may slowly be redressed; but so long as deaths from all forms of gall bladder disease are less than 3 per 1000 deaths from all causes it is difficult to justify a theoretical operation rate of 200 per 1000 with a 1½% operation mortality giving us the same three deaths per 1000 as without operation. I have chosen the most favourable assumptions. It is not unlikely that the expectation of life of patients with gall stones is reduced whether or not they survive cholecystectomy. —I am, etc.,

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1 *Registrar General's Statistical Review for England and Wales 1965, pt. I Tables, Medical.* London, H.M.S.O., 1967.

Reactions to Practolol

SIR,—In vew of the recent reports of reactions to practolol, possibly on an autoimmune basis, we were interested to observe what we believe to be the first case of practolol-induced "shoulder-hand" syndrome.

A 64-year-old woman with ischaemic heart disease and myxoedema was admitted with angina. She had been treated for two years with practolol, bendrofluazide, slow-release potassium, digoxin, glyceryl trinitrate, doxepin, and thyroxine. Eight days after admission she developed symmetrical, hot, painful swelling of both hands. Practolol was stopped and the symptoms and signs regressed over three days. Reintroduction of practolol 10 days later was associated with reappearance of the signs and symptoms within 72 hours. These again regressed when the practolol stopped five days later.

Antinuclear antibodies were present in high titre but organ-specific antibodies were negative. We also noted that the serum alkaline phosphatase, aspartate aminotransferase, γ-glutamyl transpeptidase, and bilirubin levels rose during the acute attack and are now normal.—We are, etc.,

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Treatment of Herpes Simplex with Co-trimoxazole

SIR,—I had deliberately kept my previous letters on this subject as short and non-technical as possible. However, I should be grateful for the opportunity to reply to the points made by Professor D. H. Watson and Dr. D. Haigh (1 February, p. 271).

The method of testing the effect of trimethoprim on herpes simplex virus (H.S.V.) used in the microbiology department of Raigmore Hospital was as follows: human amnion cells were inoculated with H.S.V. and trimethoprim was added to three specimens in concentrations of 2000, 1000, and 500 μg/ml respectively. The highest concentration was found to be toxic to the cells; at the lower concentrations there was considerable reduction of cytopathic effect. As I pointed out (17 August 1974, p. 473) these levels are higher than the serum levels of trimethoprim that have proved therapeutically effective, but there is some evidence to suggest that levels of trimethoprim are higher in tissue than in serum when both are estimated simultaneously,[1] and particularly with virus infections the tissue level seems likely to be more relevant. It has also been pointed out by Bushby[2] that in investigating the effect of various drugs on H.S.V. in vitro the inoculum must be small and care must be taken that the medium does not contain significant quantities of end products of folate metabolism.

Over the past 11 years or so a wide variety of drugs have been reported as effective against H.S.V., either clinically or experimentally. These have ranged from antihistamines[3 4] to antimitotic substances,[5] but most interest has centred on cytarabine and idoxuridine, both being thought to work by interference with viral DNA synthesis.[6] In particular, Delamore and Prusoff[7] found that idoxuridine reduces the incorporation of ^{3}H-thymidine into DNA-thymidine, but they noted that the specific metabolic site primarily affected in any given tissue is characteristic for that tissue. Hall *et al.*[8] pointed out that viruses may induce new enzymes such as kinases and polymerases in infected cells, and Klemperer *et al.*[9] had already reported the finding of a virus-specific thymidine kinase in H.S.V.-infected cells. I had thought that I had already made it clear (4 January, p. 41) that the mode of action of co-trimoxazole against H.S.V. is as yet undetermined but that the similarity of the proportion of responders to that of subjects whose activated lymphocytes show inhibition by co-trimoxazole of their uptake of labelled thymidine[10] leads me to suspect that thymidine metabolism in the host may be a relevant factor. The report by Hall *et al.*[8] also stressed the probable importance of cell-mediated immunity in varicella infections, and in view of the close relationship between varicella-zoster virus and H.S.V. and the well-known finding that raised serum titres of H.S.V. antibody do not seem to confer any very noticeable protection against recurrent H.S.V. lesions it would seem logical to study the host cell at least as much as the virus.—I am, etc.,

