Since 1973 we have assessed 19 RhD-negative recipients who have received kidneys from RhD-positive donors. Only one has produced RhD antibody. This was an even more convincing case of primary immunisation as it was in an 8-year-old boy. The child's first transplant was totally rejected after one month and anti-RhD was detected one month later just before a second transplant. He had received nine units of RhD-negative blood before and following the first transplant. Each of the nine blood donors was retested when anti-RhD was found in the patient and each was confirmed as RhD-negative. No anti-RhD was present in any donor serum. The antiglobulin titre of anti-RhD in the patient had risen from 1/1 to 1/8 at the time of the boy's death five weeks after the second transplant. Fractionation of the serum revealed an enzyme titre of 1/8 in the IgM fraction and of 1/2 in the IgG fraction. The risk of stimulation in this boy's case was probably high because at the time of first transplantation the implanted kidney was surgically unsatisfactory and the second kidney from the same donor was recalled from the local airport and used instead. Only simple perfusion was used for the two kidneys before implantation.

In the remaining 18 RhD-negative allograft recipients no anti-RhD was detected. Eight were tested while still on immunosuppression but 10 were tested after graft rejection and thus when immunosuppression had ceased. Only three of the kidneys had been subjected to pulsatile perfusion so probably the simple perfusion at the time of kidney retrieval is sufficient to remove most of the potentially immunising red cells. The proportion of grafts from RhD-positive donors surviving in RhD-negative recipients (8/19) does not appear to differ significantly from the overall situation.

Although the risk of anti-RhD stimulation due to transplantation does not appear to be high, we endorse the suggestion¹ that RhD-negative female patients should be protected by anti-RhD immunoglobulin at the time of transplantation, especially as a successful pregnancy has already occurred in this region after a successful renal allograft.

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¹ Huestis, D W, and Zukoski, C F, *Vox Sanguinis*, 1973, 24, 524.

Rheumatoid cervical subluxation

SIR,—Your leading article on the subject of rheumatoid atlantoaxial subluxation (24 July, p 200) performed a valuable service in drawing attention to the occurrence and possible sequelae of this relatively common but frequently overlooked complication of rheumatoid arthritis.

Unfortunately by restricting comment to subluxation anteriorly at the atlantoaxial joint the article gives a misleading picture. In addition to forward subluxation of the atlas rheumatoid involvement of the cervical spine may result in upward subluxation of the axis,^{1,2} as a result of which the tip of the odontoid process may project through the foramen magnum. Rheumatoid disease may also cause mid-cervical and occasionally lower cervical subluxation.³⁻⁵ Mid-cervical

subluxation is less common than anterior subluxation at C1-2 level but is associated in a much higher proportion of cases with overt neurological disease and seems therefore to present a greater hazard. Upward subluxation of the axis is least common of the three but its dangers are obvious. Multiple subluxation at different levels may coexist.

As you correctly point out there are no agreed indications for surgical intervention, although most rheumatologists would advise operation when there are symptoms or signs of cord compression or if there is intractable pain which cannot be relieved by the use of a collar. It is not necessary to achieve perfect reduction of the subluxation and the symptoms will usually remit provided that adequate spinal fusion is obtained.^{4,6} Where neurological signs have developed the neck should be immobilised, but care should be exercised in applying traction to the head as cases have been reported in which this has caused tetraplegia to deteriorate.⁷

Immobilisation on the Stryker frame after operation is often painful and distressing for a patient already suffering from severe crippling with multiple painful joints. For this reason the use of the halo fixation apparatus is being used at this unit and elsewhere, with the advantage of allowing the head and neck to be immobilised before operation and with the even greater advantage that the patient can be freely moved in bed and can start sitting out with the head and neck still immobilised during the postoperative period. While still in their halo apparatus most of our patients are able to walk provided that they were able to do so before operation.

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¹ Rana, N A, and Taylor, A R, *Proceedings of the Royal Society of Medicine*, 1971, 64, 717.

² Swinson, D R, et al, *Annals of the Rheumatic Diseases*, 1972, 31, 359.

³ Smith, P H, Benn, R T, and Sharp, J, *Annals of the Rheumatic Diseases*, 1972, 31, 431.

⁴ Crellin, R Q, Maccabe, J J, and Hamilton, E B D, *Journal of Bone and Joint Surgery*, 1970, 52B, 244.

⁵ Conlon, P W, Isdale, I C, and Rose, B S, *Annals of the Rheumatic Diseases*, 1966, 25, 120.

⁶ Cregan, J C F, *Annals of the Rheumatic Diseases*, 1966, 25, 242.

⁷ Hopkins, J S, *Journal of Bone and Joint Surgery*, 1967, 49B, 46.

