patients susceptible to, but not initially complaining of, a chest infection.—I am, etc.,

P. L. ZACHARIAS

Liverpool

Keratoconjunctivitis Caused by Adenovirus Type 19

SIR,—We were interested in the cases of adenovirus type 19 keratoconjunctivitis reported from Belgium and Holland by Dr. J. Desmyter and others (16 November, p. 406). Though a few strains of this virus have been isolated elsewhere in Britain during 1973-4, it was not until July 1974 that it was first detected in Scotland. The patient, a male anaesthetist aged 52 years, first developed photophobia and "gritty" discomfort of the right eye and five to six days later the left eye became affected. Ophthalmological examination confirmed the diagnosis of keratoconjunctivitis with deep scleral inflammation. A conjunctival swab was submitted for virological examination and meanwhile treatment with chloramphenicol was instituted, with no effect. Though the episode lasted one month, the patient continued his normal duties throughout. An adenovirus, subsequently identified as type 19, was isolated in human amnion cell cultures.

This appeared to be an isolated incident. There was no relevant history of recent travel abroad or contact with a similar case. However, this does raise the question whether anaesthetists may be at special risk from their proximity to the face and oronasal secretions of their patients.—We are, etc.,

ELEANOR J. BELL

Regional Virus Laboratory,
Ruchill Hospital,
Glasgow

F. W. WINTON

Microbiology Laboratory,
Vale of Leven Hospital,
Alexandria, Dunbartonshire

Forecasting Subarachnoid Haemorrhage

SIR,—In your leading article (5 October, p. 6) you stress the importance of premonitory symptoms of subarachnoid haemorrhage and advise certain procedures to be performed in order to achieve early diagnosis and treatment of patients threatened by fatal intracranial bleeding from aneurysms.

In this connexion we want to draw attention to early sequential scintigraphy of the brain in patients suspected of cerebral arteriovenous malformation as a method of investigation which is free from complications, without inconvenience to the patient, and easy to perform, thus being well suited as a screening method also in outpatients. By this investigation a sequential visualization of an intravenously injected bolus of ^{99m}Tc -pertechnetate is obtained in its initial intracranial distribution. We have described a characteristic "starfish" configuration visualizing the pathological process in cerebral arteriovenous malformations when this technique is applied.¹

Sedzimir and Robinson² found that arteriovenous malformations were the underlying pathological lesion in spontaneous subarachnoid haemorrhage in 26.6% of patients in the age group 0-20 years and in

9.3% of all ages in a series of 1847 patients.

In order to forestall haemorrhage from intracranial arteriovenous malformations we recommend the observation of the initial symptoms of such lesions—epileptic seizures which have or have had focal traits or when focal cerebral signs are present; always unilateral, ipsilateral migrainous headache with or without sensory or motor symptoms; and epilepsy in combination with headache. In such cases early sequential scintigraphy should be of value as a preliminary investigation, though angiography should also be applied for confirmation or exclusion, even if the scintigraphic study is negative, as the experience with small arteriovenous malformations is as yet too limited. It is probable that some large saccular aneurysms may also be visualized by early sequential scintigraphy, but so far we have had no experience with such lesions.—We are, etc.,

BENT DE FINE OLIVARIUS

MORTEN BUHL

University Department of Neurology,

HANS HVID HANSEN

Radiophysical Department,
Isotope Unit
Radium Centre,
Aarhus Kommunehospital,
Aarhus, Denmark

¹ Buhl, M., *et al.* To be published.

² Sedzimir, C. B., and Robinson, J., *Journal of Neurosurgery*, 1973, 38, 269.

