study to test whether, for instance, sulphasalazine is better than placebo in rheumatoid arthritis. In deciding the sample size required to show a difference or that no difference exists between a possibly effective drug and placebo, a statistician requires to know the likely improvement rates both for the drug and for natural remission.

Another reason for publishing carefully conducted uncontrolled trials of this type is that they are feasible and plausible when they come from one hospital. It would be virtually impossible for a single hospital to muster sufficient suitable patients for a controlled study. Once more than one hospital or more than one clinician is involved disparities in case selection and patient management may vitiate the results of the trial. Once we enter the league of multicentre controlled trials we enter a morass of committee work, of anonymity, and often of two-year delays, in which the seeds of originality, such as the use of sulphasalazine, may fail to germinate or may germinate only to become blighted.

J M GUMPEL

Northwick Park Hospital,
Middx HA1 3UJ

Exercise training in chronic bronchitis

SIR,—We accept Dr J E Cotes's comments (15 March, p 795) that the allocation of patients to exercise and control groups was not randomised. To facilitate the weekly supervision of the exercise group it was necessary to allocate patients according to the geographical position of their homes; to exclude those outwith the city would have greatly reduced the number available for study. The role of the research nurse was to supervise the training and to encourage the patients to continue with their daily training programme. At the conclusion of the study the patients were asked to continue with daily exercise without further supervision. and were told that they would be reassessed in six to nine months' time. After a mean period of eight and a half months, 11 patients in the exercise group were reviewed. The mean 12-minute distance fell significantly from 1104.2 to 992.3 metres ($p < 0.005$). Although this value was greater than the mean 12-minute distance on entry to the study (886.5 metres), the difference was not statistically significant. In 10 patients the walking distance deteriorated, in the other it was unchanged. The mean 12-minute distance in the control group fell from 868 metres to 740 metres, but this was not statistically significant.

These patients did not continue to take regular exercise and the benefits of training were soon lost. For worthwhile improvement to be maintained supervision with constant encouragement, a role principally filled by the nurse, is essential.

We are concerned that your readers' assessment of our study may be unduly influenced by the letter from Dr N R Andersson (29 March, p 942). His criticisms are largely invalid and demonstrate a lack of understanding and misinterpretation of our results. We have clearly stated that all patients were cigarette smokers and were advised to stop at the beginning of the study. As changes in this habit are never predictable it is not surprising that the number who gave up smoking was different in the two groups, but it is hardly something we could control. We referred to the

results of a study of unsupervised exercise in patients with chronic bronchitis¹ and stated the object of our study was to determine whether close supervision would lead to an improvement in exercise rehabilitation. We believe that the value of close supervision has been confirmed.

In the exercise group one patient died and two failed to complete the study while in the control group three patients died, not a drop-out of five and six as stated by Dr Andersson. Recruitment of patients took place over a period of months; as the total time available was limited not all subjects were studied for 12 months, a number completing follow-up after six months—hence the difference in the numbers at the initial and final assessment.

The difficulties of recruiting patients, of repeated physiological testing, and of funding the close supervision of a group of patients with a chronic disabling disease imposed limitations on this study and should be sufficient reason, for those with practical experience of these difficulties, to refute the jibe of "rushing to publication."

DAVID J M SINCLAIR
C G INGRAM

Department of Clinical Measurement,
Ninewells Hospital,
Dundee DD1 9SY

¹ McGavin CR, Gupta SP, Lloyd EL, McHardy GJR. *Thorax* 1977;32:307-11.

Indomethacin treatment of postural hypotension

SIR,—The letter from Dr I B Davies and others (19 January, p 181) prompts observations and questions concerning management of the common problem of hypotension in the elderly where simple causes have been excluded.

A prostaglandin-like substance, probably PGE_2 , was released into the renal venous blood when angiotensin II was infused experimentally into the renal arteries of dogs. Release of the prostaglandin-like substance coincided with recovery of renal blood flow and it seemed that PGE_2 might be functioning as a regulator.¹ Drugs such as indomethacin may restore falling blood pressure, and following the paper of Kochar and Itskovitz² seven or eight elderly patients with postural hypotension were treated in this department with indomethacin, the dose varying from 25 mg to 50 mg thrice daily, with elevation in blood pressure and lessening of symptoms.

