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.

R J ANCILL

Department of Pharmacology,
School of Pharmacy and Pharmacology,
University of Bath,
and Royal National Hospital for
Rheumatic Diseases,
Bath, Avon

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?

WALLY VELLA

Ministry of Defence,
Microbiological Research
Establishment,
Porton Down,
Salisbury, Wilts

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.

WILLIAM SARGANT

London W1

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.

B S MANTELL

The London Hospital,
London E1

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

cause of apparent resistance to treatment. True resistance cannot be accepted without evidence that the patient was ingesting and absorbing a pharmaceutically satisfactory preparation of vitamin D. Such evidence has not been given for any of the numerous published cases of "resistance" to vitamin D therapy, but adequate assurance on all three counts would be provided by showing that the plasma concentration of 25-hydroxycalciferol had been raised to a level consistent with the dose.¹ I suggest that no further cases of supposed resistance to vitamin D therapy should be reported without this crucial piece of information.

A M PARFITT

Bone and Mineral Research
Laboratory,
Henry Ford Hospital,
Detroit, Michigan

¹ Himsworth, H P, and Maizels, M, *Lancet*, 1940, **1**, 959.

² Dent, C E, et al, *Pharmaceutical Journal*, 1953, **170**, 126.

³ Parfitt, A M, *Australasian Annals of Medicine*, 1968, **17**, 56.

⁴ Stamp, T C B, et al, *Lancet*. In press.

Insurance companies' attitude to psychiatric illness

SIR,—Dr J T Hutchinson (19 March, p 775), says that insurance companies have made it difficult for patients to take out life insurance because they have a history of psychiatric treatment.

The insurance companies have a point in those cases in which the psychiatric condition is likely significantly to shorten life. Take, however, two patients, each of whom has suffered from some form of nervous anxiety. One of them has had psychotherapy as an outpatient and has thereby improved but the other has not and his condition has made less gainful progress. The insurance company in question will penalise the former but not the latter because they do not understand the situation. A third patient may have gone to his family doctor with similar symptoms and have been treated with tranquillisers. He will regard this as "medical" treatment and so will escape the net even if psychotherapy would have done him more good.

My personal view is that where the treatment has been confined to outpatient attendances for psychotherapy and perhaps for mild drug medication this should not be regarded as "psychiatric" treatment. I have on occasion said to a patient that he will have my backing in disregarding such circumstances while filling application forms. Alternatively I would write a certificate to this effect.

D T MACLAY

Dudley Area Health Authority,
Community Health Service,
Dudley, W Midlands

Heparin and pulmonary embolism

SIR,—I should like to report the case of a fit 57-year-old man admitted for routine cholecystectomy three months after an episode of acute biliary colic. As prophylaxis against deep vein thrombosis he was given 5000 U of heparin with his premedication of pethidine 100 mg, promethazine 25 mg, and atropine 0.4 mg, then 5000 U thrice daily postoperatively. The operation was cholecystectomy with exploration of the common bile duct and

was uneventful. On the fourth postoperative day he developed massive bilateral pulmonary emboli, which produced a 60–70% loss on lung scan and arteriography and a pulmonary artery pressure of 85 mm Hg. Leg venograms and an inferior venocavagram showed no evidence of thrombosis. Despite immediate heparinisation by constant infusion of 10 000 U four times daily and later 15 000 U four times daily, keeping the thrombin time prolonged by a factor of 3–4, his condition remained critical for several days, necessitating oxygen therapy and transfer to the intensive care unit for close monitoring of his blood gases. He eventually made a good recovery after treatment with streptokinase.

I wonder whether the use of prophylactic heparin transformed what would have been a deep vein thrombosis into early pulmonary embolisation and whether embolism which does occur in the presence of heparin prophylaxis tends to be early rather than late. Conversely, did the prophylactic heparin prevent an otherwise fatal episode?