Effective Dosage of Tricyclic Antidepressants

SIR,—It is generally agreed that a standard dose of a tricyclic antidepressant will produce a larger than 15-fold variation in steady-state plasma levels in different subjects. The steady-state nortriptyline concentration is influenced by genetically determined factors and differing rates of metabolism and is also affected by the interaction of barbiturates and certain other drugs.¹

This enormous variability of steady-state plasma levels on standard dosage poses the question of the relationship of plasma level to therapeutic effect. Most studies have concentrated on nortriptyline.²⁻⁴ With this drug there is a consensus which supports the view that both too high and too low levels are associated with a poor clinical outcome. Though in most patients given 150 mg of nortriptyline the plasma level will fall in the therapeutic range, the clinician without access to steady-state plasma levels will be unable to decide whether to raise or lower the dose. Kragh-Sørensen *et al.*⁵ have shown in their very interesting prophylactic follow-up of endogenous depressives treated with nortriptyline that relapse occurred only in those patients with serum levels outside the therapeutic range.

Our knowledge of other tricyclic antidepressants is very sparse. For example, there has been only one systematic study on the most commonly used tricyclic antidepressant, amitriptyline.⁶ This reported a high positive correlation between plasma steady-state concentration and therapeutic outcome. It also indicated that the standard dose of amitriptyline (150 mg daily) was probably insufficient in half of the patients. Results like these suggest that we urgently need further investigations on these com-

monly used drugs in both acute and long-term therapy. These studies must provide systematic measures of the severity of the illness and use clearly defined diagnostic and descriptive criteria for the patient population studied. The drug under investigation must, of course, be accurately measured and differences that arise between different laboratories explored. It is probable that some of the discrepancies reported in the literature are the result of lack of attention to these points.

The tricyclic antidepressant drugs are clearly a potent therapy for certain groups of depressive illness but it is also very evident that much work remains to be done to establish the effective dose for each particular drug for the individual patient and also the optimum time for the patient to be maintained on the medication after recovery.—We are, etc.,

ALEC COPPEN

STUART MONTGOMERY

M.R.C. Neuropsychiatry Laboratory,
West Park Hospital,
Epsom

¹ Åsberg, M., *Nortriptyline in the Treatment of Depression*, Karolinska Institute Monograph, 1973.

² Åsberg, M., *et al.*, *British Medical Journal*, 1971, 3, 331.

³ Burrows, G. D., Davies, B., and Scoggins, B. A., *Lancet*, 1972, 2, 619.

⁴ Kragh-Sørensen, P., Åsberg, M., and Eggert-Hansen, C., *Lancet*, 1973, 1, 113.

⁵ Kragh-Sørensen, P., *et al.*, *Psychological Medicine*, 1974, 4, 174.

⁶ Braithwaite, R. A., *et al.*, *Lancet*, 1972, 1, 1297.

SIR,—Dr. G. D. Burrows and Professor B. M. Davies (30 November, p. 533) have given their reasons for questioning Professor M. D. Rawlins's assertion (12 October, p. 91) that the therapeutic activity of nortriptyline occurs *only* when the plasma concentration of the drug lies between 50 and 140 ng/ml [190 and 532 nmol/l]. There are other objections.

In the first place patients 15 and 28 of the series upon which Professor Rawlins's conclusion is apparently based¹ both did well though their plasma nortriptyline concentrations were 150 ng/ml [570 nmol/l] and 164 ng/ml [623 nmol/l] respectively. The mean plasma nortriptyline concentration of another group of patients from the same source² was 141 ng/ml [536 nmol/l], one patient only having a concentration less than 50 ng/ml and several doing well at levels between 140 ng/ml and 170 ng/ml [646 nmol/l]. Dr. Burrows and Professor Davies have patients who responded only to even higher concentrations of the drug. In yet another series³ of 45 patients who had received various doses of nortriptyline plasma nortriptyline concentrations were log-normally distributed over the same range, both for those who had progressed satisfactorily and those who had not. About half of both groups fell within the 50-140-ng/ml band. It follows that adjustment of dose to bring any particular "failed" case from outside to within this band may well not be beneficial after all.

The several methods of assaying nortriptyline in blood all demand scarce resources of laboratory skill and time and if, as I believe to be the case, the information gained is of doubtful value as a guide to most individual patients' requirements, then clinicians would do better to proceed according to the clinical response than to resort to