plasma values. As adrenal AA increased, plasma cortisol concentrations diminished. Para-chloromercuribenzoate administration, inhibiting L-gulonolactone oxidase (Chatterjee, Chatterjee, Ghosh, Ghosh & Guha, 1960), administered to 2 S guinea-pigs (W) on day 54 caused weight loss, followed by death in 7 days when liver AA was 20% of normal, and plasma AA was zero. It is concluded that in times of deficiency, some female guinea-pigs are able to readjust their ascorbic acid metabolism and so compensate for the influence of the defective gene responsible for hypoascorbemia (Stone, 1966).

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Wy 23205, a new non-steroidal anti-inflammatory agent

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For aspirin, phenylbutazone and indomethacin a correlation exists between the tendency to elicit symptoms of gastro-intestinal intolerance in therapeutic use and

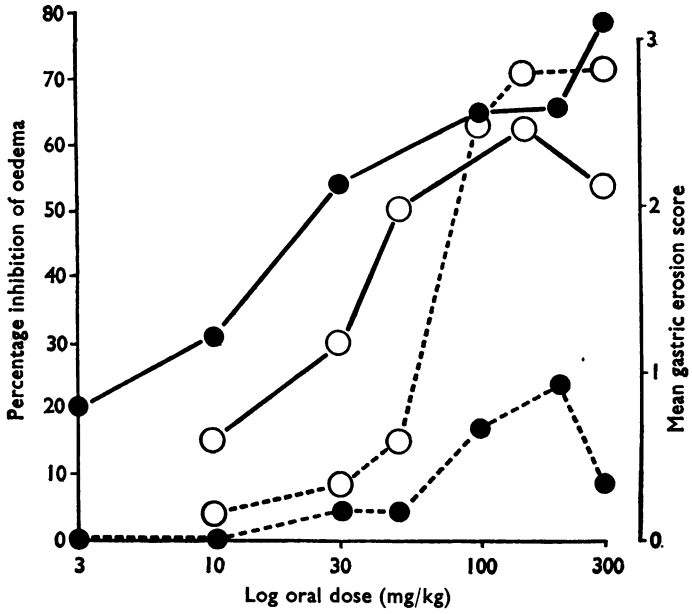

FIG. 1. Inhibition of carrageenin-induced oedema of the rat hind paw (solid lines) and gastric irritant activity (broken lines) for phenylbutazone and Wy 23205. Phenylbutazone, ○—○; Wy 23205, ●—●.

their tendency to cause gastric erosions in short-term tests in rats. Wy 23205, 3[4,5-Di-*p*-chlorophenyloxazol-2-yl] propionic acid, exhibited potent anti-inflammatory activity in a variety of animal tests. Unlike conventional anti-inflammatory drugs, it showed only a very limited tendency to cause gastric erosions in rats.

Wy 23205 was twice as potent as phenylbutazone in reducing carrageenin-induced inflammation of the rat hind paw. It reduced the severity of all the inflammatory symptoms of rat adjuvant polyarthritis, its potency being slightly less than that of indomethacin and 8–20 times that of phenylbutazone. Daily oral doses of 2 to 30 mg/kg exhibited significant anti-inflammatory activity and were well tolerated by rats suffering from polyarthritis, whereas doses of indomethacin above (10 mg/kg)/day were lethal. At doses within the ranges used to demonstrate the anti-inflammatory activity aspirin, phenylbutazone and indomethacin all caused bleeding and gastric erosions, the severity of which was maximal 12 h after the drugs were administered. With Wy 23205, on the other hand, even after doses considerably in excess of those necessary for the maximal anti-inflammatory effect, no dose-related gastric damage was elicited (Fig. 1).

In anaesthetized guinea-pigs, Wy 23205 was more potent than any other drug in suppressing the reduction of thoracic compliance caused by bradykinin. An intravenous dose of 100 μg/kg Wy 23205 completely blocked the response to 16 μg bradykinin, intravenously. Like other anti-inflammatory drugs, however, Wy 23205 did not antagonize the actions of bradykinin, histamine, 5-hydroxytryptamine or acetylcholine on the guinea-pig isolated ileum.

Thus, the pharmacological profile of Wy 23205 is that of a potent non-steroidal anti-inflammatory agent which is relatively free from gastric irritant side-effects.

Evidence that bicuculline can both potentiate and antagonize GABA

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Curtis, Duggan, Felix & Johnston (1970a, b) have shown that the convulsant alkaloid bicuculline can antagonize the depressant effects of iontophoretically applied γ-aminobutyric acid (GABA) on mammalian central neurones. Godfraind, Krnjević & Pumain (1970), however, were not able to antagonize GABA consistently with bicuculline on cortical neurones.

We, also, have found that bicuculline can antagonize GABA on cortical neurones but, additionally, have observed potentiation in some cases. In our experiments, extracellular action potentials from feline cortical neurones, firing spontaneously or driven by glutamate or (±)-homocysteic acid, were recorded via a glass micropipette and counted on an interval-time spike counter (ITSC) and also displayed on a rate-meter trace. The firing rate of all cells was depressed by iontophoretically applied GABA. The percentage inhibition of firing (calculated from the ITSC data) at successive 5 or 10 s intervals during an application of GABA was plotted against the cumulative amount of GABA applied (expressed as coulombs of charge passed by the GABA barrel). From the dose-response curves so obtained, the coulombs of GABA required to cause 50% inhibition of firing were determined. Using these estimates, the cell's response to GABA was compared before, during and after the iontophoretic application of bicuculline (50–150 nA).