bradycardia with 2·4 mg adenosine given for supraventricular tachycardia.[5]

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SIR,—We were interested to read the report by Dr Christer Sylvén and colleagues (26 July, p 227) of angina-like pain after bolus injections of adenosine in normal subjects.

We have recently studied the symptoms and cardiorespiratory effects of over 40 adenosine infusions in nine normal subjects. With its plasma half life of about 10 seconds[1] steady state plasma concentrations of adenosine can quickly be achieved. Adenosine was infused for at least five minutes in doses ranging from 40 to 120 μg/kg/min and caused dose related increases in pulse rate and resting ventilation without changes in systemic blood pressure.[2,3] During these infusions symptoms of anxiety, chest and abdominal discomfort, backache, jaw ache, and headache developed at infusion rates above 80 μg/kg/min, and their severity was thereafter dose related. These symptoms and the tachycardia were the factors that limited the higher infusion rates. Characteristic of the symptoms was their colicky nature, lasting for 30-45 seconds and occurring at intervals of 45 to 120 seconds. Other than tachycardia there were no abnormalities on simultaneous electrocardiographic records at any infusion rate.

Six of these subjects were given 60% oxygen or air to breathe in a single blind manner during adenosine infusion. Oxygen reduced both the cardiorespiratory stimulation and the symptoms caused by adenosine. In these six subjects the effects of adenosine were compared before and after intravenous theophylline or a saline placebo (given randomised and double blind; mean plasma theophylline levels 9·5 (SD 0·9) mg/l). Theophylline reduced both the cardiorespiratory and symptomatic effects of adenosine when given by infusion, as Dr Sylvén and colleagues found with injections of adenosine (although it is unfortunate that they did not compare the effects of theophylline with those of a placebo).

Adenosine infusion therefore establishes an important characteristic of the symptoms caused by this nucleoside which studies of bolus doses could not reveal. The colicky nature of the symptoms, their reduction or disappearance with an increase in inspired PO_2, and their reduction or absence after administration of theophylline raise doubts about the hypothesis of Dr Sylvén and colleagues that angina may be due to the stimulation of adenosine receptors. Angina is not classically colicky, and theophylline is not noted for its relief or prevention of angina. Although oxygen is used in the management of angina, it is given primarily to assist hypoxic myocardial tissue and is not always effective in relieving angina.

The protean manifestations of angina pectoris often make it a syndrome difficult to diagnose without the knowledge of other characteristics of the pain such as precipitating and relieving factors. Adenosine has widespread effects in the body and there are numerous receptors within the thorax that may cause pain. In certain circumstances adenosine may stimulate gastrointestinal smooth muscle,[4] and, as the authors implied, these symptoms of adenosine administration could equally be those of gastrointestinal pain. We feel that their recent hypothesis must remain in the realm of speculation.

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Opiate withdrawal: inpatient versus outpatient programmes

SIR,—I would like to make the following observation on the paper by Dr Michael Glossop and colleagues (12 July, p 103).

The authors stated that "all (patients) were physically dependent on opiates," and that the mean dose of methadone "required for withdrawal" was 37·5 mg/day. No further information is given as to how physical dependence was determined or how the methadone requirement was calculated. In practice it is often found that little or no methadone is required to suppress any abstinence syndrome.[1] One possible reason for the relative failure of the outpatient group might have been that some patients significantly increased their daily opiate intake over a prolonged period, thus engendering, rather than reducing, their dependence.

Secondly, the paper gives no indication of how long a period of abstinence was confirmed by urine analysis for the groups being compared. Fifty five per cent of the outpatient group remained in contact with the clinic, compared with 29% of the inpatient group. If one assumes that all those lost to follow up are using drugs again (the gloomiest, but most plausible, explanation) five weeks drug free as an inpatient would appear to be antitherapeutic for many patients.

Thirdly, urine analysis for drugs is notoriously unreliable. No mention is made of the authors' response to isolated positive findings in the absence of other evidence of drug use.

Finally, it seems disingenuous of the authors to compare their study with that of Edwards and Guthrie, as their paper is methodologically far less sophisticated. Edwards and Guthrie: (*a*) excluded those of poor prognosis and those unwilling to be randomly entered to their trial; (*b*) detoxified inpatients and outpatients over the same time period; (*c*) mobilised community resources to help in treatment; (*d*) followed up their sample for 12 months.