Predicting illness by numbers

SIR,—Holmes and Rahe¹ showed that, just as people can make certain judgments about the physical characteristics of objects, they can also make valid judgments about the magnitude of social readjustment—that is,

the amount and duration of change in the customary pattern of life caused by a variety of life events. The life change scoring techniques have been tested among a diversity of races and social groups and seem to succeed in what they set out to do.² It is irrational to decry them because they fail to do a different job—namely, to pick out the individuals who are most likely to break down with a myocardial infarction (leading article, 7 August, p 343).

It is a useful exercise for a physician to spend a couple of minutes estimating his patient's score if only because it reveals that many accused of functional and neurotic illness or malingering are in fact struggling with changes large enough to have broken weaker brethren. In particular, the exercise reveals that the changes perceived as precipitating a coronary breakdown are enormously variable. They may seem to be small—for example, an acrimonious telephone conversation; moderate—for example, the failure of a son to pass his examination; or large—for example, simultaneous failure in the business and domestic spheres.³ The important factor, the missing link that the life change scoring techniques cannot assess, is the patient's capacity for withstanding change at any given period of his life before he breaks down with a coronary or other illness.

The need to assess this important factor of capacity in numbers has made it expedient to arrange known aspects of behaviour in the natural order of their passage from health to breakdown⁴ (see fig). In health the arousal caused by life change increases the performance. In fatigue the gain falls off. Once the individual is "over the hump" into an exhausted condition his actual performance falls below his intended no matter how hard he tries, maladaptive behaviour patterns flourish,^{4,5} and sleep deprivation speeds the deterioration. If the arousal continues many metabolic processes become morbid,⁶ and ill health develops. Hypertension is common. Once this stage has been reached it may only require a small amount of change to precipitate (P) a breakdown. On the other hand a person in robust good health, well trained and disciplined to withstand adversity, well supported by other people, and with little to tire or upset him may be able to withstand enormous changes without even becoming exhausted.

Techniques for assessing and changing the patient's position on his curves and for raising the curve to adequate levels are being developed here.⁷ Growing experience is producing the feeling that Mackenzie's⁸ methods of estimating and expanding the "reserve

force" are unlikely to be bettered in the foreseeable future by modern pharmacological and surgical substitutes.

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¹ Holmes, T W, and Rahe, R H, *Journal of Psychosomatic Research*, 1967, **11**, 213.

² Mendels, J, and Weinstein, N, *Psychosomatic Medicine*, 1972, **34**, 527.

³ Ransley, C, and Nixon, P G F, unpublished data.

⁴ Nixon, P G F, *Practitioner*. In press.

⁵ Kennedy, A, *Lancet*, 1957, **2**, 261.

⁶ Kagan, A R, and Levi, S, *Social Science and Medicine*, 1974, **8**, 225.

⁷ Nixon, P G F, et al, *British Journal of Sports Medicine*, 1976, **10**, 54.

⁸ Mackenzie, J, *Diseases of the Heart and Aorta*. London, Oxford Medical Publications, 1908.

Prophylactic use of bronchodilators

SIR,—In your leading article "Bronchodilators, new and old" (14 August, p 387) you did not mention the prophylactic use of these drugs. When wheezing is produced by exercise or when nocturnal wheezing is a prominent clinical feature two puffs of a portable pressurised aerosol containing a long-acting β_2 -adrenoceptor stimulant such as salbutamol or terbutaline before exercising or going to bed at night frequently prevents wheezing occurring, and many young asthmatics who follow this advice can play games which would be impossible without such treatment beforehand.

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Mid-trimester termination

SIR,—With reference to your leading article on this subject (5 June, p 1357) we would like to report our series of mid-trimester abortions using a combination of intra-amniotic hypertonic urea and prostaglandin E_2 .

A series of 58 patients was analysed in 1973-4 at the North Middlesex Hospital, where the technique has since been adopted as the routine for second trimester abortion. Fifty-six of the patients were seeking mid-trimester abortions; one was a diabetic with an intrauterine death at 30 weeks and the last a patient who had suffered eclampsia at 21 weeks. Ureaphil (lyophilised urea powder) 80 g in 120 ml of physiological saline was employed, followed by 5 mg of prostaglandin E_2 , each drug being injected separately into the amniotic cavity after the extraction of as much liquor as possible. The continuing pregnancies varied in gestation from 14 to 22 weeks and the average induction interval was 11½ hours. There was no significant difference between nulliparous and multiparous patients. In one patient the method failed; the pregnancy was of some 15 weeks' gestation and the amniotic sac could not be identified; she was subsequently aborted successfully vaginally.