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1 *Drugs*, 1971, **1**, 9.
2 Bushby, S. R. M., *Postgraduate Medical Journal*, 1969, **45**, Suppl. November, p. 10.
3 Vanamee, P., *Journal of the American Medical Association*, 1970, **211**, 830.
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7 Delamore, I. W., and Prusoff, W. H., *Biochemical Pharmacology*, 1962, **11**, 101.
8 Hall, T. C., *et al.*, *Transactions of the Association of American Physicians*, 1969, **82**, 201.
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Neonatal Hyperthyroidism and Long-acting Thyroid Stimulator Protector

SIR,—We read with interest the suggestion of Dr. J. Nutt and her colleagues (21 December, p. 695) that the case of L.A.T.S.-negative neonatal hyperthyroidism reported by Thomson and Riley[1] may have been due to long-acting thyroid stimulator protector (L.A.T.S.P.).

Serum was taken in November 1974 from the mother whose case was reported by Thomson and Riley.[1] Since the previous report the patient's clinical state and therapy had remained essentially unchanged. This serum was in fact found to contain readily detectable L.A.T.S.P.,[2] whereas L.A.T.S. was not detectable. The results were as follows:

Sample	L.A.T.S. Response in Mouse Bioassay (% initial blood ^{131}I at 16h, mean ± S.E.M. (n))	
Control for L.A.T.S. (control buffer, 1 ml)	89 ± 14 (3)	N.S.
Test for L.A.T.S. (patient's serum 1 ml)	88 ± 9 (3)	
Control for L.A.T.S.P. (human thyroid extract (H.T.E.) plus standard L.A.T.S.)	120 ± 4 (5)	P<0·025*
Test for L.A.T.S.P. (patients' serum 1 ml plus H.T.E. plus standard L.A.T.S.) ..	383 ± 73 (3)	
Standard L.A.T.S. ..	886 ± 104 (5)	

*Student's *t* test.

Thyroid-stimulating activity in the mother was also detectable in the radioreceptor assay for thyroid-stimulating immunoglobulins:[3]

Sample	^{125}I-Thyroid-stimulating Hormone Bound to Human Thyroid Membranes (%)
Patient's immunoglobulins (4 mg)	17·0
Normal immunoglobulins (4 mg)	20·9

Though almost 10 years have passed since the birth of the affected infant, we believe that this case provides evidence additional to that already reported[4 5] for a causal role of L.A.T.S.P. in neonatal thyrotoxicosis. The receptor assay data confirmed the presence of human thyroid-stimulating activity in this serum.—We are, etc.,

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1 Thomson, J. A., and Riley, I. D., *Lancet*, 1966, **1**, 635.
2 Dirmikis, S., *Journal of Endocrinology*, 1974, **63**, 427.
3 Smith, B. R., and Hall, R., *Lancet*, 1974, **2**, 427.
4 Nutt, J., *et al.*, *British Medical Journal*, 1974, **4**, 695.
5 Dirmikis, S. M., *et al.*, *Lancet*, 1974, **2**, 1579.

Tranquillizers Causing Aggression

SIR,—Your recent leading article (18 January, p. 113) referring to the possibility of benzodiazepine-induced hostility has prompted me to report a further example of this phenomenon, first reported in a patient in 1960.[1]

The patient was a 35-year-old married woman who had been subject to idiopathic epilepsy since her early teens. She developed depression in the puerperium at the age of 32 and had been taking various psychotropic drugs in addition to her usual anticonvulsants. For some months she had been taking diazepam 5 mg three times a day, but often abused the drug by increasing the dose. She suddenly developed aggressive behaviour, attacking her husband and smashing some windows at home

in the process. On admission to hospital there was no further aggressive behaviour, and the sudden alteration in the patient's conduct could not be attributed to any ictal or post-ictal events.

