AH21132 gave the same relative increase in relaxation rates. The relaxation rate of the relaxation of maleate ion also increased in platelet suspensions but to a lesser degree. The greater increase in the relaxation rates of drug molecules indicates a specific binding to platelets.

The results obtained indicate that if suitable preparations of platelets can be prepared, information of binding characteristics of drugs which exhibit single peak spectra can be obtained.

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Effects of prostaglandins E_1, E_2 and D_2 on platelet aggregation: variation with animal species and ionized calcium concentration

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Prostaglandin E_1 (PGE_1) is a potent inhibitor of platelet aggregation in all animal species (Ki $\sim$ 20 nM). Prostaglandin D_2 (PGD_2) is even more effective than PGE_1 at inhibiting the aggregation of human platelets but is apparently much less potent when tested on platelets from some other species (Smith, Silver, Ingerman & Kocsis, 1974). Prostaglandin E_2 (PGE_2) is inhibitory at micromolar concentrations and there is some controversy as to whether lower concentrations enhance aggregation (Bruno, Taylor & Droller, 1974). These studies were performed using platelets suspended in media containing sub-physiological concentrations of ionized calcium. The effect of PGE_1 varies with the ionized calcium concentration (Vigdahl, Marquis & Tavormina, 1969) and platelet aggregation is also calcium-dependent to a variable extent in different animal species (Mürer, 1972). We have investigated the effects of PGE_1, PGE_2 and PGD_2 on collagen-induced aggregation of human, pig and rat platelets in platelet-rich plasma (PRP) anticoagulated with citrate (which chelates free calcium) or heparin (Gordon & MacIntyre, 1974, Gordon and Drummond, 1974).

Results are shown in Table 1. PGE_1 was most potent in man and least potent in the pig. PGD_2 was more potent than PGE_1 in man, less potent than PGE_1 in the pig and was inactive in the rat. PGE_2 was much less potent than PGE_1 in all species. In man and rat, all three prostaglandins were more potent inhibitors in citrate PRP than in heparinized PRP, but in the pig the reverse was true, and PGE_2 induced aggregation directly in pig heparinized PRP. PGE_2 never induced aggregation in human or rat PRP, although with concentrations around 0.3 μM, collagen-induced aggregation was enhanced in heparinized PRP but not in citrated PRP. Platelet aggregation induced by PGE_2 in pig heparinized PRP was inhibited by citrate, EDTA, PGE_1 and PGD_2.

It has been previously shown that platelet aggregation can be induced by endoperoxide intermediates in the PGE_2 biosynthetic pathway (Willis, 1974) and by synthetic derivatives of PGE_2 (Fenichel, Stokes & Alburn, 1975) but the results of the present study are the first demonstration of platelet aggregation induced by a stable, naturally-occurring prostaglandin.

Table 1 Effect of prostaglandins on collagen-induced platelet aggregation IC_{50} values (μM)

Prostaglandin	*Man*		*Rat*		*Pig*	
	Citrate	*Heparin*	*Citrate*	*Heparin*	*Citrate*	*Heparin*
PGE_1	0.015	0.054	0.06	0.09	0.27	0.12
PGD_2	0.008	0.015	> 200.0	> 200.0	1.4	0.15
PGE_2	6.0	22.0	75.0	135.0	67.0	*

* Induced aggregation directly.

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Enlargement of the caecum in the rat

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Enlargement of the rat caecum has been found to occur following the repeated administration of a wide range of materials which are ingested by man. These include certain antibiotics e.g. neomycin, erythrosine (Butterworth, Gaunt, Grasso & Gangolli, 1975) and modified starches (de Groot, Til, Feron, Dreef-van der Meullen & Willems, 1974). A notable feature of the above studies was that the histological appearance of the caecal tissue was reported as normal. Thus when sub-acute and chronic toxicity studies have been performed on these materials, it has been found to be difficult to determine the biological significance of this enlargement. Experiments have been performed to determine some of the factors associated with the caecal enlargement produced by erythrosine.

Groups of 10 male, 4-week old, Wistar rats were fed a diet containing 0 or 2% erythrosine (2,4,5,7-tetraiodofluorescein) for 17 weeks. At post-mortem examination the weights of the caeca, both 'full' and empty, of these animals were 9.37 ± 1.33 g (mean and 95% interval estimate) and 1.31 ± 0.22 g respectively, compared with 4.25 ± 0.70 g and 0.90 ± 0.13 g for the control animals. The total amount of faecal material passed by the animals fed erythrosine was 137% of the control value ($P < 0.01$), although there was no comparable increase in the food or water consumptions. Examination of the caecal contents revealed statistically significant changes ($P < 0.05$) in the microflora of the treated animals when compared with the controls. The total number of coliforms was increased to $8.21 \pm 0.22\ g^{-1}$ expressed as $\log_{10}$ (controls = 6.04 ± 0.48). Similarly the strict anaerobes were increased to 10.07 ± 0.38 (control = 9.44 ± 0.17) and *Streptococcus faecalis* to 5.95 ± 0.17 (control = 5.21 ± 0.47), while the lactobacilli were reduced to 4.28 ± 1.44 (control = 8.10 ± 0.27). The staphylococcal count was reduced in the treated rats to 2.24 ± 1.30 (control = 3.68 ± 0.29), but the decrease was not statistically significant. No differences were observed in the protein, lipid, or water content when expressed per unit weight of the caecal tissue. However the DNA content was increased from 871 ± 93 to 1275 ± 333 mg $100\ g^{-1}$ dry weight of tissue ($P < 0.05$).

It is postulated that erythrosine, in altering the bacterial flora of the caecum, reduced the breakdown of certain dietary constituents, which then were excreted in increased amounts. Although it cannot be assumed that the underlying mechanisms of caecal enlargement induced by different agents are the same, it is suggested that, in the case of erythrosine, the increase in bacteria and undigested material placed an extra load on the caecum leading to a 'work' or functional hypertrophy and possibly hyperplasia. Work is in progress to investigate this hypothesis.

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