- 1 Steinberg H, Sykes EA. Introduction to symposium on endorphins and behavioural processes. *Pharmacol Biochem Behav* 1985;23:857-62.
- 2 Markoff RA, Ryan P, Young T. Endorphins and mood change in long-distance running. *Med Sci Sports Exerc* 1982;14:11-5.
- 3 Dale G, Fleetwood JA, Weddell A, Ellis RD, Sainsbury JRC. β Endorphin: a factor in "fun run" collapse? *Br Med J* 1987;294:1004.
- 4 Haier RJ, Quaid K, Mills JSC. Naloxone alters pain perception after jogging. *Psychiatry Res* 1981;5:231-2.
- 5 Janal MN, Colt EWD, Clark WC, Glusman M. Pain sensitivity, mood and plasma endocrine levels in man following long-distance running. *Pain* 1984;19:13-25.
- 6 Baekeland F. Exercise deprivation: sleep and psychological reactions. *Arch Gen Psychiatry* 1970;22:365-9.
- 7 Marlatt GA, Gordon JR, eds. *Relapse prevention*. London: Guilford Press, 1985.

Peaks and troughs in demands on hospitals

SIR,—Dr M F H Bush may well be right that the occurrence of peaks and troughs in demand for hospital inpatient care has received little attention from planners and managers (12 March, p 786), but the attention that has been given has produced results partly at variance with his conclusions.

Firstly, the daily demand for emergency admissions should theoretically follow a Poisson rather than a normal distribution, and this has been confirmed in practice.¹ The fact that Dr Bush's observations in three specialties show variances very close to the corresponding mean suggests that this is probably also the case in East Suffolk. This would have some effect on the calculated number of beds to provide for admissions on 95% of occasions, particularly when the mean number of daily admissions is less than 10 or so, as occurs in two of the specialties presented.

Furthermore, Dr Bush has used two sided probability inappropriately, since the "mean and two standard deviations" approach excludes about 5% of a normal distribution in both tails together rather than just the upper tail. On half of his one day per three weeks there would be less demand rather than more. The specialties would expect to find difficulty on less than one day every six weeks, rather than one day every three weeks.

Finally, Dr Bush has suggested a model of bed use which is almost certainly not representative of reality.² In particular, no account is taken of the fact that bed occupancy as a phenomenon is dynamic rather than static. In the very trivial case, if daily emergency admissions were constant, each with a fixed length of stay, the number of admissions would balance the number of discharges every day, and no beds would need to be free (other than for part of a day to cover the change over). Dr Bush's model, however, would necessitate a number of beds kept free in advance equal to the number of admissions. In reality, it is the variation in numbers of emergencies from day to day and the variations in length of stay from one admission to the next which create the uncertainty and lead to beds sometimes being left unused. This capacity is plainly necessary, but overestimating the need by applying an inadequate model is unlikely to be helpful.

What then can be done to examine the need for capacity to cope with fluctuations in demand for admission? Firstly, bed occupancy can be modelled by a simulation technique, taking account of varying patterns of admission, discharge, length of stay, and day case work; this detailed and time consuming technique is capable of yielding a wealth of information. Alternatively, comparison can be made between local values for a range of bed use indicators and the corresponding values found in most other districts. Certainly it is desirable to examine the data carefully for accuracy, to be aware of particular local features, and to avoid using single indicators in isolation; further detail on emergency as against elective admissions would

also be useful. Comparison should preferably be with median values and certainly not with either extreme of the range. With these provisos, it is difficult to see how the approach can be decried as fundamentally unsound.

The spare capacity which must be maintained to cope with peaks in workload is best measured by turnover interval, the average length of time before a bed is next occupied. There are plainly still some unanswered questions when clinical units apparently dealing with similar emergency (and elective) loads can have such widely disparate turnover intervals as are apparent nationally.

