exploring the sexual behaviour of patients where this may be clinically appropriate or an opportunity for preventive intervention exists; and two way communication between general practitioners and consultants in genitourinary medicine.³ Coincident infection with HIV and other sexually transmitted infections, particularly those that cause genital ulceration, has been cited as a major cause of increased transmissibility of HIV.

If only out of self interest, the insurance industry should consider the long term consequences of underwriting procedures on the important sexual health promotion activities that are possible in general practice.⁴ Now that we have better epidemiological evidence about the spread of HIV, the Association of British Insurers is in a position to re-evaluate its dogged adherence to pre-existing practice. In 1993-4 the Kensington, Chelsea and Westminster health district had 1186 HIV positive residents who consulted HIV services. Their general practitioners knew of the diagnosis in only 761 of these patients.⁵ If the British insurance industry still believes that it needs protection from HIV then it should recognise that the use of general practitioners at the underwriting stage is as helpful as a condom with a large hole in it.

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*We did not receive any letters in support of P H Smee's view that insurance companies should have access to patients' records. —EDITOR

Treatment with clozapine

Black patients' low white cell counts currently mean that they cannot be treated

EDITOR,—Clozapine, an atypical antipsychotic drug, has been proved to be effective in the pharmacological management of schizophrenia that is resistant to treatment. Up to 30% of people with schizophrenia may benefit from receiving this drug because of non-response to or intolerance of typical antipsychotics (J Kane *et al*, American Psychiatric Association's annual meeting, 1995).

A major side effect of treatment with clozapine is a potentially fatal agranulocytosis. As a result, patients' white cell counts have to be monitored before and during treatment. Patients can start the drug and continue with treatment only if their white cell count is $>3.5 \times 10^9/l$. This mandatory surveillance is administered by the drug's manufacturers through the Clozaril Patient Monitoring Service.

In reviewing the use of clozapine at Springfield Hospital we have found that these haematological restrictions are more likely to affect black African and African Caribbean patients than other patients: effectively, half of all such patients put forward for clozapine treatment at this unit have been unable either to start or to continue treatment because of a "red alert" (table 1). During the same period no red alert was issued for a white patient. This is of particular concern

Table 1—Number of patients for whom "red alert" was issued because white cell count was $<3.0 \times 10^9/l$ or neutrophil count was $<1.5 \times 10^9/l$ during monitoring by Clozaril Patient Monitoring Service

Time of blood test	Red alert
Before treatment:	
Black African and African Caribbean (n = 21)	5
White (n = 40)	0
During treatment:	
Black African and African Caribbean (n = 16)	4
White (n = 35)	0

as in our catchment area, the London boroughs of Merton and Wandsworth, the prevalence of schizophrenia among the black population is up to four times that among the local white population.¹ Reports have indicated that some ethnic minorities are at greater risk of agranulocytosis induced by clozapine and that this may be linked to certain HLA subtypes.² Our data, however, raise concerns about the normal ranges for white cell counts and neutrophil counts used by the Clozaril Patient Monitoring Service.

It has been established that African and African Caribbean patients have an apparently low white cell count and neutrophil count because of margination.³ Consequently, alternative normal ranges have been proposed for this population and are taken into account in ordinary haematological clinical practice. For example, for African men a suggested "normal" range is $2.8-7.2 \times 10^9/l$ for the white cell count and $0.9-4.2 \times 10^9/l$ for the neutrophil count.³ Currently, counts at the lower end of these ranges would prevent a patient from starting clozapine treatment or lead to the immediate withdrawal of established treatment. Surely it is now time for the Clozaril Patient Monitoring Service to review its normal ranges so that African and African Caribbean patients are not barred from this treatment on the grounds of their ethnic background alone.

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Reply from Clozaril Patient Monitoring Service

EDITOR,—We have been aware for some time that the strict haematological limits used by the Clozaril Patient Monitoring Service may exclude patients who normally have low white cell counts from receiving clozapine. Lawton *et al* reported "normal neutropenia" in an Afro-Caribbean patient taking clozapine and expressed similar concerns to those raised by Nigel Fisher and Barbara Baigent.¹ In answering Lawton *et al* we explained why the safety limits were set so strictly and provided data to support the hope that black Afro-Caribbeans are not at increased risk of agranulocytosis while taking clozapine despite their lower neutrophil counts before treatment and higher rates of neutropenia during treatment.² More recently, account has been taken of ethnic origin in patients with benign neutropenia.

