bradykinin. Groups of 50 animals were injected s.p. with 1 μg/paw histamine or 2.5 μg/paw bradykinin and produced normally distributed inflammatory responses (Lilefors test) at 15 min although the variation in response was considerable.

Equieffective mediator concentrations, *viz.* histamine (2.5 μg/paw), 5-HT (10 μg/paw), bradykinin (2.5 μg/paw), were used for an evaluation of mediator antagonists injected s.c. 30 min prior to s.p. injection of the mediator. Responses were recorded at 15 and 30 min prior to s.p. injection of the mediator. Tripolidine (2.5 mg/kg), a H_1 antagonist, completely inhibited the histamine induced response but was ineffective on 5-HT and bradykinin-induced paw oedemas. Cimetidine (100 mg/kg), a H_2 antagonist, significantly inhibited only the histamine oedema. Methysergide (2.5 mg/kg), a 5-HT antagonist significantly inhibited the 5-HT induced oedema but was without effect on histamine and bradykinin. Cyproheptadine (10 mg/kg), a combined histamine and 5-HT antagonist, completely abolished the histamine oedema but was without effect on the other mediators.

We have furthermore examined the effect of s.p. injection of the IgG fraction of rabbit anti-guinea pig immunoglobulin (anti-IgG, 5–200 μg/paw) in the guinea pig paw. This preparation produced a dose related oedema that peaked at 3 h. Triprolidine, methysergide and cyproheptadine all partially inhibited the anti-IgG oedema for up to 3 h. Although phenylbutazone failed to suppress the first 1.5 h of the anti-IgG oedema, it did produce significant inhibition (oral ED_{50} 33 mg/kg) of the 3 h response. Dapsone, an anti-leprotic agent that possesses anti-inflammatory activity (Williams, Capstick, Lewis & Best, 1976; Lewis, Gemmell & Stimson, 1978) inhibited both the early phase (0–1.5 h) and late phase (1.5–4 h) of the response. However, dapsone was more effective at 1.5 h (oral ED_{50} 34 mg/kg) than at 3 h (oral ED_{50} 60 mg/kg).

In summary, we have confirmed and extended existing data (Sparrow & Wilhelm, 1957) on the sensitivity of the guinea pig to various inflammatory mediators and evaluated the effects of a variety of antagonists on these responses. The large variation in the guinea pig response to these inflammatory mediators suggests that in comparison with the rat pedal oedema in the guinea pig is not an ideal model for evaluation of new anti-inflammatory drugs. Nevertheless, the use of an 'irritant' such as anti-IgG can be used in order to select and further evaluate non-steroidal anti-inflammatory drugs.

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Investigations of *Harpagophytum procumbens* (Devil's Claw) in the treatment of experimental inflammation and arthritis in the rat

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Harpagophytum procumbens (H.P.) or Devil's Claw as it is more commonly known is a herbal remedy that is advocated in the treatment of a variety of diseases, including rheumatoid arthritis (Seeger, 1973). Investigations of H.P. in animal models of inflammation have been carried out previously (Zorn, 1958; Eichler & Koch, 1970) but none have used the commonly accepted techniques of carrageenin oedema and adjuvant-induced arthritis in the rat.

Devil's Claw was provided as a dried aqueous extract of the secondary root of H.P., 1 g of powder being extracted from 2 g of root.

In the carrageenin test 30 male Wistar rats (120–160 g) were starved overnight and then dosed orally with either indomethacin (5 mg/kg) or Devil's Claw (1 g/kg). Controls received 0.5% tragacanth. One h later carrageenin (0.1% w/v in saline) was injected into the rear right foot of each animal. The volumes of both rear feet were then measured at hourly intervals by means of a mercury reservoir connected to a pressure transducer. Volumes were recorded directly from a suitably calibrated meter output of a Devices M2 recorder. All measurements were performed 'blind'. Results are expressed as the increase in volume of the right (injected) foot over the left expressed as a percentage of initial foot volume. Analysis of the results at the peak of the reaction (4 h) using Student's *t*-test showed that indomethacin produced a 63% inhibition of swelling ($P<0.001$) whilst Devil's Claw had no significant effect (−6% $P>0.1$).

Adjuvant arthritis was induced in 40 female SPF Sprag Dawley rats (120–140 g) by injection of 0.1 ml of *Mycobacterium tuberculosis* in light paraffin oil (1 mg/ml) into their rear right feet. Rear foot volumes and body weights were measured at intervals over 21 days. Drugs were administered orally every day.

