relapse the particular treatment was stopped and deemed a "treatment failure," and treatment with inhaled and oral bronchodilators was started until clinical stability was regained before the next treatment period began. In cases where the exacerbation was considered to be due to a chest infection appropriate treatment was given until clinical stability returned, then the interrupted period was restarted and continued for a full three weeks.

Thirteen patients required intervention with additional bronchodilator therapy during at least one of the four treatment periods because of significant symptomatic deterioration in the absence of chest infection. Thus 24 of the 100 treatment periods were adjudged to be "failures"—nine during the placebo period, eight during salbutamol, six during theophylline, but only one during combined treatment with theophylline and salbutamol. Chest infections necessitated interruption of treatment on only six occasions. Using "treatment failure," when it occurred, or daily peak flow rate readings when treatment periods were completed in full, we ranked each treatment period in order of preference to permit between treatment comparisons with Friedman's test. Combined theophylline-salbutamol therapy was better than placebo ($p < 0{\cdot}001$) and salbutamol ($p < 0{\cdot}002$) but not theophylline; theophylline was better than placebo ($p < 0{\cdot}012$) but no different from salbutamol or combination therapy; and salbutamol was no different from placebo.

Thus patients with chronic bronchitis and airways obstruction appeared to derive more benefit from combined therapy with inhaled salbutamol and oral theophylline than from either drug alone. This would appear to indicate an important role for theophylline in this type of patient and, contrary to Dr Cochrane's advice (15 December, p 1644), would suggest that theophyllines should be used before inhaled β_2 agonists and inhaled anticholinergics have both proved ineffective. This study also illustrates the need to assess therapy in some clinically meaningful way pertinent to the circumstances in which the drug is likely to be used.

D G McDevitt

Department of Pharmacology and Clinical Pharmacology,
Ninewells Hospital and Medical School,
Dundee DD1 9SY

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SIR,—I read with great interest the leading article by Dr G M Cochrane (15 December, p 1643) and Dr W V Evans's paper on theophylline (p 1649). I have recently measured the serum theophylline concentrations of 20 patients receiving long term treatment with oral sustained release preparations of theophyllines in general practice.

A "therapeutic" serum concentration of theophylline is usually taken as 10-20 mg l.[1 2] Only two of the 20 patients had a therapeutic blood value (mean 12·2 mg l); the remaining 18 had subtherapeutic blood concentrations (mean 6·2 mg l). I examined the subtherapeutic group in closer detail and attempted to increase their dose of theophylline to ensure a therapeutic serum concentration. In five I suspected non-compliance; two other patients had suffered adverse effects on a higher dose and their dose had been reduced; and among the remaining 11, in whom the dose was increased, only four could tolerate it and seven could not. In this survey 19 out of 21 patients had a subtherapeutic level and when their dose was increased poor patient tolerance was a major limiting factor. I therefore support the view that the routine, indiscriminate use of theophyllines is hard to justify.

D W Brown

Wakefield WF2 6DP

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ABC of poisoning: psychoactive drugs

SIR,—I see that Drs John Henry and Glyn Volans are still advocating gastric lavage in tricyclic antidepressant poisoning for up to 12 hours after the overdose (10 November, p 1292). This opinion is, in my view, outdated and not supported by any hard clinical evidence that (*a*) this procedure results in recovery of meaningful amounts of unabsorbed drug from the stomach or (*b*) it reduces total drug absorbed. I accept that some benefit may be obtained up to four hours, but I challenge the authors to produce any data which show worthwhile recovery of ingested tricyclic antidepressant drugs after this time. Gastric lavage is not without risk: in a recent study in Newcastle upon Tyne (in press) two patients with tricyclic antidepressant poisoning suffered cardiac arrests shortly after gastric lavage and the vast majority of patients in the study had falling plasma concentrations from the time of admission.[1] So why do it?

M G Bramble

Middlesbrough General Hospital,
Middlesbrough,
Cleveland TS5 5AZ

1 Bramble MG, Lishman AH, Dissey B, Purdon J, Hall RJC. An analysis of plasma levels and 24 hour ECG recordings in tricyclic antidepressant poisoning: implications of management. *Q J Med* (in press).

**The authors reply below.—ED, *BMJ*.

SIR,—We thank Dr Bramble for raising this important issue and, indeed, we were pleased to provide the laboratory analyses for his study.[1] Nevertheless, we feel that the view which he puts forward is insufficiently supported with evidence on which we could change our advice concerning the use of gastric lavage for poisoning by tricyclic antidepressant drugs.

We do not have evidence that clinically important amounts of these drugs are removed from the stomach by lavage and regret that, through no fault of Dr Bramble, his study has failed to prove the converse since the necessary samples were not collected. Similarly while we accept that two of his patients suffered cardiac arrest shortly after lavage, we are not aware that others have described the same problem with tricyclic antidepressants, and our day to day monitoring of cases reported to the National Poisons Information Service has not reinforced his suggestion that the procedure is any more dangerous than is already acknowledged. We are not suggesting that every patient presenting up to 12 hours after overdose should receive gastric lavage. The decision to go ahead with this procedure, even in patients presenting early, should be based on clinical evidence that a large quantity of drug has been taken. Several workers believe that lavage is appropriate several hours[1-3] and even up to 24 hours after ingestion,[4] and this seems reasonable to us on present evidence since these drugs inhibit gastric emptying.

