incidence of allergic complications than those with no detected antigen in blood.³ Furthermore, high concentrations of antigen in CSF at diagnosis with slow disappearance of antigen were associated with neurological damage. Thus, while I agree with the authors' two conclusions, which, I respectfully submit, are self-evident, there are well-known immunological techniques which can improve diagnostic accuracy and which also have some prognostic and epidemiological value.

L G EVANS-JONES

Department of Paediatrics,
Chester City Hospital,
Chester CH2 3EH

¹ Greenwood, B M, Whittle, H C, and Dominic-Rajkovic, O, *Lancet*, 1971, **2**, 519.

² Evans-Jones, L G, et al, *Archives of Disease in Childhood*, 1977, **52**, 320.

³ Whittle, H C, et al, *American Journal of Medicine*, 1975, **58**, 823.

SIR,—Drs Oliver Smales and Nicholas Rutter (3 March, p 588) have once again drawn attention to the difficulties in diagnosing meningococcal meningitis, particularly in an early infection or when antibiotics have been used.

The detection of meningococcal, pneumococcal, and haemophilus antigen by counter-current immunoelectrophoresis is a well-established diagnostic procedure, as efficient as Gram stain and culture combined, and cheap and easy to perform; and it gives an answer in 45 minutes.^{1,2} The technique is particularly valuable when antibiotics have already been given. It would have been interesting to know how the technique would have fared in the early cases that posed a diagnostic problem for Dr Smales and Dr Rutter.

ANTHONY BRYCESON

Hospital for Tropical Diseases,
London NW1 0PE

¹ Greenwood, B M, Whittle, H C, Dominic-Rajkovic, O, *Lancet*, 1971, **2**, 519.

² Whittle, H C, et al, *American Journal of Medicine*, 1975, **58**, 823.

SIR,—I am glad that Dr O R C Smales and Dr N Rutter (3 March, p 588) have called attention to the importance of a second lumbar puncture when the initial result is unexpectedly normal in patients clinically suspected of having meningitis. I have several times found a second sample taken within two or three hours to be grossly abnormal, perhaps because of layering in the spinal canal. If meningitis is strongly suspected clinically, it may be well worth while obtaining another specimen as soon as the normal report is received.

T H HUGHES-DAVIES

Central Hospital,
Honiara, Solomon Islands

Epilepsy and learning

SIR,—Your leading article on epilepsy and learning (3 March, p 576) suggests that school medical officers should have an opportunity to hear about pupils' learning problems from school teachers. This comes about only if the child is known to suffer from epilepsy. Parents do not necessarily share this information with the school. The school doctor can also be uninformed because both family doctors and hospital paediatricians increasingly consider medical information confidential.

Dr Dorothy M Sell (10 February, p 416) makes this point about sharing medical information in general about children with special educational needs. Information about an epileptic child with behaviour and learning problems in class is helpful; to know about epileptic children before they start a swimming lesson can be vital.

Incidentally, your reference to school doctors "of the new style" having particular schools is relevant only in the context of the DHSS circular you cite: it is a new style for the DHSS. Before 1974 it was the old style, and in the 14 years preceding 1974 I worked in four different parts of the country and always had my own particular schools. Most likely school doctors have had their own particular schools since 1907.

C R HAINES

School Health Service,
Cambridgeshire Area Health
Authority (Teaching),
Peterborough PE1 1YF

Stopping lithium prophylaxis

SIR,—Dr D G Wilkinson (27 January, p 235) reports withdrawal symptoms in a patient with bipolar manic depressive psychosis who had stopped taking lithium after taking it for six years.

In a controlled study of prophylactic treatment of alcoholism by lithium carbonate¹ 20 patients (11 depressed and nine non-depressed) took lithium for a mean time of 41.0 weeks. Each patient was examined at intervals of six weeks, and the lithium dose was adjusted to give serum concentrations of 0.8-1.2 mmol (mEq)/l. The mean lithium level was 0.86 (SE 0.03) mmol/l—0.91 (SE 0.05) mmol/l for non-depressed patients and 0.80 (SE 0.03) mmol/l for depressed patients. The lithium was abruptly withdrawn at the end of the study (mean time 41 weeks) and no withdrawal signs were reported by the patients.

