the concentrations used and the DNA-berberine mixture (P/D = 11/1) at various concentrations up to 10^{-5} M strictly followed Beer's Law. Thus DNA-berberine fluorescence enhancement at pH 3·7 possibly reflects high quantum yield complex formation with the DNA bases, which are still closely arranged, providing the relatively hydrophobic environment for interaction (Love et al 1978). Many drugs have been known to bind preferentially to regions in the DNA molecule (Pack & Loew 1978; Weisblum & de Haseth 1972; Jorgenson et al 1978). On interaction with the drugs, regions with different binding affinity may give different fluorescence quantum yields. Perhaps, as DNA concentration increases, berberine migrates from lower affinity binding sites to higher affinity binding sites with a consequent enhancement in fluorescence but no significant change in the u.v.-visible spectra. When the P/D ratio reaches 110/1 all drug molecules have occupied the high affinity sites. From our studies, chloroquine and quinacrine binding to DNA did not lead to such high fluorescence enhancement over pH 2·5 to 11·5.

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LETTER TO THE EDITOR

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Relationship between inhibition of prostaglandin production and gastric mucosal damage induced by anti-inflammatory drugs may depend on type of drugs and species

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Recently, it was reported that inhibition of prostacylin (PGI_2) production may be related to the appearance of gastric lesions induced by non-steroid anti-inflammatory (NASI) drugs in rats (Whittle et al 1980). In terms of quantitative relevance to studies in man it is PGE_2 and not PGI_2 which is the main prostaglandin in the human gastric mucosa (Peskar et al 1980) and, as well, in pig (Rainsford & Peskar 1979), dog (Skoglund et al 1980) and cat (S. J. Kontureck and R. Gryglewski, personal communication). However, prostacyclin is the predominant prostaglandin in the rat mucosa, so that studies in this species might give unique results of limited relevance to the situation in man. Moreover, the fact that PGI_2 is derived mainly from vascular tissues and its production and/or functions may be regulated by PGE_2 (Tomasi et al 1978; Gordon et al 1979) indicates that the ratio of both these prostaglandins may be more important in determining the relevance of prostaglandin inhibition in the development of gastric mucosal damage by NSAI drugs.

We have, therefore, compared the gastric ulcerogenic effects of NSAI drugs with their effects on the levels of PGE_2 and 6-keto $PGF_{1\alpha}$ (stable PGI_2 hydration product) in the gastric mucosa and 15-keto-13,14-dihydro-$PGF_{2\alpha}$ (-k-H_2-$PGF_{2\alpha}$, the $PGF_{2\alpha}$ metabolite) in plasma of pigs. This species has (i) a stomach resembling that of man in respect of morphology and function (c.f. rat), and (ii) similar responses in the gastrointestinal mucosa to a variety of NSAI drugs as observed clinically in man (Rainsford & Peskar 1979). The pigs were dosed orally for 10 days with the drugs using procedures as described previously (Rainsford 1978) (see also footnotes to the Figure). The prostaglandin content of

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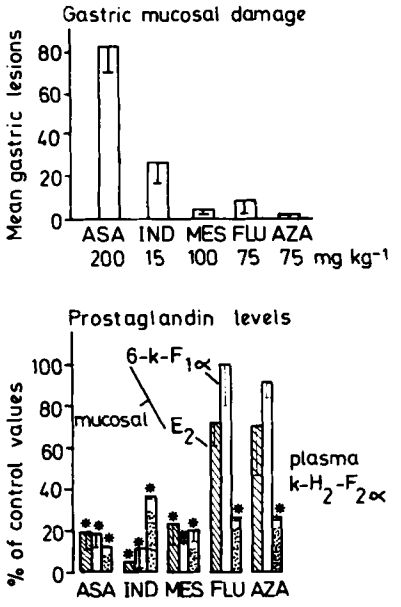

FIG. 1. Relationship between degree of gastric damage (expressed as numbers of gastric lesions) and production of PGE_2 and 6-keto $F_{1\alpha}$ (stable PGI_2 hydration product) in the gastric mucosa, and plasma levels of 15-keto, 13,14-dihydro $PGF_{2\alpha}$ (-k-H_2-$PGF_{2\alpha}$, the PGF_α metabolite) of pigs dosed orally with NSAI drugs for 10 days (at equipotent anti-inflammatory doses).

* Denotes a statistically significant reduction ($P < 0.05$, Student's t-test, n = 3–4 animals per group) in prostaglandin production with respect to the group controls. The mean control values for mucosal PGE_2, 6-keto-$PGF_{1\alpha}$ and plasma k-H_2-$PGF_{2\alpha}$ were 1·46 ± 0·43 ng mg^{-1} wet weight, 0·43 ± 0·39 ng mg^{-1} wet weight and 0·31 ± 0·14 ng ml^{-1} respectively (n = 15 animals). Gastric mucosal damage was assessed as described previously (Rainsford 1978).
ASA = aspirin, IND = indomethacin, FLU = flufenamic acid, AZA = azapropazone.

freeze-clamped mucosa and platelet-free plasma (with 0·1 mg ml^{-1} indomethacin) obtained 1 h after killing was determined by radioimmunoassays (Peskar et al 1978; Peskar et al 1979).

The results (Fig. 1) show that aspirin and indomethacin both markedly reduced gastric mucosal and plasma prostaglandin levels and caused extensive lesions in pigs. This is in agreement with the previous results in rats (Whittle et al 1980). However, the prodrug meseclazone (which is metabolized to the active drug, 5-chlorosalicylic acid following intestinal absorption—see Edelson et al 1975), markedly reduced both mucosal and plasma prostaglandin levels but caused very little damage to the gastric mucosa.

Flufenamic acid, which is a moderately potent inhibitor of prostaglandin production (Ham et al 1972) in vitro was ineffective in inhibiting the mucosal PGE_2 and 6-keto $PGF_{1\alpha}$ content in pigs, although plasma levels of k-H_2-$PGF_{2\alpha}$ were inhibited by this somewhat irritant drug. Similar results were obtained with azapropazone also a moderately potent prostaglandin synthesis inhibition in vitro (Ham et al 1972), but which causes very little gastric mucosal damage (Fig. 1).

In conclusion, we confirm the association between inhibition of both mucosal prostaglandin E_2 and I_2 production and gastric mucosal damage for the classical prostaglandin synthesis inhibitors, aspirin and indomethacin. However, the results with other NSAI drugs clearly indicate that there is an equivocal relationship between mucosal prostaglandin production and gastric mucosal damage.

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