Dr Bramble's paper, which we have not yet seen in its final form, should be taken as a hypothesis which needs to be further tested. We should be pleased to discuss with others the design of any study proposed to investigate this problem and will provide the necessary laboratory facilities for analysis of samples provided by gastric aspirate lavage and blood.

Glyn N Volans
John A Henry

Poisons Unit,
New Cross Hospital,
London SE14 5ER

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Prevalence of migraine in patients with diabetes

SIR,—We have read with considerable interest the observation of Ms Burn and colleagues that the prevalence of migraine in diabetic patients is less than that in the normal population.[1] Some of our previous observations may be relevant to this fact.

We have previously shown that while cerebral blood flow and its age related decrease in diabetic patients and normal subjects is similar, cerebrovascular reactivity in diabetics is abnormal.[2 3] For example, cerebral blood flow increases after carbon dioxide challenge in normal subjects, whereas in over half of diabetic patients it either falls or does not increase. Carbon dioxide is the most potent dilator of cerebral blood vessels, and the absence of its dilatory effect on cerebral vasculature in diabetics indicates a fundamental fault in the ability of this vasculature to respond to enhanced metabolic requirements. Since cerebral vasodilatation is an essential component of the pathogenesis of migraine, the impaired ability of cerebral vasculature to dilate is probably important to the relative "protection" of diabetic patients from developing migraine.

The mechanism underlying the diminished vasodilatory capacity of cerebral vasculature in diabetics is probably very complex. Diminution in the secretion of prostacyclin (PGI_2) in diabetes mellitus may appear to be an obvious contributory mechanism, as suggested by us previously.[2 3] However, PGI_2 infusion in the human has been shown to cause a fall in cerebral blood flow.[4] Whether this PGI_2-induced fall in cerebral blood flow is due to a diffuse vasodilatation which results in a "steal" from cerebral vasculature or whether it is the direct result of a paradoxical vasoconstriction of cerebral vessels requires further elucidation. Changes in blood glucose concentrations have not hitherto been associated with altered vascular reactivity, but fatty acids and other lipids probably do contribute to alterations in the response of vascular smooth muscle to vasoactive agents.[5] Fatty acids also inhibit the secretion of PGI_2[6] and accelerate its degradation.[7]

The role of platelets in the pathogenesis of migraine, especially in terms of the "protection" offered by diabetes mellitus, is even more perplexing. Activation of platelets, platelet hyperaggregability, and the release of vasoactive substances from platelets have all been incriminated in the pathogenesis of migraine.[8] Platelets are known to be hyperactive and hyperaggregable in diabetes mellitus and release more thromboxane A_2,[9] especially when macrovascular disease is concomitantly present.[10] Yet diabetes mellitus offers protection from migraine. This would suggest that the answer to the diabetic's "protection" from migraine lies not in platelets but in blood vessels themselves.

P DANDONA
I M JAMES
A G BECKETT

Departments of Chemical Pathology and Human Metabolism,
Clinical Pharmacology and Medicine,
Royal Free Hospital and School of Medicine,
London NW3 2QG

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Leptospirosis?

SIR,—I read with interest the case of fatal intracerebral haemorrhage associated with leptospirosis reported by Dr Margaret A Forwell and her colleagues (8 December, p 1583). The authors clearly presented a clinical case of intracerebral haemorrhage; however, their diagnosis of leptospirosis is not proved. Indeed, there are several aspects of the bacteriological and serological findings that would prejudice their diagnosis.

The bacteriological evidence does not support a diagnosis of leptospirosis let alone confirm it. The authors claim that leptospires were "seen" but not isolated from the blood of the patient. The membranes of red blood cells are often mistaken for leptospires by inexperienced workers; these "pseudo-leptospires" will mimic the characteristic morphology and "paddle wheel" motility of leptospires.[1] Therefore leptospires cannot be identified solely on morphological appearance.

Guinea pigs were inoculated with the patient's blood and subsequently died. At necropsy the animals showed pathological changes typical of leptospiral infection and leptospires were "confirmed" by Dieterel's method. Fibrils from healthy renal tissues will often be mistaken for leptospires, and a paper recently presented at the Commission of the European Council for Veterinary Research (Baskerville A, Belfast 1984) showed conclusively the gross inaccuracy of relying on histological evidence to support the diagnosis of leptospirosis. He showed that what appeared to be leptospira like organisms stained by Dieterel's method could be seen in tissues from accredited gonobiotic guinea pigs.