While the withdrawal signs reported by Dr Wilkinson were diagnosed as an acute toxic confusional state, the description of the patient after stopping the lithium would fit the diagnosis of a bipolar manic depressive psychosis in relapse.

JULIUS MERRY

Department of Psychiatry,
Epsom District Hospital,
Epsom, Surrey KT18 7EG

¹ Merry, J, et al, *Lancet*, 1976, **2**, 481.

Early evidence of asbestosis

SIR,—I cannot agree with your expert's reply to the question about guidelines for examining employees of a building firm who handle asbestos (10 February, p 388), where it was stated that "the earliest evidence of asbestosis is seldom radiological." In examining workers one rules out biopsy or necropsy evidence which might show pulmonary fibrosis too slight to affect either radiological, physiological, or clinical findings. It is also assumed that your expert agrees that the presence of asbestos fibres or typical ferruginous bodies (asbestos bodies) in sputum can indicate only asbestos exposure and not asbestos disease.

I have just concluded a search of the literature since 1960 on the subject of early diagnosis of asbestosis. Seven papers which reported the findings of authors with extensive

experience of routine examination of asbestos workers¹⁻⁷ concluded that the use of high-quality x-ray films was the best means of routine surveillance. This can well be supplemented by simple lung volume measurements with a robust instrument such as the vitalograph. Regular comparison with the baselines provided by initial examinations enables each man to be used as his own control for early diagnosis.

W J SMITHER

Cape Group of Industries,
London W1Y 4AB

¹ Pilat, L, et al, *La Medicina del Lavoro*, 1971, **62**, 495.

² Cassan, G, et al, *Archives des Maladies Professionnelles, de Médecine, du Travail et de Sécurité Sociale*, 1973, **34**, 560.

³ Lewinsohn, H C, *Royal Society of Health Journal*, **92**, 2.

⁴ Beverley, W H A, *Journal of the Society of Occupational Medicine*, 1973, **23**, 61.

⁵ Weill, H, et al, *Archives of Environmental Health*, 1975, **30**, 88.

⁶ Weill, H, et al, *Archives of Environmental Health*, 1976, **31**, 172.

⁷ Smither, W J, in *Proceedings of the 3rd International Conference on Pneumoconiosis*, ed H A Shapiro, p 80. Cape Town, Oxford University Press, 1970.

* *Our expert writes: "The point I wished to make in my brief answer was that unlike, say, silicosis, in which the earliest non-invasive evidence is usually radiological, one should not rely on radiology alone as a monitoring check for asbestosis. Diagnosis of a condition in which the early radiological changes are slight and sometimes equivocal demands that as many other indices as possible should be looked for. Radiology apart, even with sophisticated lung function facilities I would still attach importance to auscultation of the chest for late inspiratory crackles. Details concerning early diagnosis are well discussed by Parkes.¹ I, of course, agree with your correspondent about the finding of asbestos fibres or ferruginous bodies in the sputum and, as in my original answer, I strongly endorse the value of pre-exposure baselines for the various tests."—ED, *BMJ*.

¹ Parkes, W R, *Occupational Lung Disorders*. London, Butterworths, 1974.

Minor hazard of amniocentesis

SIR,—Your leading article on the hazards of amniocentesis (16 December, p 1661) has prompted us to comment on what we have found to be a minor hazard associated with prenatal diagnosis. All laboratories engaged in chromosomal analysis from amniotic fluid cells have experienced, or at least are aware of, the problem of maternal cell contamination. We have recently experienced a source of "maternal cell contamination" hitherto unreported to the best of our knowledge.

A specimen was received labelled as amniotic fluid for chromosome analysis. A culture was initiated in the usual manner using the cell pellet from the specimen obtained after centrifugation. The cells were observed to be growing a few days after culturing, and had an epithelial-like appearance. This cell type from amniotic fluid usually undergoes senescence in a few weeks, and satisfactory chromosome preparation can be difficult to achieve if not obtained early.¹ The procedure used here for amniotic cell chromosome analysis is to subculture primary cultures once before harvesting the cells. Our attempt to subculture the cells from this specimen after approximately 10 days in culture was not successful.

Meanwhile, an aliquot of the fluid was sent to another laboratory for α -fetoprotein assay, as is the routine practice. This laboratory reported that there was no α -fetoprotein in the specimen, and that it

had a creatinine level of 2.30 mmol/l (26 mg/100 ml) and was presumably urine. This was confirmed by further examination in our clinical chemistry laboratory.