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- 1 Newell DJ. Provision of emergency beds in hospitals. *Br J Prev Soc Med* 1954;8:77.
- 2 Morris D, Handyside AJ. Effects of methods of admitting emergencies on use of hospital beds. *Br J Prev Soc Med* 1971;25:1.

Prenatal screening

SIR,—Reading the Personal View in your journal is generally enjoyable in that a particular point of view is offered. The two articles on prenatal screening (20 February, p 566) were atypical in attempting to make small, albeit very personal, events have a more universal meaning. Single episodes of poor communication between patient and medical attendants were seized on and drawn out of perspective. The cause for very personal difficulties were being sought elsewhere.

Professor Drummond and his wife have reason to feel aggrieved that no offer of genetic counselling was made to a pregnant woman of 38. (The implications of the Alton bill would diminish the ability of the doctor to offer that service.) However, to take this oversight, wrestle with a guilty conscience, and then draw up a vague list of recommendations for reform is carrying the matter a little far.

I agree that individuals do vary in their attitude toward possible outcomes after prenatal testing, and that very difference is the basis of genetic counselling. We have not moved into the eugenic society where it is demanded that fetuses with a particular condition should be aborted. Resources will vary from region to region for the foreseeable future and money taken to standardise prenatal counselling for low risk conditions may not be welcomed by those faced with reductions in numbers of midwives or closure of neonatal intensive care cots.

Louise Knight was also treated badly but is seeking to absolve herself for being unable to cope with the implications of a prenatal test. There is a limit to the amount of information that can be offered to a patient to allow her to make an "informed decision." The doctor will always have difficulty in judging that amount. Major factors (risk of abnormality occurring, risk of miscarriage) obviously have to be discussed at length, although, as Professor Drummond identifies, different weights will be placed on these. The delivery of a live child with Down's syndrome is a result that will have major consequences for years. A miscarriage after amniocentesis, although catastrophic, will in most cases be an easier burden to carry and usually offers the option of starting again. In my experience the introduction into the discussion of rarer factors, especially those of a disputed scientific validity, may result in a confused patient and limited opportunity for a decision. Social and medicolegal forces demand a perfect outcome in a pregnancy and also the acquisition of

all possible information about a prenatal test. The confusion resulting from such an acquisition may make a decision about the test impossible and the outcome of the pregnancy less than perfect.

The doctor should advise the patient (despite the protestations of Ms Knight) but cannot decide for her. This is because the decision is in essence whether to allow a baby to die, and the patient initiates that process. Only after that decision is made should the problems concerned in the testing be considered. It will never be easy.

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Drug points

Erythromycin and nightmares

Drs R J BLACK and T A J DAWSON (Department of Dermatology, Craigavon Area Hospital, Craigavon BT63 5QQ) write: Following Dr Williams's communication (16 January, p 214) we report a further case of nightmares associated with erythromycin. A 21 year old woman was given erythromycin (Erymax) 250 mg once a day for acne. The night after starting treatment she had a terrifying dream in which she thought she witnessed the death of her mother. Nevertheless, she continued to take the erythromycin for the next month and experienced at least two nightmares each week. The erythromycin was then discontinued and the dreams stopped. When reviewed at the dermatology clinic one month later the patient had had no further nightmares. There was no history of nightmares or any other psychological disturbance.

Nifedipine for epilepsy?

Drs J W A S SANDER and S D SHORVON (Chalfont Centre for Epilepsy, Chalfont St Peter, Buckinghamshire SL9 0JR) write: Like Dr John G Larkin and colleagues (20 February, p 530), we decided to study the antiepileptic effects of nifedipine. We used nifedipine in 11 patients with intractable partial epilepsy. Nifedipine was given at 10 mg three times daily in addition to the patients' regular antiepileptic regimen for at least four weeks. In three a considerable improvement (>75%) was observed, and this was maintained for up to five months. Thus we support the suggestion that further studies are warranted to assess the potential antiepileptic properties of this drug and other calcium channel blockers.

