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 view of the recent reports of reactions to practolol, possibly on an auto-immune 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 $\mu\text{g}/\text{ml}$ 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 Bushby² 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 antimetabolic 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 Prusoff⁷ found that idoxuridine reduces the incorporation of ³H-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 Klempner *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 thymidine¹⁰ 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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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 Riley¹ 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 re-

port 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 $\pm$ S.E.M. (n))
Control for L.A.T.S. (control buffer, 1 ml)	89 $\pm$ 14 (3)
Test for L.A.T.S. (patient's serum 1 ml)	88 $\pm$ 9 (3)
Control for L.A.T.S.P. (human thyroid extract (H.T.E.) plus standard L.A.T.S.)	120 $\pm$ 4 (5)
Test for L.A.T.S.P. (patients' serum 1 ml plus H.T.E. plus standard L.A.T.S.)	383 $\pm$ 73 (3)
Standard L.A.T.S.	886 $\pm$ 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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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