The cells cultured were presumably bladder epithelium. The diagnostic hazard is, of course, mistakenly concluding that the chromosome complement from such cells represents that of the fetus. Since these cells may be difficult to subculture, such an error may be more liable to occur in laboratories that examine metaphases in cell colonies from primary cultures. It is of interest that this sample was one of three of the 144 amniotic fluid specimens sent to our laboratory last year which were found to be urine. This occurred in spite of the fact that all of the amniocenteses were done with the aid of ultrasound by experienced obstetricians. It is often considered desirable for the patient's bladder to be full during this procedure, as it was in these cases, to buoy or support the uterus, especially when the placenta is anterior.² This may, of course, increase the risk of bladder puncture.

It is difficult to distinguish between urine and amniotic fluid because of the similarity in colour and appearance. An aliquot of supernatant should be tested for creatinine or urea content if the sample is suspected of being urine. Attempted cultures from all of the urine specimens we received would have been classified as culture failures if we had not been alerted by the laboratory doing our α -feto-protein determinations that the samples were not amniotic fluid.

RICHARD L NEU
J T LANMAN JUN
M WINGATE
ROBIN M BANNERMAN

Departments of Pediatrics, Medicine, and
Obstetrics and Gynecology,
State University of New York at Buffalo,
The Children's Hospital of Buffalo,
Buffalo, New York 14222

¹ Nadler, H L, and Ryan, C A, in *Human Chromosome Methodology*, ed J J Yunis, p 191. New York, Academic Press, 1974.

² Sandler, M A, Sznajda, S M, and Bitky, L L, *Radiology*, 1979, **130**, 195.

Hulka-Clemens clips

SIR,—Had the date of the recent article by Dr G A Clarke and others (10 March, p 659) been 1 April, I would have assumed it to be some sort of hoax. However, it cannot be allowed to pass without comment.

The Hulka clips are an unreliable method of sterilisation. In this unit we have seen two patients who have become pregnant after sterilisation in this manner over the last 12 months, the operations on both patients having been completed at the hospital which has unfortunately given its name to the clip applicator. For the authors of this article to postulate abdominal transmigration of sperm on such flimsy evidence is absurd. The reality of the matter is that this is just another straightforward failure of the Hulka clip.

N TRICKEY

Heatherwood Hospital,
Ascot, Berks SL5 8AA

"Outwith my competence"

SIR,—On 3 March the word "outwith" appeared at least twice in your correspondence columns (p 616, Mr F P Jones—"outwith the scrotum"; and p 621, Professor W St C Symmers—"outwith my competence").

What does it mean? Or rather, what extra meaning does it convey that the word "out-

side" does not? The reason I address this query to you and your readers is that I have noticed the word creeping into use over the last year or so and it has always been from the mouths or pens of doctors.

The Shorter *Oxford English Dictionary* says the word is "chiefly northern, now Scots," and 50% of the examples quoted above were indeed from Aberdeen. However, before the word is exported too widely to England and becomes 1979's most fashionable new usage perhaps its usefulness could be demonstrated or its use abandoned.

KARL SABBAGH

Richmond, Surrey

*"Outwith" is widely used in educated speech in both Scotland (Mr Jones) and Northern Ireland (Professor Symmers). We feel sure that Mr Sabbagh did not insist on Scotsmen and Ulstermen who contributed to his BBC programmes using exclusively "English" English. Nor do we do so in our correspondence columns, where we try to retain the individual flavour of the contributions.—Ed, *BMJ*.

Amitriptyline plasma concentration and clinical response

SIR,—We read with interest the paper by Dr S A Montgomery and others (27 January, p 230) entitled "Amitriptyline plasma concentration and clinical response." We agree that the relationship between "plasma concentrations and clinical response is more complex" for the antidepressants than would be expected. The diverse findings of several groups with amitriptyline illustrate this point. In addition to the studies quoted, Zeigler *et al*¹ found a negative correlation between plasma concentration (total amitriptyline and nortriptyline concentration) and clinical response in 18 outpatients; Kupfer *et al*² found a negative correlation between plasma concentration (total amitriptyline and nortriptyline concentration) and clinical response in 16 inpatients; Corona *et al*³ found a positive correlation between plasma concentration and clinical effect in 77 female patients; and Vandel *et al*⁴ found a curvilinear relationship in 62 patients. We would also agree that the investigation of this relationship is a difficult problem, the sources of variation pointed out by Dr Montgomery being those most likely to give differences between groups. There is a clear need to identify responders to tricyclic antidepressant therapy and to investigate relationships between plasma values and clinical response within this group.