It is probable that in this case diazepam could be incriminated in the precipitation of aggressive behaviour. Though there was a long history of epilepsy, there was no evidence of alteration in epileptic status clinically, nor could personality deterioration be demonstrated. Further, E.E.G. recordings had been made 15 and four years previously, and a recent record revealed no deterioration. The E.E.G.s consistently showed paroxysms of polyspike activity, there being no indication of temporal lobe foci. It is, of course, well recognized that temporal lobe epilepsy or a temporal lobe abnormality carries an increased risk of personality disorder or behaviour disturbance.[2]

If drugs of the benzodiazepine group are occasionally responsible for the release of aggressive outbursts, then caution is necessary in their administration not only for anxiety and tension, but perhaps even more so in epileptic disorders, where diazepam in particular has gained some popularity on account of this combination of anxiolytic and anticonvulsant properties. Paradoxical reactions with excitement are already known to occur.[3]—I am, etc.,

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1 Ingram, I. M., and Timbury, G. D., *Lancet*, 1960, **2**, 766.
2 Herrington, R. N., *Current Problems in Neuropsychiatry, British Journal of Psychiatry Special Publication No. 4*, 1969.
3 Martindale, *The Extra Pharmacopoeia*. London, Pharmaceutical Press, 1973.

Postoperative Management after Thymectomy

SIR,—In their interesting paper on the management of thymectomy (8 February, p. 309) Dr. A. B. Loach and colleagues were unwise, in our view, to have proposed a critical level of 2 litres for the preoperative vital capacity with respect to the need for postoperative artificial ventilation. The number of patients in their study (21) is surely too small to justify such a conclusion. Indeed in their own series there was one exception, and of their eight other patients who required artificial ventilation no fewer than four had values for the vital capacity that lay so close to the "critical" level (one was actually 2 litres) that any confidence in it must be immediately undermined, given the variability inherent in the measurement. While the authors properly stress that other clinical factors must be taken into account when the vital capacity is close to the critical level, the concept of such a level is nevertheless likely to invite a false sense of security in those who choose to use it.

Dr. Loach and his colleagues suggest that there are two "safe" policies for management of the postoperative period—namely, either preoperative tracheostomy with artificial ventilation and withdrawal of anticholinesterases or (their own recommendation) an unchanged drug regimen in the postoperative period with tracheostomy selected principally on the preoperative vital capacity. We would like to propose an alternative which is in current use here. Nasotracheal intubation is undertaken at the time of induction of anaesthesia and anticholinesterase medication is substantially reduced or withdrawn for, like Osserman and Genkins,[1] we have usually found the drug requirements to be reduced postoperatively. An edrophonium (Tensilon) test is carried out daily to assess anticholinesterase requirements and the vital capacity is charted four-hourly. The patient breathes spontaneously oxygen-enriched air. If respiratory distress develops artificial ventilation is begun, and in some cases in which the vital capacity is low artificial ventilation is also instituted electively at night. After the fourth postoperative day a steadily increasing vital capacity is usually a sign that the tube may be removed.[2]

A potential drawback of our method is the discomfort associated with the presence of a nasotracheal tube, but in the event it has proved to be well tolerated. This management policy seems to us to retain the safeguard of a secure airway, which is lacking in the regimen proposed by Dr. Loach and his colleagues, while avoiding the morbidity associated with tracheostomy.—We are, etc.,

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1 Osserman, K. E., and Genkins, G., *Mount Sinai Journal of Medicine*, 1971, **38**, 497.
2 Newsom Davis, J., *British Journal of Hospital Medicine*, 1974, **11**, 933.

