chemical properties to cimetidine also failed to raise prolactin in healthy volunteers after intravenous injection. They speculated that the specific effect of cimetidine on prolactin was due to a particular feature of the cimetidine molecule itself.

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The stimulation of lysosomal enzyme secretion from human polymorphonuclear leucocytes by leukotriene B_4

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The structure of LTB_4 (isomer III), a metabolite of arachidonic acid formed after initial lipoxygenase action, has been confirmed as 5(*S*),12(*R*)-dihydroxy-6-*cis*-8-*trans*-10-*trans*-14-*cis*-eicosatetraenoic acid (Corey et al 1980). Its principal biological activities in vitro are to stimulate the aggregation and movement (chemokinesis and chemotaxis) of leucocyte cell types (Smith 1981) and it is equipotent to the complement-derived peptide C5a, and to the synthetic cytotaxin FMLP, formyl-methionyl-leucyl-phenylalanine (Bray et al 1981). A further effect of cytotaxins on leucocyte function in vitro is degranulation and the release of lysosomal enzymes. One group of workers (Goetzl & Pickett 1980) found that LTB_4 (isomer III) is only approximately one third as active as the chemotactic peptides, C5a and FMLP, in stimulating lysosomal enzyme release while others (Palmer et al 1981) reported that the leukotriene was apparently as active as FMLP. We have therefore studied the effects of LTB_4 (isomer III) and FMLP, separately and in combination, on the release of β-glucuronidase and lysozyme from human peripheral polymorphonuclear leucocytes (PMNs). In addition we have examined the effects of the closely related slow reacting substances, LTC_4 and LTD_4, in the system.

Cell suspensions (>98% PMNs) were prepared from 100 ml samples of heparinized blood, obtained by venepuncture from normal male subjects, aged 25 to 40 years, by dextran sedimentation, Ficoll Hypaque separation and hypotonic lysis of residual red cells (Walker et al 1979). The cells were resuspended at a concentration of 1×10^7 cells ml^{-1} in Eagle's Minimum Essential Medium (MEM) buffered to pH 7·4 with HEPES. LTB_4 (isomer III) was prepared as described previously (Ford-Hutchinson et al 1980), FMLP and cytochalasin B (Sigma Chemical Co.) were dissolved in dimethylsulphoxide (DMSO) and serial dilutions were made in MEM. The final concentration of DMSO never exceeded 0·05%. In each experiment 0·25 ml aliquots of the cell suspension were incubated in a shaking water bath for 15 min at 37 °C with cytochalasin B (final concentration of 5 μg ml^{-1}). LTB_4 (isomer III), FMLP, LTC_4 or LTD_4 were added in 0·25 ml MEM to give the final concentrations described in Table 1 and the incubation was continued for a further 15 min. The mixtures were then removed, centrifuged for 10 min at 300 *g* and lyosyme, β-glucuronidase and lactate dehydrogenase activities measured in the supernatants by conventional methods (Smolelis & Hartsell 1943; Fishman et al 1967; Anon 1970). The results (Table 1) are expressed as a percentage of the total enzyme recovered from cells exposed to 0·2% (v/v) Triton X 100.

FMLP caused a dose-dependent release of the two lysosomal enzymes over the range 10^{-9} to 10^{-6} M, the ED50s being $2·5 \times 10^{-8}$ M and 2×10^{-8} M for β-glucuronidase and lysozyme respectively. LTB_4 (isomer III) produced a much weaker response and LTC_4 and LTD_4 were without effect

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Table 1. Effects of FMLP and LTB_4 (isomer III) on the release of lysosomal enzymes from human polymorphonuclear leucocytes.

Final concn. of cytotaxin M	Release of enzyme: β-Glucuronidase FMLP	β-Glucuronidase LTB_4	Lysozyme FMLP	Lysozyme LTB_4
0	2·5 ± 1·0*		16·3 ± 1·6	
10^{-9}	4·9 ± 1·0*	4·9 ± 1·1*	32·3 ± 3·1*	18·0 ± 2·1*
10^{-8}	5·5 ± 1·7*	6·2 ± 1·8*	37·1 ± 3·3*	26·0 ± 2·0*
10^{-7}	27·0 ± 5·9*	8·3 ± 2·3*	62·0 ± 4·9*	28·0 ± 1·6*
10^{-6}	43·9 ± 1·4*	4·4 ± 0·5*	82·0 ± 1·8*	28·9 ± 2·0*

The results are expressed as percentages of the release induced by exposure of the cells to Triton X 100 and are given as the means ± standard error of at least 5 separate experiments.
* Student's t-test $P < 0.05$ from results of corresponding control experiments.

at concentrations up to 10^{-6} M. The amounts of β-glucuronidase and lysozyme released by FMLP (10^{-9} to 10^{-6} M) in the presence of LTB_4 (isomer III) (10^{-6} M) were found to be between 60 to 80% of the predicted value for a completely additive effect of the two cytotaxins. In all the experiments the release of the cytoplasmic enzyme lactate dehydrogenase, was always less than 10%.

Two conclusions may be drawn from the results of the present work. First, the equipotence of LTB_4 (isomer III) and other cytotaxins, FMLP and C5a, with respect to aggregating and chemokinetic effects on human peripheral PMNs (Smith 1981) does not apply to their effects on the release of lysosomal enzymes from this cell type. LTB_4 (isomer III) is relatively much weaker than FMLP in terms of enzyme release than as a chemokinesin (cf. Goetzl & Pickett 1980). Secondly, it has been reported that a lipoxygenase-derived product of arachidonic acid may be concerned in the stimulation of enzyme release from human and rabbit PMNs by FMLP (Smolen & Weissmann 1980; Naccache et al 1979). It appears from this work that a substance, other than LTB_4 (isomer III), may be active metabolite involved. The present results suggest that neither LTC_4 (see Goetzl & Pickett 1980) nor LTD_4 are likely candidates. It will be of interest to examine other lipoxygenase-derived metabolites particularly since neither 5-HETE nor a mixture of tri-HETEs exhibit such activity (Goetzl & Pickett 1980).

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A comparison of the behaviour of tablet and capsule formulations in vivo

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The behaviour of solid dosage forms in vivo can be studied by using a suitable radiolabelled formulation and monitoring externally using a gamma camera or a profile scanning technique (Alpsten et al 1976; Digenis et al 1976; Hunter et al 1980). The observations and gastric emptying curves of Hunter et al led to the postulation that the capsule, on entering the stomach, adhered to the stomach wall. From there, dispersion of the capsule contents could take place providing a meal had been consumed, or the capsule contents were emptied from the stomach undispersed if the capsule was administered after an overnight fast.

The lack of overall movement before emptying, noted both by Hunter et al, and Digenis et al, tends to support this postulate, and may lead to the proposition that adherance to the stomach wall is a function of the adhesive nature of the gelatin capsule. This communication presents a comparison of the gastric emptying of a tablet and a capsule formulation.

Model formulations were prepared from Amberlite resin IRA-410 (BDH Ltd), 690–850 μm size fraction, for the capsules, and Amberlite resin CG-400CL (BDH Ltd)

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