Neuroleptic malignant syndrome

Dr R D MANN (Committee on Safety of Medicines, London SW8 5NQ) writes: Dr P Finucane and others (2 January, p 18) reported a case of the neuroleptic malignant syndrome in an elderly patient and commented that this was the fourth case of this syndrome reported from Britain. There have in fact been more reports than that and the Committee on Safety of Medicines (*Current Problems* No 18) noted in September 1986 that by July of that year 17 reports of neuroleptic malignant syndrome had been received (five of which were fatal). Currently, we have 59 reports of this syndrome and 13 of these cases were fatal. We note Dr A M P Kellam's important comments on the treatment of this condition (30 January, p 361) and are anxious that all cases of this important syndrome should be reported on yellow cards.

Ventricular arrhythmia precipitated by flumazenil

Drs T G SHORT, T MALING, and D C GALLETLY (Departments of Anaesthesia and Medicine, Wellington School of Medicine, Wellington, New Zealand) write: A 30 year old woman was admitted to our

intensive care unit after taking an overdose of an unknown quantity of oxazepam and chloral hydrate. On admission she was deeply unconscious with no eye opening, vocal response, or motor response to pain. She had a weak gag reflex and slow, shallow respiration. Her pulse rate was 140 beats per minute and was in sinus rhythm. Her systolic blood pressure was 90 mm Hg. Initial management included endotracheal intubation, intermittent positive pressure ventilation, and gastric lavage.

One hour after admission she was still in a coma and needing ventilatory support so an intravenous dose of 0.5 mg flumazenil was given slowly to antagonise the benzodiazepine component of her overdose. The patient became restless with an extensor response to pain and increased respiratory effort. Within seconds of the injection, however, she developed multifocal ventricular beats with short runs of ventricular tachycardia (figure). Two 50 mg bolus injections

Electrocardiogram showing ventricular arrhythmia after the administration of flumazenil.

tions of lignocaine had no effect on the arrhythmia, which settled slowly over twenty minutes to occasional multifocal ventricular ectopic beats. During this time her level of consciousness returned to that immediately prior to the administration of flumazenil.

During the arrhythmia her heart rate was between 120 and 150 beats per minute and her systolic blood pressure was 110 to 120 mm Hg. Biochemical results when the flumazenil was given were sodium 143 mmol/l, potassium 4.2 mmol/l, glucose 8.0 mmol/l, arterial oxygen pressure 23 kPa, pH 7.39, arterial carbon dioxide pressure 4.3 kPa, and bicarbonate 19 mmol/l.

The patient was extubated 20 hours after admission by which time her electrocardiogram was normal. Further questioning disclosed that she had a nine year history of physical dependency on benzodiazepines and had developed insomnia, anxiety, and phobias on attempted withdrawal.

Flumazenil is a competitive antagonist of benzodiazepines. It may be given after overdose to decrease the time during which mechanical ventilation is needed, shorten the stay in an intensive care unit, and allow communication with the patient. Potential disadvantages include the possibility of withdrawal states in patients dependent on benzodiazepines and the potential for resedation because of its short half life (60 minutes) compared with sedative benzodiazepines.¹

In this case the rhythm disturbance was similar to that reported from chloral hydrate overdose,^{2,3} although its precipitation by flumazenil may have occurred through at least two mechanisms. Firstly, the direct effect of chloral hydrate on the heart may have been exaggerated by the reversal of the dampening effect of benzodiazepines on sympathetic nervous system activity.⁴ Secondly, the patient was physically dependent on benzodiazepines and may have suffered an acute withdrawal reaction on administration of the antagonist. This may have caused enhanced sympathetic activity, although arrhythmias are not characteristic of benzodiazepine withdrawal.⁵

In this patient the rapid clearance of flumazenil was an advantage because the cardiac effects wore off as she became resedated. β Adrenergic blockade might have been a more appropriate antiarrhythmic treatment than lignocaine. It has been shown to be successful in treating chloral hydrate cardiotoxicity³ and would have reduced the sympathetic effects on the heart caused by the benzodiazepine withdrawal or the presence of an endotracheal tube. An alternative approach may have been to give additional benzodiazepine to overcome the activity of the flumazenil.

