lysosomes are of interest since lysosomal enzymes are involved in the acute inflammatory reaction.² In previous observations we have found that the actions of some anti-inflammatory aromatic acids and anti-inflammatory steroids are concentration-dependent.^{3,4} The anti-inflammatory activity of steroids has been related to their stabilising action on lysosomes.⁵ It was therefore of interest to investigate the effect of concentration of the non-steroidal anti-inflammatory drugs azapropazone, oxyphenbutazone, and phenylbutazone on lysosomes. The gastrointestinal ulcerogenic action of anti-inflammatory drugs may result, in part at all events, from lysosomal damage consequent on high local concentration of these compounds, such as may be achieved after oral administration. We have shown that this may result in the intracellular release of acid hydrolases such as cathepsins, with consequent damage to surrounding tissues.³

In experiments on isolated lysosomes we have consistently shown a biphasic effect of azapropazone, oxyphenbutazone, and phenylbutazone on the release of acid hydrolases. The equilibrium concentrations which are attained under normal therapeutic conditions stabilise lysosomes, and this property may be a significant factor in their anti-inflammatory action.¹ However, at higher concentrations, such as may be attained locally in the gastrointestinal tract, lysis of lysosomes with liberation of powerful proteolytic enzymes has been demonstrated. The effect of phenylbutazone was very much more powerful than that of the other drugs.

Phenylbutazone was shown to have a much more powerful ulcerogenic action than azapropazone in experimental animals (rats, rabbits), though the latter drug was not devoid of action in high concentrations such as those which may be released locally after oral administration of therapeutic doses. Both drugs were demonstrated to be capable of producing ulcers in the pyloric region, with which lysosomal damage was correlated, while duodenal ulceration was induced by phenylbutazone but not by azapropazone. Using the quantitative index of ulcerogenic effect proposed by Münchow⁶ as a measure of the severity of ulceration azapropazone was less than one-quarter and one-half as strongly ulcerogenic as phenylbutazone and flufenamic acid respectively. Its effect was approximately equal to that of mefenamic acid. The therapeutic ratio between ulcerogenicity ED_{50} and anti-inflammatory ED_{50} was 2.2-2.5 for azapropazone, 1.0 for phenylbutazone, 2.0-2.5 for mefenamic acid, and 1.2 for flufenamic acid and indomethacin. Evidence of liberation of lysosomal enzymes in the tissues was histochemically demonstrable in subulcerogenic doses, thus raising the possibility that these drugs may induce a preulcerogenic state in concentrations insufficient to produce ulcers.

Thus our results have shown that even in the absence of anticoagulants azapropazone has ulcerogenic potential, though admittedly much less than that of phenylbutazone. The importance of Dr Powell-Jackson's observations is that an enhanced ulcerogenic activity of azapropazone is demonstrable in the case of patients concurrently treated with warfarin and is presumed to be due to an interaction between the drug and warfarin analogous to that which takes place with phenylbutazone. No studies appear to have been carried out on the interaction between azapropazone and warfarin. However, azapropazone has no

significant effect on normal prothrombin time, and does not enhance the effect of nicoumalone. The mechanism of the ulcerogenic action of azapropazone in patients on anticoagulants is clearly worthy of further investigation, but the conclusions to be derived from our experimental work is that ulcerogenesis can occur with this drug even in the absence of anticoagulants, though it is far less likely than with phenylbutazone.

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¹ Lewis, D A, Capstick, R B, and Ancill, R J, *Journal of Pharmacy and Pharmacology*, 1971, **23**, 931.

² Weissman, G, *Annual Review of Medicine*, 1967, **18**, 97.

³ Lewis, D A, *Journal of Pharmacy and Pharmacology*, 1970, **22**, 909.

⁴ Lewis D A, Symons, A M, and Ancill, R J, *Journal of Pharmacy and Pharmacology*, 1970, **22**, 902.

⁵ Weissman, G, and Dingle, J T, *Experimental Cell Research*, 1961, **25**, 207.

