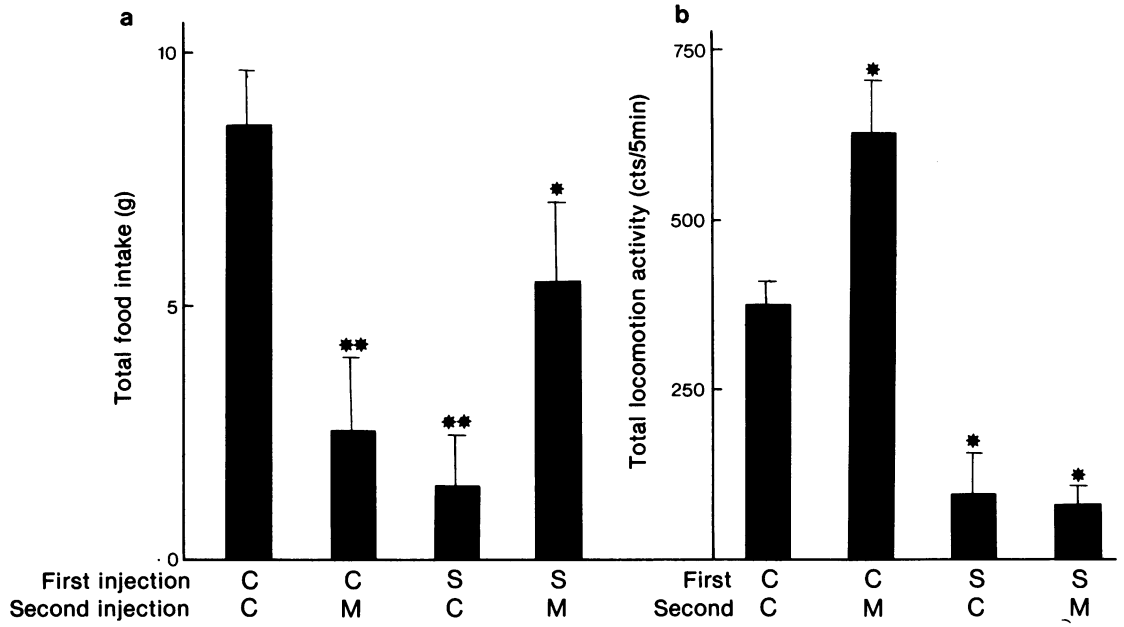

Figure 1a Food intake (g) in a 1 h feeding test, following 20 h food-deprivation (mean + s.d.). Mazindol (2.5 mg/kg s.c.) injected 30 min before the test; spiperone (0.1 mg/kg i.p.) injected 2 h before the test. $n = 10$ per group. **b** Locomotor activity (photobeam interruptions) in a 5 min open-field test (mean + s.d.). Drug doses and injection times as in the feeding experiment. $n = 7$ per group. In both experiments, rats were adapted to a reversed light cycle, and run in the dark phase. C, control; M, mazindol; S, spiperone. $^{*}P < 0.01$; $^{**}P < 0.001$.

ioural responses (including feeding and locomotor responses) seen with spiperone alone. This conclusion was supported by further tests with spiperone (0.03 mg/kg) used in the same two experimental procedures described above. Spiperone, at this lower dose, significantly attenuated the anorexia produced by mazindol (2.5 mg/kg), but did not, when given alone, either reduce food intake or depress locomotor activity. Hence, it is possible to antagonize mazindol-induced anorexia with the dopamine receptor blocking agent, spiperone, under conditions which probably do not involve a non-specific behavioural depressant action of spiperone. This suggests that at a sufficiently low dose, spiperone can be used to antagonize drug-induced anorexia, involving an action relatively specific to feeding.

Mazindol was generously donated by Wander Pharmaceuticals, and spiperone by Janssen Pharmaceutica.

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An appraisal of the anti-inflammatory activity of copper salts

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First reports of the effective use of copper complexes to treat rheumatoid arthritis and other connective tissue diseases appeared in the 1940s (see Sorenson & Hangarter, 1977) although the prophylactic value of copper bracelets in the same diseases has been claimed for considerably longer. More recently copper complexes of nonsteroidal anti-inflammatory

drugs have been claimed to be more effective anti-inflammatory agents than the parent anti-inflammatory drug in models of inflammation produced in the rat and, furthermore, demonstrated to possess anti-ulcer activity in this species (Sorenson, 1976). However, other studies have only in part confirmed the increased potency and reduced ulcerogenic effect of the copper anti-inflammatory complex over the parent compound (Rainsford & Whitehouse, 1976; Boyle, Freeman, Goudie, Mangan & Thomson, 1976; Williams, Walz & Foye, 1976). Problems in the interpretation of data as a result of differences in the animal models of inflammation studied, the choice of vehicle for these studies and, in particular, the route of administration chosen to examine these compounds have plagued these investigations. We have consequently attempted to examine copper aspirinate in two simple models of inflammation (kaolin paw oedema and u.v. erythema) in both the rat and the guinea-pig and compared it with the effects produced by the parent compound, aspirin. Furthermore, the effects of different routes of administration of copper aspirinate have been examined in order to establish whether such a compound is likely to be acting directly or indirectly via the counter-irritant phenomenon.

Kaolin paw oedema was produced in the rat (Wistar strain, 80–100 g) as previously described (Lewis, Cottney & Sugrue, 1975) and an equivalent model of kaolin induced paw oedema was established in the guinea-pig (Dunkin–Hartley strain, 150–180 g) using the same amount of kaolin (0.1 ml of a 10% w/v suspension of kaolin in 0.9% saline) to produce the inflammatory response. Ultra-violet erythema was produced in rats as previously described (Law & Lewis, 1977) and guinea-pigs were treated in a similar manner except that animals were exposed for 120 s instead of the 90 s exposure time employed in the rat. Animals that were previously starved for 18 h were treated orally with compounds and sacrificed 6 h later in order to evaluate the extent of gastric irritation produced by the compounds. Compounds were administered in 5% mulgofen.

In the rat, copper aspirinate inhibits both kaolin paw oedema (ID_{50} 220 mg/kg) and u.v. erythema (ID_{50} 280 mg/kg) after oral administration but is no more effective than aspirin in these models. However, it is less irritant towards the stomach in this species. Copper aspirinate is more effective in both models after subcutaneous administration (ID_{50}'s 80 mg/kg and 140 mg/kg, respectively), unlike aspirin administered subcutaneously which is no more effective than after oral dosage.

In the guinea-pig, copper aspirinate (ID_{50} 145 mg/kg) is twice as effective as aspirin (ID_{50} 270 mg/kg) in suppressing kaolin paw oedema, when both compounds are administered orally. Neither compound is particularly effective after subcutaneous administration. Copper aspirinate (ID_{50}'s 50 mg/kg and 13 mg/kg) is also more effective than aspirin (ID_{50}'s 320 mg/kg and 140 mg/kg) in u.v. erythema models after oral and subcutaneous routes, respectively. However, copper aspirinate is also more irritant to the stomach of guinea-pigs than is aspirin.

This comparison between copper aspirinate and aspirin failed to produce a clear difference in activity between the two compounds and highlights the importance of species, model of inflammation and route of drug administration in interpreting data obtained with copper complexes.

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