We did not encounter any complications due to the alleged increase in blood concentration of fibrin degradation products or a fall in fibrinogen level and platelet count. We did, however, observe two severe reactions to prostaglandin, with hypotension, bradycardia, shivering, and dyspnoea; one patient ruptured her uterus and in retrospect was probably unsuitable for the technique since she was a

grand multipara who had delivered five babies vaginally. The only other complication was an episode of haemoglobinuria in a patient who appears to have suffered an accidental intravenous injection of hypertonic urea. The urine of this patient contained 4 g of haemoglobin per litre. An intravenous infusion of dextrose produced a good diuresis and the urine was cleared of haemoglobin. The patient failed to abort after 24 hours and an oxytocin infusion was started, after which the cervix dilated and a dead fetus was delivered after 12 hours. There was no incidence of severe haemorrhage. Prophylactic antibiotics in the form of co-trimoxazole were administered for five days. Fourteen patients required evacuation of retained products of conception and a further two were readmitted for persistent vaginal bleeding, but in only one of these cases were chorionic villi retrieved. One patient was readmitted for pelvic infection in spite of prophylactic antibiotics.

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Effects of beta-blocking drugs on insulin-induced hypoglycaemia

SIR,—The report by Dr R J Newman (21 August, p 447) that acebutalol did not impair blood glucose recovery following insulin-induced hypoglycaemia complements the report by myself and Dr D Barnett (31 July, p 272) that atenolol did not impair blood glucose recovery under similar conditions. The cardioselective or β_1 -adrenergic blocking drugs thus offer a new therapeutic approach to the treatment of angina pectoris and hypertension in diabetic subjects since they would seem to be free of hypoglycaemic side effects.

The recovery of the blood glucose level from hypoglycaemia is dependent on several mechanisms, including hepatic glycogenolysis, lactate feedback from muscles to liver for gluconeogenesis, and decreased peripheral glucose uptake. The major mechanism involved is hepatic glycogenolysis and these results suggest that the adrenergic receptors mediating hepatic glycogenolysis are of the β_2 type. This hypothesis is further supported by the observation of Dr A G Leitch and others (14 February, p 365) that intravenous infusion of salbutamol, a β_2 stimulant, produced a rise in plasma glucose levels. The report by Dr Newman that metoprolol did delay the return to normoglycaemia and that it was not significantly different from propranolol is unexpected. The β_1 -blockers share the ability to antagonise the effects of catecholamines on the heart but differ in their effects on other tissues. Although Dr C Davidson and his colleagues (3 July, p 7) have shown that the antihypertensive activity of β -adrenergic antagonists is not significantly influenced by their ancillary pharmacological properties, these might be responsible for the differences

seen in the blood glucose recovery rates. The important ancillary properties of these β -blockers are shown in the table below.

There is no correlation between these ancillary pharmacological properties and the rate of blood glucose recovery from hypoglycaemia. The simple conclusion is that some β_1 -blockers are more specific than others. Atenolol and acebutalol are claimed to be highly specific β_1 -blockers and they would seem to have advantages over other β -blockers for use in subjects prone to hypoglycaemia.

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Hypertension as a problem of public health

SIR,—Currently the investigation and treatment of hypertension usually depends on the patient's consultation of his doctor for related or unrelated symptoms. Since hypertension is common and treatable and since it is often symptomless perhaps a public health approach to the problem would be best. As a pilot study a sharply demarcated population such as that of the Isle of Wight could be subjected to a full screening procedure and by experiment the best strategy for the investigation and treatment could be established. There is little doubt that the magnitude and importance of the problem of hypertension is such that it cannot be adequately dealt with within the current framework of medical practice.

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Treatment of blood/injury/illness phobia

SIR,—Most people know of someone who faints at the sight of blood. Many doctors may remember medical students in their own set—even themselves—who did so on the first day in the operating theatre or in casualty. It seems, then, not an uncommon part of the human repertory but one that may be outgrown—or treated. Our inquiries from veterinary surgeons suggest that it is peculiarly human. If injecting or operating on an animal they do not worry about bradycardic syncope in the animal—only in the watching human.

Some people are so afraid of blood, tissue injury, injections, and venepuncture that they refuse necessary medical and surgical procedures. In marked contrast to other phobias, who become tachycardic in the presence of the phobic stimuli and rarely faint, blood/injury/injection phobics after initial tachycardia become profoundly bradycardic and faint—a very effective avoidance mechanism.¹ Experience has shown, however, that they can be successfully treated using a behavioural approach^{2,3}—for example, by exposing them to the phobic stimuli in a graded way, perhaps while they are tilted slightly head-down to prevent the fainting.

We are particularly interested in treating

Beta-blocking agent	Cardioselectivity	Intrinsic sympathomimetic activity	Membrane stabilising activity	Blood glucose recovery from hypoglycaemia
Atenolol	+	—	—	No delay
Acebutalol	+	+	+	No delay
Metoprolol	+	—	—	Delayed
Propranolol	—	—	+	Delayed