Failure to establish "neurophysiological dependence"; failure to randomise patients to treatment groups, using different withdrawal regimens for the two groups; and failure to provide significant psychosocial support for the outpatient group make it very hard to accept either the clinical or the policy implications of the study.

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AUTHORS' REPLY—Many of Dr McBride's criticisms appear to be due to a hasty reading of our paper since several are already answered in the text. Some of his points, however, are due to his misunderstanding the purpose of our study.

Firstly, determining the presence of physical dependence and assessing the dose requirements for withdrawal are fundamental problems for all who are clinically involved with these issues. In the absence of any definitive or agreed procedures, repeated opiate positive urine results plus the presence of clinical signs and self report data were all of some use in these tasks. Further information on methods of determining dependence and establishing methadone requirements at this clinic are given elsewhere.[1] The existence of the opiate withdrawal syndrome is well documented. It would be unfortunate if Dr McBride's suggestion was interpreted to mean that abrupt and unmodified withdrawal was an appropriate method of detoxifying opiate addicts. He suggests that the outpatient groups may have been using extra drugs without our knowledge. This would have been possible only if they had been using extra methadone, since any other opiate or non-opiate drug would have been detected by the urine analysis that was conducted at each clinic attendance. In any case additional drug use would have increased the failure rate for the outpatient programmes and would have reinforced rather than weakened our conclusions.

Secondly, Dr McBride appears to be confused about the aims of our study. This is clearly stated in the first sentence of the Discussion. We were comparing methods of getting opiate addicts off drugs. We were not looking at ways of preventing subsequent relapse. These two phases of treatment are known to be independent,[2] and detoxification alone is known to be ineffective as a means of preventing relapse.[3]

Thirdly, on what basis does Dr McBride assert that urine analysis for drugs is "notoriously unreliable"? The DHSS guidelines of good clinical practice state that urine analysis is a necessary and centrally important part of diagnosis.[4] Our own procedures, which require the passing of specimens under supervision, and analysis based on chromatographic methods backed up with the more sensitive glucuronidase hydrolysis, have always proved reliable. Perhaps Dr McBride could suggest a better objective means of detecting the use of drugs? Our results were not based solely on urine analysis but used other clinical data to suggest the use of drugs. Urine analysis was used as a confirmatory measure.

Finally, (*a*) our study clearly included subjects willing to be randomly allocated to the different treatment options and our results showed this not to have a significant effect (paragraph 2, Results); (*b*) the different time periods for the inpatient and outpatient programmes are discussed in both paragraph 2 of the Methods section and paragraph 4 of the Discussion; (*c*) our paper is obviously not intended to challenge the findings of Edwards and Guthrie.[5] We refer to that important

and influential paper because we are also comparing inpatient versus outpatient treatment techniques (albeit with entirely different clients). We acknowledge that the outpatient programme in our study was less intensive than that of Edwards and Guthrie (paragraph 3 in Discussion) and that more intensive outpatient methods may lead to improved outcome (final paragraph, Discussion); (*d*) again, Dr McBride appears to have misunderstood the purpose of our study. We were evaluating the success of different detoxification procedures per se and neither intending nor attempting any long term follow up study.

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SIR,—We would like to take issue with the statement by Dr Michael Gossop and others (12 July, p 103) that methadone reduction is "agreed to be the most effective and safe technique currently available" for withdrawal.

Several papers in recent years have compared detoxification from opiate addiction by gradually decreasing doses of oral methadone with abrupt withdrawal of opiates and supression of the withdrawal syndrome by clonidine.[1-4] In terms of withdrawal discomfort and numbers of patients completing detoxification the two procedures have proved equally effective. In only one of the four studies quoted[2] was withdrawal discomfort worse in the clonidine treated group, and in only one of these studies[3] did any patients transfer to methadone reduction.

In contrast to clonidine, methadone reduction prolongs withdrawal from opiate dependence. The withdrawal period in Dr Gossop's study was 21 days for inpatients and 56 days for outpatients. A clonidine detoxification programme, in contrast, need take only 10 days for withdrawal from methadone[5] and less for withdrawal from heroin.[6] This has important implications for early entry to an abstinence orientated treatment programme and also for the issue of cost effectiveness that Dr Gossop and his colleagues raise in their introduction.

An additional advantage of clonidine over methadone is its lack of potential for abuse. There is consequently no danger of resale on the black market when it is prescribed to outpatients. A proportion of the methadone prescribed to outpatients is probably used in this way, thus effectively maintaining unregistered addicts.