Several specific points from Dr Montgomery's paper need clarification. Presumably the placebo period was five to seven days, long enough to eliminate "placebo responders." The response rate was 60%, which is the usual placebo response. Were patients who responded early in the trial continued on treatment until they had completed six weeks' drug treatment? The authors made a mathematical error in that 58%, not 72%, of patients were within the 80-200 μ g/l range. What percentage of patients inside the therapeutic range actually improved and what were the criteria of improvement? Did any patients outside the "therapeutic" range improve? What proportion of individuals had plasma values less than 80 μ g/l? All would agree that not enough drug does not produce the desired clinical response, and that these patients should not be included in the regression analysis. Were any attempts

made to titrate non-responding patients' plasma values to the "therapeutic" range and measure response? The mean values of plasma amitriptyline and nortriptyline are given to two decimal places. Surely these should be quoted at best only to the nearest 5 μ g/l. We assume that these values were measured using gas chromatography by the method of Dawling and Braithwaite,⁵ which has a precision of 2.5% at "therapeutic" concentrations. Were these all new patients or had some or all been previously reported? No simple relationship between plasma concentration and age was found in this study. Nies *et al*⁶ found that steady state levels of amitriptyline were influenced by age and sex. This may be an important source of variation between studies examining relationships between plasma concentrations and clinical response. The method of measuring plasma concentrations is another source of variation. Interlaboratory comparison of assays is required.⁷

This trial highlights the problems of studies attempting to correlate plasma values and clinical response. All clinicians would agree with the general findings of the results of the study. For endogenous depressions, not enough drug does not produce a therapeutic effect; too much drug may be associated with dangerous cardiac abnormalities.⁸ This disagreement between groups is primarily concerned with defining the upper and lower limits of tricyclic antidepressant plasma concentrations.⁹ For individual patients who respond to tricyclic antidepressants a relationship between plasma concentrations and clinical response has been demonstrated.¹⁰

T R NORMAN
G D BURROWS
K P MAGUIRE

Department of Psychiatry,
University of Melbourne,
Victoria 3050

BRUCE SCOGGINS

Howard Florey Institute,
University of Melbourne,
Victoria 3050

¹ Zeigler, V, *et al*, *Clinical Pharmacology and Therapeutics*, 1976, **19**, 795.

² Kupfer, D J, *et al*, *Clinical Pharmacology and Therapeutics*, 1977, **22**, 904.

³ Corona, G L, *et al*, *Pharmacopsychiatrie*, 1977, **10**, 299.

⁴ Vandel, S, *et al*, *European Journal of Clinical Pharmacology*, 1978, **14**, 185.

⁵ Dawling, S, and Braithwaite, R A, *Journal of Chromatography*, 1978, **146**, 449.

⁶ Nies, A, *et al*, *American Journal of Psychiatry*, 1977, **134**, 790.

⁷ Burrows, G D, *et al*, *Biochemical Medicine*, 1978, **20**, 125.

⁸ Burrows, G D, *et al*, *British Journal of Psychiatry*, 1976, **129**, 335.

⁹ Burrows, G D, *et al*, *Communications in Psychopharmacology*, 1978, **2**, 393.

¹⁰ Burrows, G D, *et al*, *Clinical Pharmacology and Therapeutics*, 1974, **16**, 639.

Blood specimen collection tubes for coagulation tests

SIR,—It has been brought to our attention that unsilicified glass tubes with liquid citrate are now marketed labelled "for coagulation studies." The Anticoagulant Control Panel wishes to emphasise that use of such tubes may cause inaccurate results of coagulation tests and therefore lead to an error in diagnosis or dangerous instability in the control of anticoagulant therapy.

Blood specimens for coagulation tests should be collected with a plastic syringe and transferred to a plastic tube containing 0.109 mol/l liquid trisodium citrate, which has been freshly added in the proportion of 1