Unless the patient already has a tracheostomy we find that this procedure is seldom necessary. But in patients who have poor pulmonary function (for example, a vital capacity of less than 1·5 l), when the pleura was inadvertently opened at the operation, or when there is *any doubt* about adequate ventilation, then we never hesitate to leave the endotracheal tube in situ and to ventilate the patient for at least 48 hours. Analgesics are given liberally, but no other drugs. After 48 hours the cholinergic drugs are restarted and usually within 24-48 hours the patient can be weaned off the ventilator and may then be extubated. Otherwise, with careful supervision, the patient may remain thus intubated for 5-7 days. We have found it to be exceptional for the patient then to need tracheostomy.

Each patient is a problem on his own and only careful and continuous observation by experienced personnel will point the way to the dosage and frequency of the drugs and the need for assisted ventilation.[1-3]—We are, etc.,

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1 Lange, M. J., *British Journal of Surgery*, 1960, **48**, 285.
2 Lange, M. J., *Practitioner*, 1966, **196**, 448.
3 Lange, M. J., *Proceedings of the Royal Society of Medicine*, 1968, **61**, 751.

SIR,—We read the paper by Dr. A. B. Loach and others (8 February, p. 309) with interest and, while applauding the application of clinical measurement in patient management, we would like to make the following observations.

We agree that preoperative ventilatory function tests are of value in anticipating ventilatory support requirements in the postoperative period. However, the suggestion that a static vital capacity measurement of less than 2 litres (irrespective of sex and weight) is the principal criterion for a safe management policy in which 12 days of artificial ventilation via a tracheostomy becomes mandatory appears to us to be far too rigid.

Undoubtedly the advent of the intensive care unit, assisted ventilation, and the closest co-operation between clinician and anaesthetist has now made surgery of the thymus gland for myasthenia a relatively safe procedure. While we agree with many of the issues raised in the article, there are certain different approaches which we consider worth mentioning. These are best highlighted by briefly indicating our routine.

A prolonged inpatient spell to prepare the patient, and staff, thoroughly for thymectomy is considered wise.

The administration of cholinesterase inhibitors is continued right up to the time of the operation.

We believe it good practice that every patient undergoing thymectomy should be nursed for at least 48 hours in the intensive care unit.

It is our experience that cholinesterase inhibitors are not necessary in the immediate postoperative period. Careful observation will usually indicate their need within 6-12 hours after thymectomy. At such time the drugs may be restarted, usually in a reduced dosage.

Measurement of Neonatal Growth

SIR,—The studies of Dr. H. B. Valman and his colleagues (3 August, p. 319) and Dr. Sheila A. McKenzie (4 January, p. 38) have again drawn attention to the uncertainty which surrounds the question of optimum milk requirements for low-birth-weight infants in the early weeks of life.

One reason for this continuing uncertainty is a persistence in using weight gain as the main standard of reference for neonatal growth. In clinical practice weight gain is still the most widely used measure of neonatal growth, but it should not be relied upon as the sole measure since it can so readily be influenced by factors which are not generally considered to be growth, such as variations in the state of hydration, fat, and mineral accumulation.[1] In older children length or height is a most important measurement and in neonates it is a much better single criterion of growth than is weight since it is unaffected by the accumulation of water and fat.[1] Head circumference is also an important measurement in the neonatal period since it accurately reflects intracranial volume[2] and cellular brain growth.[3] It is difficult therefore to understand why these other measures of growth are so infrequently used in studies of infant growth and nutrition.

The accompanying figures illustrate the importance of evaluating growth of length and head circumference in addition to weight gain. These show the growth during the first month of life of 23 healthy preterm infants who were born between 28 and 32 weeks' gestation. The infants were fed either expressed breast milk or a modified cow's milk. Average daily milk intake between the 7th and 28th days was 204 ml/kg. The infants were weighed on an Avery scales accurate to 10 g, crown-heel length was measured with a Neonatometer,[4] and the