The only significant limitation to the usefulness of clonidine is its hypotensive effect. This limits the use of effective doses and, in our view, restricts its safe prescription to inpatient detoxification programmes, although it has been widely used for outpatients in the USA.[5] Lofexidine, a clonidine analogue with much lower hypotensive potency, has proved effective in open trials.[7-9] We are currently conducting a double blind comparison of clonidine and lofexidine in the suppression of opiate withdrawal. Our own experience has convinced us of the value of a clonidine detoxification programme,[10] and we have now used it successfully for almost three years.

Certainly methadone reduction is "the most commonly used withdrawal procedure for opiate addicts." However, it does not warrant this position of popularity and is not uncontested. We believe that clonidine offers definite advantages over methadone reduction and should therefore now provide the preferred treatment for opiate withdrawal.

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Backache and the Guillain-Barré syndrome

SIR,—The Lesson of the Week by Drs J E Clague and R R MacMillan (2 August, p 325) is correct but should be accepted with caution. Back pain can occur with the Guillain-Barré syndrome and this cannot be disputed. However, there is no way of accurately predicting which patients with backache are likely to develop Guillain-Barré syndrome and therefore the backache is of little or no diagnostic value without the presence of neurological symptoms or signs, and it is only retrospectively that the pain can be attributed to acute demyelination of the peripheral nerves.

A general practitioner with an average list of 2000 patients will see 200 cases of backache each year.[1] The incidence of backache in the general population is about 10 000/10.[5] The incidence of Guillain-Barré syndrome is about 1·7/10,[5] and between 10%[2] and 55%[3] of patients will have muscle pain or, less commonly, localised backache. One of the paper's main references[3] reported that in only four of 29 cases (14%) was pain the most prominent early symptom, three cases had transient low backache on the day of, or the day before, the onset of the weakness, and pain preceded weakness by one to five days. The likelihood of a patient presenting with localised backache after being diagnosed as having Guillain-Barré syndrome must be about one in 20 000 to one in 50 000.

Secondly, as there was such a direct relation with heavy lifting to the onset of backache in the second case, and the interval between the onset of pain and the demonstration of neurological signs was so long, the pain may not have been related to the Guillain-Barré syndrome or indeed may have precipitated the Guillain-Barré syndrome.

Finally, one of the most important pointers to the diagnosis of Guillain-Barré syndrome is a preceding upper respiratory tract or gastrointestinal viral infection, which occurs in 60%-70% of cases[4] and hence provides the alternative name "acute idiopathic postinfectious polyneuropathy."[5] No comment on preceding infection was made.

As the Lesson of the Week is often read with particular interest and remembered, it would be unfair to give the impression that the most important point or "take home" message is, "Guillain-Barré syndrome should be considered in the differential diagnosis of back pain"; rather the message should be that "Guillain-Barré syndrome should be considered when backache is associated with neurological signs, especially within a few weeks of a viral illness."

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Prevalence of multiple sclerosis in a south London borough

SIR,—In their assessment of the prevalence of multiple sclerosis in a south London borough (26 July, p 237) Drs Edward S Williams and Ronald O McKeran arrived at an estimate of 115/100 000—the third highest in the United Kingdom.

If whole families in which a proband with multiple sclerosis occurs are examined, as strongly recommended by Charcot,[1] then the prevalence of multiple sclerosis, wherever studied, becomes much greater. We may be sure that the disease is much more widespread than would appear from the number of patients who are diagnosed.

In a study of 473 English families 19 mothers out of 275 studied and 2 out of 133 fathers had clinical multiple sclerosis.[2] Thus 21 out of 408 parents of a proband themselves had multiple sclerosis (5·15%); and if we take the usually accepted figure for prevalence as 60/100 000 (certainly too low) then this means that the prevalence of multiple sclerosis in the parents of a proband was $(100\,000/408)\times 21\times(1/60)=85{\cdot}8$ times as common as in the general population. For siblings of a proband the corresponding figures were $8/319=2{\cdot}51\%$ and $(100\,000/319)\times 8\times(1/60)=41{\cdot}8$ times as common among siblings as in the general population.

However, when we included in the estimate of multiple sclerosis the multiple sclerosis diathesis brought out by laboratory testing[2] then among the parents of a proband clinical and potential multiple sclerosis was 188·5 times as common as in the general population; and for siblings it was 245 times as common. In the absence of a specific test for multiple sclerosis, as opposed to multiple sclerosis diathesis, it is impossible to say how many people with multiple sclerosis diathesis do in fact