Finally, several serial samples of the patient's serum showed no serological evidence of infection; neither IgG nor IgM antibodies were detected. The authors quote the work of Adler and Faine[2] in support of the absence of antibodies in their patients despite their evidence of leptospira in the patient's blood. Adler and Faine do not state that serological tests may give negative results even in proved infection; on the contrary, they state that antibodies are detected in all cases where the organisms have been isolated from the patient's blood, and IgM is always shown. The authors' patient did not produce IgM after three weeks of illness.

A positive diagnosis of leptospirosis can only be made with the bacteriological isolation of leptospires and a fourfold rise on serological testing. Therefore the paper by Dr Forwell and others does not prove that the patient described either suffered from leptospirosis or died of its complications.

SHEENA WAITKINS

Leptospira Reference Unit,
Public Health Laboratory Service,
County Hospital,
Hereford HR1 2ER

1 Rahman M, Macis FR. Pseudo-leptospires in blood culture. *J Clin Pathol* 1979;**32**:1226-7.
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Tuberculosis in health service staff

SIR,—The leading article by Dr Freda Festenstein (17 November, p 1327) draws attention to the continuing risk to health service staff from tuberculosis and highlights the need for careful procedures to prevent the disease in this group. As suggested, occupational health services, where they exist within the NHS, are well placed to implement such preventive measures.

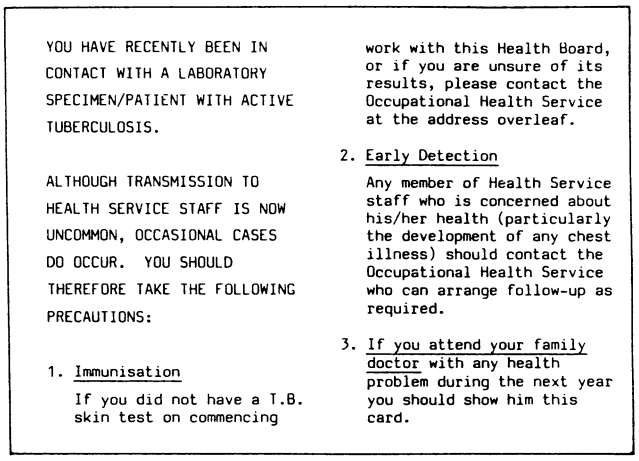
Even where careful procedures have been established, however, many health authorities still perform routine chest radiography on employees who have had casual contact with an open case of pulmonary tuberculosis. This x ray examination is normally carried out several weeks after the exposure and comes to be accepted by staff as a reassurance that all is well. Evaluation of about 4000 chest radiographs taken for this purpose over five years within the Greater Glasgow Health Board area detected no cases of active tuberculosis, yet a small number of employees continued to develop the disease related to occupational exposure. These findings suggest that routine radiographs in these circumstances did not contribute substantially towards early detection of the disease. Other factors to be considered include: possible unnecessary exposure to radiation; the false sense of security implied by a normal radiograph; and the overall cost of the procedure. At the same time, employing authorities have a duty under the Health and Safety at Work, etc, Act (1974) to inform employees about specific risks to which they are exposed at work, and the offer of routine chest radiography does not satisfactorily fulfil this requirement.

For these reasons a tuberculosis contact card was designed (see figure) to inform the employee of his exposure; to identify those whose tuberculin state is in any doubt; and to act as a reminder to both the employee and his family doctor that tuberculosis could be a possible cause of ill health during the ensuing months. In most cases the issue of an individual contact card has acted as a substitute for the routine chest radiograph in the follow up of casual ward contacts in staff. There may, of course, be special circumstances where closer surveillance would be appropriate. The arrangement, now in operation for one year, is currently being evaluated and may be of interest to others concerned with the health and safety of NHS staff.

IAN S SYMINGTON

Occupational Health Service,
Greater Glasgow Health Board,
Glasgow G1 1JA

SIR,—Dr M S Gatley (12 January, p 162) has taken my comments on the presence of a strongly positive tuberculin reaction (17 November, p 1327) out of context, implying that I suggested that such a reaction should raise the suspicion of current infection in all cases. This is certainly not so, and I would refer to previous correspondence on this subject.[1] The importance of the tuberculin reaction must be judged according to the individual circumstances—for example, age, BCG state, and history of tuberculous



YOU HAVE RECENTLY BEEN IN CONTACT WITH A LABORATORY SPECIMEN/PATIENT WITH ACTIVE TUBERCULOSIS.

ALTHOUGH TRANSMISSION TO HEALTH SERVICE STAFF IS NOW UNCOMMON, OCCASIONAL CASES DO OCCUR. YOU SHOULD THEREFORE TAKE THE FOLLOWING PRECAUTIONS:

1. Immunisation

If you did not have a T.B. skin test on commencing work with this Health Board, or if you are unsure of its results, please contact the Occupational Health Service at the address overleaf.

2. Early Detection

Any member of Health Service staff who is concerned about his/her health (particularly the development of any chest illness) should contact the Occupational Health Service who can arrange follow-up as required.

3. If you attend your family doctor with any health problem during the next year you should show him this card.

Tuberculosis contact card