Devil's Claw was given to one group of animals at 100 mg/kg (about five times the recommended human dose) and to another at 1 g/kg (about 1/15th of the amount shown to be without effect in acute toxicity studies). Other groups received either tap water (controls) or indomethacin (3 mg/kg). Indomethacin inhibited both the primary reaction (−17% on Day 5, $P<0.01$) and the secondary reaction (−30% on Day 18, $P<0.001$). Devil's Claw (100 mg/kg) produced no significant effect on either the primary or secondary reaction, but at 1 g/kg the reaction was consistently greater than the controls in both the injected and uninjected feet. Only on Day 7 was this statistically significant (+16% $P<0.05$).

If these tests can be regarded as predictive of efficacy in humans, Devil's Claw when used at the recommended dose would not be expected to show anti-arthritic activity. The possibility that high doses of Devil's Claw potentiate adjuvant arthritis in a manner similar to that seen with levamisole and penicillamine (Trabert, Rosenthal & Muller, 1976; Arrigoni-Martelli & Bramm, 1975) requires further investigation.

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Inhibitory effects of gold salts in adjuvant arthritis and on lysosomal enzyme activity

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We recently reported that oral but not parenteral forms of gold possess potent acute anti-inflammatory effects, but that none of the gold salts possessed marked activity in adjuvant arthritis produced in Wistar rats (Brown, Bruin, Lewis, McNeillie & Smith, 1978). This latter observation was in contrast to the reports of others (Walz, DiMartino & Sutton, 1974) and consequently we have re-examined the effects of several gold salts in the inbred Lewis rat, a strain previously reported to be susceptible to the anti-arthritic effects of gold (Walz, DiMartino, Sutton & Misher, 1972). In addition to measuring the progression of the disease we have examined the effect of these treatments on serum hydrolases known to be elevated during adjuvant arthritis (Collins & Lewis, 1971). Indeed, it has been suggested that gold salts may exhibit inhibitory effects on lysosomal enzyme activity or release from inflammatory cells, and that this is a major mechanism for their anti-rheumatic activity (Walz, DiMartino & Sutton, 1974). The effects of gold salts on β-N-acetylglucosaminidase (β-NAG), β-glucuronidase, cathepsin B_1 and cathepsin D, all extracted from mouse peritoneal macrophages have also been examined *in vitro* for comparison with the *in vivo* studies.

Adjuvant arthritis was induced in male Lewis rats (180–200 g) by injection of 0.05 ml *Mycobacterium butyricum* in liquid paraffin (10 mg/ml) into the left hind paw only.

Aurothiomalate (s.c.), triethyl phosphine gold chloride (S K & F 36914, oral) and S-triethyl phosphine gold 2, 3, 4, 6-tetra-O-acetyl-1-thio-β-D-glucopyranoside (S K & F D-39162 oral) significantly suppressed the symptoms of adjuvant arthritis when administered at a dose of 5 mg Au kg^{-1} d^{-1} for 20 days from the day of adjuvant administration. Serum cathepsin D was elevated (33%) in the arthritic control animals when measured on day 21. None of the orally active gold salts significantly influenced this level.

The effect of aurothiomalate, S K & F 36914, S K & F D-39162 and sodium gold chloride dihydrate was studied on β-NAG, β-glucuronidase, cathepsin B_1, cathepsin D, and the cytoplasmic enzyme lactate dehydrogenase (LDH) from purified mouse macrophages, *in vitro*. Aurothiomalate significantly inhibited β-glucuronidase ($ED_{20} = 1 \times 10^{-2}$M) and cathepsin B_1 ($ED_{50} = 6 \times 10^{-3}$M) but not β-NAG, cathepsin D or LDH. S K & F D-39162, a compound reported to inhibit the release of lysosomal enzymes from rat leucocytes but not their activity (DiMartino & Walz, 1977) only inhibited cathepsin B_1 ($ED_{50} = 8 \times 10^{-3}$M), but both S K & F 36914 and sodium gold chloride dihydrate strongly inhibited all the hydrolytic enzymes and LDH.

In conclusion, we have confirmed the activity of gold salts in adjuvant induced arthritis in the Lewis strain of rat, a result markedly different from our previous findings with the Wistar strain of rat (Brown *et al.*, 1978). We have also demonstrated that gold salts have little influence on elevated serum hydrolase