre, Helander, Sung, Wiebelhaus & Sachs, 1971). This action could account for the observed anti-secretory activity of AH 6696.

In a sub-acute toxicity test in beagles AH 6696 (15 mg/kg orally twice daily for 8 weeks) caused lesions in the pancreas and fibrotic changes in the liver (D. Poynter, personal communication). Thus, AH 6696 has an interesting mechanism of action for inhibiting gastric acid secretion but is too toxic for use in man.

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A comparison between sulphinpyrazone and other drugs on the thrombocytopenia occurring in the Arthus reaction in the guinea-pig

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As has been shown previously in the rabbit (Butler & White, 1975) the complement-dependent thrombocytopenia of the Arthus reaction (Margaretten, Howes & McKay, 1974) may be useful for the investigation of drugs *in vivo* which are capable of having an effect on the reactivity of platelets. A range of such drugs has now been compared in guinea-pigs.

The animals were immunized with 2 mg alum-precipitated ovalbumin given subcutaneously into each of four sites on the back. Two weeks later a boosting dose of antigen (1 mg) was injected and one week after this the animals were challenged intradermally in the shaved abdomen with different doses of antigen dissolved in 0.1 ml of physiological saline.

During the first 15 min after the injection of 100 μg, 500 μg or 1 mg of ovalbumin to groups of five animals there was a mean dose-related fall in the platelet count to 74% (not significant), 53% ($P < 0.05$) and 33% ($P < 0.02$) of control, respectively. There was no statistically significant change in the platelet count during the next 15 min in either of the two groups receiving the higher dose of antigen. Blood samples were taken by cardiac puncture and anti-coagulated with sodium citrate (3.8%). Platelet-rich plasma (PRP) was separated by centrifugation of the blood at 200 *g*