All these patients had had troublesome falls of systolic and diastolic blood pressure levels of more than 20 mm Hg on standing, without acceleration of the heart rate and often with syncope. Most had an abnormal Valsalva response, pyramidal signs, and some features of Parkinsonism; continence was variable. Serum potassium levels were normal, or if low were corrected without benefit. Poor hydration was corrected and supporting stockings were provided. Cerebellar abnormalities were not seen; none had obvious neuropathy or recent severe ischaemic heart disease. Plasma volume, aldosterone, catecholamines, and metabolites were not estimated. Whether our patients suffered from an incomplete or variant form of the Shy-Drager syndrome we cannot say, and they were not studied as meticulously as those of Professor Abate and his colleagues.³

Flurbiprofen may have a more potent blocking effect than indomethacin⁴: the percentage inhibition of PGE_2 production is reported to be greater than with indomethacin. A small number of our patients were changed from indomethacin to flurbiprofen but did

less well. Other non-steroidal anti-inflammatory agents may well influence hypotension, and one must look forward to the effects of these being studied, perhaps by those with the resources available at St Mary's Hospital, London, and in Wisconsin and Bologna.

R L G SUTCLIFFE

St Edmund's Hospital,
Northampton NN1 4DS

¹ McGiff JC, Crowshaw K, Terragno NA, Lonigro AJ. *Circ Res* 1970;26-27, suppl 1:121-30.
² Kochar MS, Itskovitz HD. *Lancet* 1978;ii:101-4.
³ Abate G, Polimeni RN, Cuccurullo F, Puddu P, Lenzi S. *Br Med J* 1980;ii:1466-8.
⁴ Perkins CM, Lee MR. *Lancet* 1978;ii:1058.

Unrecognised dehydration during parenteral nutrition

SIR,—When drawing attention to the importance of allowing correctly for the water content of certain solutions administered intravenously, Drs R W G Prescott and J C Stoddard (22 March, p 847) failed to emphasise another, more important, cause of inadequate fluid replacement, which I have often seen and which their article illustrates.

In two of their three cases the rise in plasma sodium concentration is shown in the table as having occurred in association with a *positive* water balance and a *negative* sodium balance. There is no way in which this can occur, as both changes lead to hyponatraemia. On the assumption that the plus and minus signs are correct, the explanation would seem to lie in the statement that "... taking insensible losses into account, the fluid replacement was inadequate." This, presumably, was a retrospective assessment, the insensible losses having been ignored when the fluid balance was calculated in order to formulate treatment. It is this which would have been the prime cause of the hypernatraemia, as the cumulative effect of the insensible losses over five days would have far exceeded the 700-1200 ml overestimation of the water intake. To explain the data given, the insensible losses would have to have been very large.

G WALTERS

Department of Chemical Pathology,
Bristol Royal Infirmary,
Bristol BS2 8HW

Bladder cancer as a prescribed industrial disease

SIR,—The article by Sheena N Somerville and others (23 February, p 540) and their letter (22 March, p 867) drew attention to a possible under-claiming for social security benefits in respect of industrially induced primary neoplasm of the epithelial lining of the urinary tract. While we have no other evidence that under-claiming for this prescribed disease (No 39) occurs, the following advice may nevertheless improve the present state of affairs.

If a consultant considers that one of his patients has the condition he should advise him to seek the help of the local office of the Department of Health and Social Security. The patient will then be afforded every assistance in completing a claim form and the office will try to confirm the occupational history. With the patient's consent his clinical history will be obtained from his GP or from hospital, as seems most suitable. A consultant's opinion, normally from the one in clinical

charge of his case, will be obtained on the claim. I would endorse the article's warning against advising patients that their claims are likely to succeed, as in some cases this may well give rise to unjustified hopes. There is useful information in the booklet *Notes on the Diagnosis of Occupational Diseases*.¹

It is only if the relevant occupational exposure occurred subsequent to 5 July 1948 that cases will be dealt with as claims to PD 39 under the Social Security Act 1975. If the industrial exposure was before 5 July 1948 a different scheme applies. Under the post-July-1948 scheme the major benefit is based on disability; but under the pre-July-1948 scheme benefit is related to total or partial incapacity for work.