The Clozaril Patient Monitoring Service was established because of the unusual history of clozapine. In 1975 the drug was withdrawn voluntarily from several countries after the occurrence of 16 cases of agranulocytosis, eight of which were fatal.³ Recognition of the drug's efficacy in schizophrenia led to calls for its reintroduction with mandatory haematological monitoring. The haematological limits used by the Clozaril Patient Monitoring Service were deliberately set with a margin of safety to protect the majority of patients irrespective of ethnic background. These limits, however, are arbitrarily defined and should not be portrayed as normal ranges.

Over the past five years this rigorous monitoring has successfully minimised mortality due to agranulocytosis. Analysis of 6316 patients taking clozapine showed a cumulative incidence of agranulocytosis of 0.8% over four and a half years, with just two deaths.⁴ Recent (unpublished) analysis of 11 000 patients treated over the first six and a half years since the drug's introduction adds further reassurance, as the rates of neutropenia and agranulocytosis have remained consistent and no further associated deaths have occurred.

Now that this body of data has been established it is reasonable to start exploring whether the safety limits can be selectively relaxed under controlled conditions. It will be necessary to show that any such relaxation is not associated with unacceptable excess risk. This may open up the possibility of treatment for an important minority of patients who cannot currently receive clozapine because of presumed benign neutropenia due to their ethnic origin. In the meantime, we must ensure that the principle of the greatest good for the greatest number is not sacrificed.

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Physical therapy has little effect on acute low back pain

EDITOR,—In his article on back pain in the ABC of work related disorders Malcolm I V Jayson advocates that "physical therapy should be arranged if symptoms last for more than a few days."¹ Apart from the major impact that this would have on resources for physical therapy in the NHS, such an emphasis is ill advised in the light of evidence on the effectiveness of physical therapy. Exercise therapy does not shorten the course of acute low back pain or influence disability and absence from work.^{2,3} Back schools in primary care have not been proved to have any beneficial effect, while assessment is needed of the cost effectiveness of intervention in companies along the lines of the "Swedish back school model" for patients with acute and recurrent low back pain.⁴ Research into the effectiveness of manual therapy in low back pain may have shown some beneficial effect initially, but that effect disappears within weeks when comparison groups are studied.⁵ This result is consistent with the generally good prognosis of low back pain.

When the potential side effects of physical therapy (such as dependency) and the cost are taken into account there is not enough evidence to promote the maintenance of physical activity in the acute phase of low back pain.

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Use of interferon beta 1b for multiple sclerosis

Patients will put up with side effects because of their desire to beat the disease

EDITOR,—As a physician who has both multiple sclerosis and a doctorate in clinical pharmacology, I am probably in a unique position to answer Peter Harvey's question of why interferon beta 1b was licensed.¹

Multiple sclerosis, particularly the relapsing-remitting form, is a notoriously difficult illness on which to perform clinical trials. This probably accounts for the large number of initially promising treatments that later proved to be useless. To my knowledge, interferon beta 1b is the only treatment that has been shown to have a significant beneficial effect on multiple sclerosis in large randomised controlled trials. If one reads the results of the trials carefully (as Harvey obviously has) it is apparent that the drug is not the panacea that the popular press would lead us to believe that it is. It also has unpleasant side effects. These are the reasons why I do not take it myself. Its development and the trial methods, which used magnetic resonance imaging, have, however, led to hope of better treatments to come and better ways of evaluating them.

Harvey has not taken into account another important factor, which is the desperate desire of people with multiple sclerosis (and their families) to do something to treat the disease. This desire becomes especially strong during an acute relapse. Unless something better is discovered before then, I will probably end up taking interferon beta 1b after my next bad relapse.

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- 1 Harvey P. Why interferon beta 1b was licensed is a mystery. *BMJ* 1996;313:297-8. (3 August.)

Manufacturer defends the drug

EDITOR,—It was disappointing to read Peter Harvey's letter dismissing the value of interferon beta 1b in the treatment of patients with relapsing-remitting multiple sclerosis.¹ Harvey takes no account of the results of controlled clinical trials showing a significant reduction in severity and frequency of relapses (up to 30-50%),^{2,3} with the most severe cases benefiting most, or of the accumulating data showing that generally there is a reasonable correlation between findings on magnetic resonance imag-

ing and clinical status.³⁻⁵ Individual cases do not render the overall evidence invalid.