MARIAN RODEN

Academic Department of Surgery,
Royal Free Hospital,
London NW3

Misdiagnosis of urinary tract infection

SIR,—Professor A W Asscher (21 May, p 1332) is right to stress the importance of making an accurate initial diagnosis when a patient presents with symptoms suggesting a urinary tract infection. But I think he should have mentioned a very important cause for the persistence or reappearance of symptoms after treatment. This is that the symptoms may not be due to a pyogenic infection at all (and organisms cultured from a so-called midstream specimen of urine may be simply contaminants).

I frequently receive referral letters stating that a patient "has suffered from repeated urinary tract infections [*sic*] despite several courses of antibiotics, though the midstream specimens of urine are usually sterile." Each year I see on average two patients with advanced bladder tumour, one with genito-urinary tuberculosis, and one with bladder stones whose referral has been delayed by many months *only* because they were subjected to inappropriate and repeated courses of antibiotic therapy and the possibility of the true diagnosis never considered.

ROGER HOLE

North Ormesby Hospital,
Middlesbrough, Cleveland

Rise in antibodies to human papova virus BK and clinical disease

SIR,—Since the isolation of the human papova virus BK seroepidemiological studies have shown that infections with this virus are very common and often occur in children.¹ An accompanying clinical disease has not yet

been established, although a mild respiratory illness of children has been recorded at the time of appearance of antibodies against BK virus.²

We have investigated retrospectively serial serum samples from 77 patients which had been sent to our department for clinical virological examination. Three cases of primary BK virus infection, one in a child and two in adults, were found as indicated by the appearance of haemagglutination-inhibiting antibodies. The clinical findings and serological data on different days of the illness are shown in the table. Acute upper respiratory symptoms accompanied by neurological involvement occurred in all three patients.

Our findings suggest that primary infection by BK virus in older patients may be followed by acute inflammatory polyradiculoneuropathy (Guillain-Barré syndrome). It remains to be determined whether the BK virus is the aetiological factor. Seroconversions against other viruses (influenza A and B, adenovirus, respiratory syncytial virus, herpes simplex virus, echovirus 9, and measles virus) could not be detected. In one patient (the third in the table) a slight rise (<8 to 32) of complement-fixing antibodies against psittacosis was found.

A causal relationship between upper respiratory tract infections and inflammatory polyradiculoneuropathy has been extensively documented³ for a number of viruses and our findings suggest that BK virus may also be implicated.

J V D NOORDAA
P WERTHEIM-VAN DILLEN

Virus Laboratory,
University of Amsterdam

¹ Padgett, B L, and Walker, D L, *Progress in Medical Virology*, 1976, **22**, 1.

² Mantyjarvi, R A, et al, *Annals of Clinical Research*, 1973, **5**, 283.

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Further assessment of the normal cholecystogram

SIR,—Mr M H Gough (9 April, p 960) does not mention ultrasound in his excellent review of cholecystography. The value of ultrasound B scanning to assess the presence of calculi in the non-functioning gall bladder has been established.^{1 2}

It has become our practice to scan patients with a normal cholecystogram when the clinical symptoms are strongly suggestive of gall stones. Out of a large group of patients we have found gall stones in three when the cholecystogram appeared normal. At laparotomy two of these patients had gall stones but the third has not been explored. We have also detected calculi in the common bile duct in a patient with transient jaundice when a follow-up intravenous cholangiogram appeared normal. This patient had calculi in the duct when operative cholangiography was performed. The presence of pancreatitis in association with cholecystitis may also be demonstrated.

The majority of calculi are rapidly detected by conventional techniques and we do not

Clinical features and rise in BK virus antibody titre in three patients

Patient No	Clinical features	Age (years)	Rise in antibody titre
1	Upper respiratory tract infection, convulsions	3	<16 (day 3)→64 (day 13)
2	Respiratory infection, Guillain-Barré syndrome	45	<16 (day 9)→128 (day 24)
3	Respiratory infection, Guillain-Barré syndrome	33	<16 (day 13)→128 (day 28)