The manufacturers of the drug (Roche, Basle) have one previous unpublished report of an unspecified cardiac arrhythmia occurring after flumazenil reversal of a combined oxazepam and chloral hydrate overdose. We urge caution in the use of flumazenil to reverse the

benzodiazepine component of mixed drug overdose when cardiotoxic drugs such as chloral hydrate may have been taken or the patient's state of dependency on benzodiazepines is not known.

- 1 Ashton CH. Benzodiazepine overdose: are specific antagonists useful? *Br Med J* 1985;290:805-6.
- 2 Wiseman HM, Hampel G. Cardiac arrhythmias due to chloral hydrate poisoning. *Br Med J* 1978;2:960.
- 3 DiGiovanni AC. Reversal of chloral hydrate associated arrhythmia by a beta-adrenergic blocking agent. *Anesthesiology* 1969;31:93.
- 4 Marty J, Gauzit R, Lefevre P, et al. Effects of diazepam and midazolam on baroreflex control of heart rate and on sympathetic activity in humans. *Anesth Analg* 1986;65:113-9.
- 5 Smith DE, Wesson DR. Benzodiazepine dependency syndromes. In: Smith DE, Wesson DR, eds. *The benzodiazepines, current standards for medical practice*. Lancaster: MTP Press Ltd, 1985:235-48.

Psychiatric symptoms associated with carbamazepine

Dr G MATHEW (Cell Barnes Hospital, St Albans, Herts AL4 0RG) writes: A 24 year old man with epilepsy and mild mental handicap whose treatment was changed in January 1987 from sodium valproate to carbamazepine presented with mood swings, episodic aggressive outbursts, and thought disorder. He talked of hearing sounds in a different language and was convinced that inanimate objects altered his voice. He expressed paranoid ideas and his affect was one of fear and hostility. His sensorium remained intact and serum carbamazepine concentrations did not show toxicity. In June 1987 carbamazepine was tapered off and sodium valproate reintroduced. A week after stopping carbamazepine he showed a pronounced sustained improvement in his mental state and behaviour.

A 5 year old girl with epilepsy was given carbamazepine. She developed a severe phobia of water. This disappeared on stopping the drug.

Carbamazepine is recognised to have psychotropic effects and reported symptoms include schizophreniform psychosis, explosiveness with rage and confusion, fear of being poisoned, and severe behaviour disorder.¹ In a case reported from Spain delusions occurred during treatment with carbamazepine and disappeared on its withdrawal only to reappear on challenge with the drug.² Neither the Committee on Safety of Medicines nor the manufacturer knows of any other cases of psychosis caused by carbamazepine.

Psychotic symptoms may occur in anticonvulsant toxicity; however, brain damaged or mentally impaired people are sensitive to marginally raised concentrations of anticonvulsant drugs.³ Doctors need to be aware that psychiatric symptoms induced by carbamazepine at non-toxic concentrations may occur as idiosyncratic reactions in some people.

- 1 Dalby MA. Anti-epileptic and psychotropic effect of carbamazepine in the treatment of Psychomotor Epilepsy. *Epilepsia* 1971;12:325-34.
- 2 Mastach L. Un caso de psicosis delirante en relacion con un tratamiento de carbamazepina. *Gaceta Clin* 1983;55 (12):691-3.
- 3 Franks RD, Richter AJ. Schizophrenia-like psychosis associated with anti-convulsant toxicity. *Am J Psychiatry* 1979;136:7:973-4.