Because the carcinogens responsible for causing urothelial tumour were withdrawn from industrial use in the early 1950s, the number of cases should show a decline over the next decade.

F J DARBY

Department of Health and Social Security,
Keysign House,
London W1R 2HT

¹ Department of Health and Social Security. *Notes on the diagnosis of occupational diseases*. London: HMSO, 1979.

Management of acute illness in infants

SIR,—Few would disagree with the recommendations of Dr A N Stanton and others (29 March, p 897) from their uncontrolled study of children admitted to hospital that "daily reassessment by a professionally qualified person should be the normal practice when a child has major symptoms."

I wish they had made the point that a doctor with adequate postgraduate training in paediatrics should be able to appreciate the significance of the behavioural and other symptoms often elicited by careful history taking. Before calling on the unspecialised health visitor to remedy yet another lacuna in the services we should ensure that all general practitioners have, within the setting of a hospital team, an experience of serious illness in infancy and childhood which enables them to acquire the clinical judgment and competence to assess the sick young child in the first place.

Health education of parents is another way in which avoidable infant deaths may be reduced; but while the doctor can advise and inform parents he himself must first be adequately trained.

E B KNIGHT-JONES

Newark, Notts

Interaction between oral contraceptives and other drugs

SIR,—I should like to make some comments concerning the paper by Drs Janet F Bacon and Gillian M Shenfield (2 February, p 293).

They have suggested that the decreased blood levels of steroids associated with co-administration of rifampicin and oral contraceptives is due to an interruption in the entero-hepatic circulation of steroids. However, administration of rifampicin causes proliferation of the smooth endoplasmic reticulum of the hepatocyte and induces drug-metabolising enzyme systems in the liver (the cytochrome P450 content of the liver is increased). Steroid

hormones are eliminated mainly by metabolism in the liver. Hence the hepatic clearance (or rate of removal from the body) of steroid hormones is increased when these are given in conjunction with enzyme-inducing agents such as rifampicin, phenobarbital, glutethimide, and phenytoin.^{1,2} An increase in hepatic clearance results in decreased plasma levels of the drug.

This mechanism of drug interaction is a common one and may explain the reported results.

HELEN M BURT

Faculty of Pharmaceutical Sciences,
University of British Columbia,
Vancouver, Canada

¹ Acocella G. *Clin Pharmacokinet* 1978;3:108-27.

² Gibaldi M. *Biopharmaceutics and clinical pharmacokinetics*, 2nd ed. Philadelphia: Lea and Febiger, 1977:109-51.

Multiple sclerosis: what can and cannot be done

SIR,—The difference between the poor result (75% success) obtained with the erythrocyte electrophoretic mobility (E-UFA) test¹ in Göttingen referred to by Drs S Poser and W Poser (19 January, p 184) in their comments on our paper (15 December, p 1591) and the excellent results of coded trials in England,² Italy,³ and America⁴ led us to conclude that the difference must lie in the biological material. Since many German patients with multiple sclerosis (and most errors were among this group) were currently, or recently had been, under heavy medication with adrenocorticotrophic hormone (ACTH), as well as other drugs, while we ourselves had always worked with cases currently free from corticosteroid treatment, we made a specific study of the effect of ACTH on the E-UFA test result. This has shown that a positive result in multiple sclerosis is converted into a negative one after a few days' treatment and that this false result persists for about three weeks after cessation of the steroid course. On the other hand, a patient not having multiple sclerosis initially giving a negative result with the E-UFA test converts to a positive one, which again persists for three weeks.⁵ This phenomenon, incidentally, affords an explanation for the very short life (5-10 minutes) of ACTH in the blood, there being rapid adsorption on to the red blood cell surface. Early or untreated cases were not available in Göttingen, nor were mothers for confirmatory testing.