Harvey fails to recognise that a reduction in the frequency and severity of attacks can make an immense difference to the quality of life of a patient with multiple sclerosis. It can mean the difference between being able to work or not, being able to go shopping or not, and between independence or reliance on others. To dismiss these improvements as inconsequential does a disservice to both patients and the drug.

While it is true that some patients experience side effects, such as flu-like symptoms in the first few weeks of treatment, simple measures can be taken to minimise this; in our experience the dropout rate due to side effects in the first six months of treatment is of the order of only 3%. The issue of neutralising antibodies is not a simple one as suggested by Harvey, and antibody titres do not correlate strongly with a reduction in the drug's effectiveness. Above all, it must be a clinical judgment whether an individual patient should continue treatment, depending on the benefit received.

As clinical experience with interferon beta 1b increases I hope that those who adopt polarised positions will come to modify them. In the meantime, Schering will put the evidence forward by whatever means possible, including in the *BMJ*; this is especially important when contacts of any kind with the company are spurned, as in Harvey's case. It is patients who stand to suffer by being denied an effective treatment.

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Importance of relapses must not be underestimated

EDITOR,—Peter Harvey asserts that patients with multiple sclerosis are interested in disability and, by implication, are not interested in relapses.¹ While many patients with multiple sclerosis cope successfully with relapses, for a considerable proportion of patients relapses are frequent and severe, causing great distress and disruption to normal life. It is strange to condemn the first licensed product to show an effect on relapses because it has not also been shown to affect disability without acknowledging the importance of relapses in patients' lives.

Equally, it is rather negative to place so much emphasis on the side effects of this drug without giving equal weight to the potential benefits. Experience even before the product was licensed in 1995 shows that patients with multiple sclerosis are capable of weighing the evidence on treatments and reaching rational conclusions; hence the lack of the feared stampede for interferon beta 1b. The Multiple Sclerosis Society has put great effort into ensuring that the evidence has been available to patients in a balanced and intelligible form and has looked to doctors to do likewise.

Harvey's view is incapable of defence without better evidence than anecdote from the narrow context of the clinic. In Britain the shortage of neurologists means that few neurologists can afford extensive contact with their patients with multiple sclerosis, and the waiting times for outpatient appointments and admissions ensure that patients are rarely seen by their consultant during an exacerbation. It is not surprising, therefore, that the importance of relapses to patients is often underrated by British neurologists, and this may go some way to explaining the differences in levels of prescribing of interferon beta 1b between Britain and other countries.

Harvey falls into the same trap as the authors of the landmark studies of interferon beta^{2,3} in making assumptions about the treatment priorities of patients with multiple sclerosis. In the context of carefully designed, multimillion dollar clinical trials it seems strange to those of us in daily contact with large numbers of patients that neither investigators nor pharmaceutical companies have sought firm evidence on this. Given the current range of possibilities, would patients with multiple sclerosis prefer their relapses to be treated or not? This is an important issue that has not yet been investigated, even though further costly large scale trials continue to be advocated. The Multiple Sclerosis Society is interested in potential collaborations on this question and would be pleased to hear from others of like mind.

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Practice in endoscopic cholangiopancreatography in Denmark differs from that in Britain

EDITOR,—Jacob Rosenberg and colleagues' conclusion that premedication with metoprolol prevents myocardial ischaemia during endoscopic cholangiopancreatography has important implications for routine technique in this procedure.¹ The applicability of this finding to current clinical practice in Britain, however, is unclear since there are considerable differences between the British Society of Gastroenterology's guidelines and the practice in this Danish study.²

In the study group patients did not receive preoxygenation with supplemental oxygen, morphine rather than pethidine was used as the opiate, and larger doses of hyoscine bromide were used than is common in Britain. The use of lignocaine spray in heavily sedated patients is also contrary to the British Society of Gastroenterology's advice. The high incidence of myocardial ischaemia (53%) and the presence of myocardial infarction in the relatively small group of 19 patients treated with placebo suggests that placebo conditions may have been substantially suboptimal. Continuous monitoring of blood pressure during endoscopic cholangiopancreatography is currently not routine in many centres in Britain but would clearly be necessary if premedication with a β blocker was used.

The study highlights the importance of tachycardia and illustrates the risk of myocardial ischaemia, but further data will now be required to determine whether premedication with metoprolol improves safety in patients receiving