Benzylamine oral rinse and rash

Mrs MARGARET TURNER (Department of Pharmacy) and Dr ROGER LAITT (Department of Surgery, Hope Hospital, Salford M6 8HD) write: A 21 year old man with Crohn's disease developed severe painful mouth ulceration after seven days of ventilation after an emergency laparotomy for a perforated colon. Benzylamine oral rinse (Diffam, Riker) was started at a dose of 10 ml four times daily. Within three days the patient had a maculopapular, morbilliform rash over the trunk and limbs. The rash spread progressively and intensified over the next three days. The mouthwash and ranitidine, which had been administered concurrently, were discontinued. Over the following 48 hours the rash receded, and ranitidine was restarted with no adverse sequelae. There have been at least 40 reports to the Committee on Safety of Medicines of skin reactions associated with topical benzylamine cream, including seven of photosensitivity.¹ The manufacturer has also received a report of

a rash around the mouth after use of the oral rinse. The widespread rash described here has not been previously reported in patients using the oral rinse. The preparation is cosmetically coloured with quinoline yellow and patent blue V. The proposed hypersensitivity reaction may be due to systemic absorption of the drug or the colouring agents.

- 1 Anonymous. Diffam—a topical NSAID. *Drug and Therapeutics Bulletin* 1986;24:19-20.

Severe toxic erythema caused by diltiazem

Drs RIADH A WAKEEL, MICHAEL P GAVIN, and MARTIN KEEFE (Department of Dermatology, Stobhill General Hospital, Glasgow G21 3UW) write: Diltiazem is a calcium antagonist used to treat angina. Severe cutaneous reactions have been reported,^{1,2} but this is not clear from the datasheet or the *British National Formulary*,³ which simply list rashes among side effects of the drug. We describe a case of severe toxic erythema which followed treatment with diltiazem.

In August 1987 a 48 year old woman with a three month history of angina was admitted as an emergency because of sudden onset of a generalised rash. Her angina had originally been treated with atenolol 50 mg daily and nifedipine 10 mg three times a day. Ten days before admission she had had severe chest pain and nifedipine had been replaced with diltiazem 60 mg three times a day. On examination the skin showed a confluent annular eruption with target lesions (figure)

Confluent annular eruption on the arm with target lesions.

symmetrically distributed over the face, neck, trunk, and limbs. The hands and feet were spared. There was no blistering and no mucosal lesions. Histological examination of a lesion on the chest showed non-specific subacute dermatitis. The histological and clinical appearances together were consistent with a diagnosis of toxic erythema. Other causes⁴ were excluded. Treatment consisted of replacing diltiazem with isosorbide mononitrate and a short course of oral prednisolone. The rash rapidly resolved with desquamation of skin in the affected areas. The patient was discharged after five days.

The time course and resolution after withdrawal of diltiazem are strongly suggestive of a drug eruption. By November 1987 the Committee on the Safety of Medicines had received 158 reports of skin reactions to diltiazem, including two severe reactions (exfoliative dermatitis and toxic epidermal necrolysis). The manufacturers are aware of four severe reactions. Clinicians should be alerted to this severe adverse reaction to diltiazem. Patients with angina are often taking several drugs and withdrawal of medication can be hazardous. It is essential therefore that adverse reactions should be clearly documented to allow selective drug withdrawal where necessary.

- 1 Larvijsen APM, Von Dijke C, Vermeer BJ. Diltiazem associated exfoliative dermatitis in a patient with psoriasis. *Acta Derm Venereol (Stockh)* 1986;66:536-8.
- 2 Quigley MA, White KL, McGraw BF. Interpretation and application of world-wide safety data on diltiazem. *Acta Pharm Toxicol* 1985;57 (suppl 11):61-73.
- 3 British Medical Association and Pharmaceutical Society of Great Britain. *British national formulary. Number 13*. London: BMA and Pharmaceutical Press, 1987:96.
- 4 Champion RH. Erythema. In: Rook A, Wilkinson DH, Ebling FJG, Champion RH, Burton JL, eds. *Textbook of dermatology*. 4th ed. Vol 2. Oxford: Blackwell Scientific, 1986:1084.