⁶ Münchow, O, *Arzneimittel-Forschung*, 1954, **4**, 341.

Interferons and rabies

SIR,—During the past 24 months, if my arithmetic does not play me false, we have seen four deaths from rabies in Britain—and this in spite of intensive care units and devoted attention, where it was possible to do so, by our medical and paramedical staff.

At the close of last year a scientist from this famous establishment was pulled through a most serious viral infection (Ebola fever), against which we have as yet no protective prophylactic vaccine, by interferon (IF) and specific serotherapy plus, of course, expert medical attention as noted above in the case of the rabies patients. It would seem, therefore, that an opportune moment has arrived to have a supply of IF (or possibly an IF inducer) stocked and ready available for treatment of the next rabies patient at some national designated centre. Is this not worth a trial, I wonder, in view of the 100% failure rates recorded so far in this country since I qualified in 1946?

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Lithium carbonate in schizoaffective states

SIR,—I have now used lithium carbonate in many manic-depressive states for 12 years, having talked personally with Cade, on a visit to Australia, about its value and the two deaths from overdosage. For a long time blood lithium concentrations were not available, but no trouble occurred with small doses, which one lowered if hand tremor or gastric upset occurred. Nobody can now doubt its value when working at the bedside, but recently I have also been seeing a very interesting phenomenon when lithium carbonate is used, often alone or together with the phenothiazines, to control recurrent schizoaffective breakdowns.

Patients are sent to me for consultation in deep depression filled to the brim with phenothiazines but with no delusions. Their illness had often started with an attack of

apparent schizophrenic excitement with delusions and hallucinations. These had been damped down and over-damped down, by phenothiazines and the patient became depressed, anergic, and often sent to a back ward of a mental hospital as a deteriorating schizophrenic, to be kept on phenothiazines indefinitely and looked after by a junior registrar.

One only has to reduce the dosage of phenothiazines greatly and give lithium for the patient to recover, and in many cases there are no more attacks of schizophrenic excitement. Any further depression on lithium in these patients can be dealt with by the addition of antidepressant drugs. Nothing would induce me to continue to torture such patients by double-blind sampling them; most have had so much suffering already. But from clinical observation it seems that lithium carbonate may be found as helpful as the phenothiazines in what one must, I suppose, call "schizoaffective" states. I sincerely hope it will be tried "anecdotally" at the bedside by psychiatrists and by general practitioners, who are taking over so much of our present psychiatric treatment now it has become so physical and simple to give.

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Endocrine versus cytotoxic treatment in advanced breast cancer

SIR,—In concluding that cytotoxic therapy is the treatment of choice for premenopausal women with locally recurrent or metastatic breast cancer Dr J Priestman and his colleagues (14 May, p 1248) are not making a fair comparison. They match ovarian ablation alone, a manoeuvre of known limited effectiveness, against repeated cycles of powerful cytotoxic drugs. They appear to ignore completely the great palliative value of simple radiotherapeutic techniques, which may be added to endocrine treatments but cannot be applied while continuing with chemotherapy.

A more realistic study would be the comparison of cytotoxic and non-cytotoxic policies, the latter to include not only ovarian ablation but also radiotherapy, non-virilising androgens, and corticosteroids given as required.

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Vitamin D "resistance" and bioavailability of calciferol tablets

SIR,—The suggestion by Dr C R Paterson that calcitonin may increase vitamin D requirement in hypoparathyroidism (9 April, p 952) is interesting, but the documentation of a subnormal response to treatment in the reported case is inadequate.

It has been shown on several occasions¹⁻³ that the ergocalciferol tablets available in the United Kingdom are most unsatisfactory because they contain substantially more than the stated quantity when new,³ are subject to unpredictable deterioration and loss of strength when old,⁴ and are sometimes very poorly absorbed.² In current jargon, the bioavailability of calciferol tablets BP is unpredictable and sometimes very low.

Problems related to the quality of the vitamin D preparation used are by far the commonest