The Posers alone advance Thompson's heuristic hypothesis⁶ to the status of a "proved fact." Our own results can only be interpreted as supporting it. Dr J H D Millar (19 January, p 184) points out that the value of γ -linolenate—based on the supposition, now discarded,⁷ of its immunosuppressive activity—is not yet substantiated. There is no doubt that γ -linolenate alters the character of the red blood cell membrane,⁸ and the original anomaly is not due to a plasma factor.⁹ The real value of the E-UFA test lies largely in early diagnosis, and above all in prophylaxis⁷ and the possibility of setting up a controlled trial among children singled out as "multiple sclerosis candidates" before myelin is fully laid down. Encouraged by the confirmations cited above, we formally propose that a positive E-UFA test be added to the Schumacher criteria for diagnosis of multiple sclerosis.

The Posers pass over the critical analysis by Seaman *et al*⁴ of recorded false results and

choose to ignore Claude Bernard's warning¹⁰ about the importance of all the details of investigative procedures. They take a very selective and unsophisticated view of myelin constitution, neglecting all-important steric considerations. So far as the inability of Seaman *et al* to pick up a few patients with (unspecified) "minimal neurological findings" is concerned, note should be taken of Fog's opinion¹¹ that "the percentage of false diagnosis of multiple sclerosis is about 20% . . . and in both directions," and the similar uncertainties expressed by Bauer at the same symposium. Dr Millar was present at this symposium and accorded his assent. We too have patients referred by both general practitioners and consultants who cannot make up their minds early in the disease (and sometimes late).

E J FIELD
GRETA JOYCE

Multiple Sclerosis Research Unit,
Newcastle upon Tyne NE1 7RU

¹ Field EJ, Joyce G, Smith BM. *J Neurol* 1977;214:113-27.

² Field EJ, Joyce G. *Lancet* 1977;ii:658.

³ Bisaccia G, Caputo D, Zibetti A. *Boll Ist Sieroter Milan* 1977;56:583-8.

⁴ Seaman GVF, Swank RL, Tamblyn CH, Zukoski CF jun. *Lancet* 1979;ii:1138-9.

⁵ Field EJ, Joyce G. *IRCS Med Sci* 1980;8:82.

⁶ Thompson R. *Biochem Soc Symp* 1973;35:103-11.

⁷ Field EJ. *J R Soc Med* 1979;73:487-8.

⁸ Field EJ, Joyce G. *Europ Neurol* 1978;17(2):67-76.

⁹ Field EJ, Joyce G. *Lancet* 1979;ii:1012-3.

¹⁰ Bernard CM. *Introduction à l'étude de la médecine expérimentale*. p 27-8. London: Ballière et fils, 1865:27-8.

¹¹ Fog T. *Acta Neurol Scand* 1974; suppl 58:50.

Treatment of meningitis

SIR,—Dr P J Geiseler (23 February, p 566) in making a case against the administration of antibiotics before lumbar puncture to patients with clinically diagnosed meningitis quotes his review¹ of 1316 cases of community-acquired purulent meningitis. This is a most impressive number of cases and the study could yield some worthwhile information. As his paper is in press, perhaps Dr Geiseler would be good enough to say whether in his study he looked at the effects of corticosteroids on the survival rate in bacterial meningitis. It would be very interesting and most useful to know what percentage in his study were treated with corticosteroids, and particularly what percentage of the 103 fatal cases had been given corticosteroids before death.

Some clinicians are not convinced that any advantage from the administration of corticosteroids in severe life-threatening meningitis has been demonstrated² and Dr Geiseler's review might provide that evidence.

J S CARGILL

Department of Pathology,
Victoria Hospital,
Blackpool, Lancs FY3 8NR

¹ Geiseler PJ, Nelson KE, Levin S, Reddi KT, Moses VK. *Rev Inf Dis* (in press).

² Anonymous. *Br Med J* 1979;iii:953.

* * * We sent a copy of this letter to Dr Geiseler, whose reply is printed below.—ED, *BMJ*.

SIR,—In response to Dr Cargill's inquiry, we did not study the effects of corticosteroids on survival in our review of 1316 cases of community-acquired bacterial meningitis. It would have required a controlled study, which was not performed.