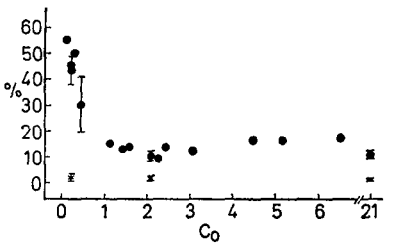

FIG. 2. Plots of the % absorption (●) and tissue accumulation (×) against initial concentration of amoxicillin, C_0 (μg ml^{-1} × 10^{-2}) at pH 7·0 from the rat small intestine by the *in situ* recirculating perfusion technique. The perfusion solution (9 ml) was recirculated at a rate of 2 ml min^{-1}. The small intestine was a 30 cm length from the pylorus. Vertical bars represent the standard error.

removed from the intestine almost completely transfers into the blood. The relation between amount absorbed and the initial drug concentration suggests that the absorption of amoxicillin is likely to follow the simultaneous kinetics of a simple diffusion process predominant at high concentrations and a Michaelis-Menten process which can only be seen at low concentrations. Recently, Miyazaki, Ogino & others (1977a) have observed, by the method of the isolated everted rat intestine, that there was no uphill transport of amoxicillin. These findings together with site specificity in absorption as observed in the *in situ* loop method suggest that facilitated diffusion and not active transport is involved in the absorption of low dose of amoxicillin. The present observations, however, do not demonstrate the nature of the transport mechanism, and are nothing more than an indication of a saturable rate-limiting step in the absorption process of amoxicillin.

With the *in situ* recirculating absorption experiment for ampicillin at low concentration, the extents of the absorption were relatively low and variable in each animal. For example, at 17 μg ml^{-1}, the percent absorption was 9·6 ± 8·1%. Owing to the unexpectedly low percentage of absorption and its large variance, we could not judge whether for ampicillin there was an absorption phenomenon similar to that for amoxicillin. The large degradation seen with the perfusion technique compared with the *in situ* loop method occured with both antibiotics, and their degradation percentages were of the same order of magnitude; 28·7 ± 8·6% at concentration of 17 μg ml^{-1} for ampicillin and 29·1 ± 21·8% at concentration of 21 μg ml^{-1} for amoxicillin.

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The mechanism of the release of prostaglandin-like activity from guinea-pig isolated ileum

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Botting & Salzmann (1974) demonstrated that PGE_2 was released from guinea-pig isolated ileum during field stimulation, but that the release was only pronounced at frequencies of 10 Hz and above. Since Hughes (personal communication) had shown that noradrenaline release from intramural nerves of field-stimulated guinea-pig ileum was only easily detectable at similar frequencies it was possible that the synthesis of prostaglandin was a consequence of neuronal release of noradrenaline.

This suggestion was investigated using strips of guinea-pig terminal ileum suspended in an organ bath (volume 5 ml). The bath fluid and other experimental conditions were as described previously (Botting & Salzmann, 1974). The tissue was left for 90 min during which the fluid was changed every 10 min. The bath fluid was then collected and replaced with fresh solution every 15 min. During alternate periods field stimulation was applied by silver electrodes connected to an S.R.I.

stimulator delivering square wave pulses (50 V) 0·7 ms duration at 20 Hz. Each sample of bath fluid was acidified (N HCl) to pH 3·5, and extracted twice with double its volume of ethyl acetate. The extracts were dried on a rotary evaporator and the residue taken up with 1 ml of Krebs fluid. The prostaglandin content was assayed against standard prostaglandin E_2 on rat stomach strip (Vane, 1957) superfused with Krebs solution containing methysergide, mepyramine and hyoscine, 0·1 μg ml^{-1} in each case, and indomethacin, phentolamine and propranolol, 1·0 μg ml^{-1} in each case. The field stimulation experiments were repeated with the following drugs in the bathing fluid from the start of the experiment: hyoscine hydrobromide ($2{\cdot}3 \times 10^{-7}$ M), phentolamine mesylate ($3{\cdot}6 \times 10^{-6}$ M), propranolol hydrochloride ($3{\cdot}4 \times 10^{-6}$M), phentolamine plus propranolol, guanethidine sulphate ($3{\cdot}4 \times 10^{-7}$M). The results with these treatments were expressed as percentage increase in PG content during the stimulation period compared with the mean content in the rest periods preceding and following the stimulation.

Additional experiments were performed on tissues where, instead of the stimulation period, noradrenaline hydrochloride ($4{\cdot}9 \times 10^{-6}$M) was included in the bath fluid for 15 min.

The results are summarized in Fig. 1. They represent 100 estimations on 33 tissues. The resting output of PG assayed as PGE_2 varied from 0·21 to 3·7 ng g^{-1} min^{-1}. Stimulation at 20 Hz always caused an increased release of PG ($P < 0{\cdot}001$, paired t-test), as did addition of noradrenaline ($P < 0{\cdot}001$, paired t-test). Hyoscine did not significantly reduce the output of PG during stimulation, but phentolamine ($P < 0{\cdot}01$), propranolol ($P < 0{\cdot}001$) and phentolamine plus propranolol ($P < 0{\cdot}001$) significantly reduced the stimulated output of PGE_2-like activity. In the presence of guanethidine there was no detectable increase of PG release during stimulation.

These results suggest that the release of PG-like activity from guinea-pig isolated ielum during field stimulation is caused by the release of noradrenaline from intramural sympathetic nerves, and is secondary to the stimulation of α- and β-adrenoceptors. Such a

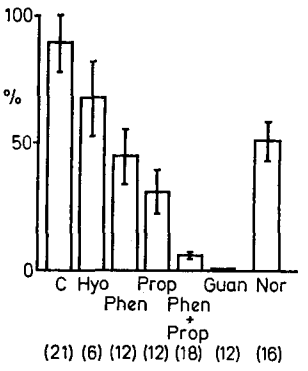

FIG. 1. The effect of antagonist drugs on the output of prostaglandin (assayed against PGE_2) from guinea-pig isolated ileum during field stimulation. C, control; Hyo, hyoscine; Phen, phentolamine; Prop, propranolol; Guan, guanethidine. Nor, noradrenaline added to bath fluid surrounding the ileum instead of field stimulation. Number of experiments in brackets. Ordinate—% increase in PG-like activity.

phenomenon has been reported as occurring in other tissues by Hedqvist (1973) and Ferreira, Moncada & Vane (1973). Apart from this release of PG by a post synaptic action of sympathetic neurotransmitter, other workers have suggested that PG are essential modulators for cholinergic transmission in guinea-pig ileum (Ehrenpreis, Greenberg & Comaty, 1976). The present results suggest that PG involvement in acetylcholine release may be less direct, possibly by initially reducing release of noradrenaline by negative feed back inhibition (Hedqvist, 1973) with consequent lifting of the inhibition of acetylcholine release produced by the action of endogenous noradrenaline on presynaptic α-receptors on cholinergic nerves in the ileum (as demonstrated by Drew, 1977).

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