experiments (Jasani & Lewis, 1971) indicated that estimation of changes in lactic dehydrogenase and β-glucuronidase activities may be used to assess the magnitude of increase in the number of lymphocytic cells which are the main migratory cells in the homograft reaction. It is now concluded that acid phosphatase activity can be used as a reliable index of epithelial regeneration, since there is a good correlation between the degree of epithelial hyperplasia observed on histological examination of the grafts and their acid phosphatase content.

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A pro-inflammatory effect of adrenaline in thermal injury

K. L. GREEN (introduced by M. GINSBURG)

School of Pharmacy, Leicester Polytechnic, Leicester LE1 9BH

Thermal injury induced by immersing the hind paws of rats in water at 46·5° C for 60 min causes the formation of an inflammatory oedema (Rocha e Silva & Antonio, 1960). Whilst studying the anti-inflammatory activity of catecholamines it was found that local injection of adrenaline (0·1–1 μg) or noradrenaline (0·2–1 μg) 15 min prior to heating the hind paws of rats potentiated thermic oedema. This was unexpected, since catecholamines antagonize paw oedema induced by injection of irritants or pro-inflammatory mediators (Green, 1972).

Studies by Rocha e Silva & Antonio (1960); Starr & West (1967) and Rocha e Silva, Garcia Leme & De Souza (1969) have implicated bradykinin as the mediator in thermic oedema. It was therefore of interest to establish whether catecholamines potentiate thermic oedema by enhancing the formation of bradykinin. Heated paws were co-axially perfused either with Tyrode's solution alone or with Tyrode containing graded concentrations of adrenaline. The perfusate was subsequently assayed for bradykinin, kinin-forming activity and kininase activity as described by Starr & West (1967). Rat uterus, rat duodenum and guinea-pig ileum were used as assay preparations, the bathing solutions containing sotalol hydrochloride (10^{-5}–10^{-4} g/ml) and phentolamine hydrochloride (2×10^{-6} g/ml) to antagonize the effects of adrenaline. Perfusate collected over 30 min from heated control paws contained bradykinin 14·1±2·7 ng (S.E. of mean, $n=8$) whereas perfusate from paws perfused with adrenaline (0·5 μg/ml) contained bradykinin 7·6±2·2 ng. Adrenaline had no significant effect on kinin-forming activity but increased kininase activity 76%. These results indicate that the potentiation of thermic oedema by adrenaline is not due to activation of kinins. Furthermore, adrenaline suppressed the increase in vascular permeability induced by injection of bradykinin or kallikrein.

The pro-inflammatory effect of adrenaline was antagonized by pretreatment with phenoxybenzamine (10 mg/kg, I.V.) but not by propranolol (10 mg/kg, I.P.). Like adrenaline, local injection of vasopressin (25 M.U.) was found to potentiate thermic oedema, suggesting that this property may be common to vasoconstrictor agents. A thermistor probe inserted into the paw showed that a temperature gradient of 1·2±0·2° C existed across the skin of control paws heated at 46·5° C compared with a temperature gradient of only 0·1–0·2° C in heated paws injected with adrenaline (1 μg), although both adrenaline-treated and control paws had similar internal temperatures after 30 min of heating. However, even small changes in temperature are of importance in the development of thermic oedema, since it was found that paws heated at 47·5° C for 15 min and then at 46·5° C for 45 min had significantly greater oedema than paws which were heated at 46·5° C for 60 min.

The pro-inflammatory effect of adrenaline in thermic oedema may therefore be attributable to a reduction in blood flow in the injected paws, with the result that heat

is less readily dissipated from the paws causing a greater rise in paw temperature and consequently greater injury.

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Some observations on blood level data following oral administration of aspirin as tablets and capsules

J. GARNHAM*, DEBORAH C. HICKS, K. RAYMOND, E. SHOTTON (introduced by P. TURNER)

Department of Clinical Pharmacology, St. Bartholomew's Hospital, London, E.C.1 and Department of Pharmaceutics, The School of Pharmacy, Brunswick Square, London, WC1N 1AX

Experimentally prepared capsules and commercially available tablets of aspirin, each of 500 mg, were tested and were shown to conform to the British Pharmacopia tests for uniformity of weight, uniformity of active ingredient and five single-capsule assays yielded results of 97·7% (S.D.=0·62%) active ingredient. From single-tablet assays they contained 100·6% of aspirin (S.D.=1·72%).

Two capsules or two tablets, were administered in a randomized cross-over experiment, to 9 healthy volunteers, two weeks being allowed before the second test was commenced. Venous blood was withdrawn before and at various times after administration, and plasma salicylate levels determined after alkaline hydrolysis.

In every subject, the tablet preparation produced a higher concentration of salicylate in the plasma 0·5 and 1 h after administration than did the capsule formulation, and the peak levels occurred earlier and more consistently for the tablet at about 2 h.

The time to reach maximum blood level varied from about 2 to 4 h for the capsules. Average peak salicylate levels between the two groups were virtually identical (66·2 μg/ml and 64·1 μg/ml; S.D., 10·8 and 10·3).

Extrapolation of the log concentration *vs.* time graph, after peak levels to a common time scale, showed similar elimination rates for the two formulations, and confirms that the individual peak levels obtained differed little between the formulations.

A polynomial regression of the first few points up to the maximum indicated a lag time in the appearance of salicylate in the plasma, and this was significantly higher for the capsule which averaged 0·23 h and 0·07 h for the tablet. The disintegration time in water of the experimental formulation was 519–524 s, and that of the commercial preparation only 14–18 s, but, whereas the tablet almost immediately became dispersed in water, it was approximately 45 s before the edges of the capsule broke open to release some of the contents. Thus, the delayed and less consistent maxima plasma salicylate levels of the capsule formulation may be due to the slow release of the drug from the dosage form. Quantitative pharmacokinetic data and dissolution rate profiles are being evaluated.

Hepatic clearance of propranolol in dogs

A. BRECKENRIDGE, P. BURANAPONG, C. T. DOLLERY, C. F. GEORGE*, D. MACERLEAN and M. L'E. ORME

MRC Clinical Pharmacology Research Group, Royal Postgraduate Medical School, Ducane Road, London, W.12

Studies in which ^{14}C-propranolol was given to man indicate that this drug is almost totally absorbed after oral dosing (Paterson *et al.*, 1970). However, peak plasma con-