months three patients with severe hyperthyroidism accompanied by hypercalcaemia. In two of these anorexia and vomiting were conspicuous symptoms. This caused some puzzlement and was responsible for considerable delay in diagnosis. Thus in the only two cases I have seen of vomiting with hyperthyroidism hypercalcaemia was present, and I have always assumed since then that this combination should prompt a request for a serum calcium determination.

It would be interesting to know if any such determinations were made in the case of the patients described.

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*We sent a copy of the above letter to Dr Rosenthal, whose reply is printed below.—Ed, *BMJ*.

SIR,—In answer to Dr Sanderson's inquiry, in the discussion on p 210 of our paper, at the start of the fifth paragraph, we state: "There was no evidence of any serious metabolic disorder other than thyrotoxicosis in our patients." For lack of space we could not include all negative findings in the case histories. However, in all our patients the serum calcium was within our normal range of 2.2-2.6 mmol/l (8.8-10.4 mg/100 ml).

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Histamine H₂ antagonists and cluster headache

SIR,—Although histamine has been implicated in the pathogenesis of cluster headache,¹ conventional antihistamine preparations (H₁ receptor antagonists) have so far proved to be inefficient in its treatment. Recent reports showing that the carotid vessels seem to possess histamine H₂ receptors^{2,3} and the fact that a histamine H₂ receptor antagonist (cimetidine; SK&F92334) is currently undergoing clinical trials have led us to examine the possibility of histamine involvement in cluster headache via histamine H₂ receptor sites.

Our preliminary data are derived from 10 male patients suffering from cluster headache who took part in a double-blind study. Each was allocated to one of four schedules in which cimetidine and placebo were interchanged at weekly or two-weekly intervals. The dosage of cimetidine was 400 mg four times a day and the study was continued for a six-week period. The patients recorded the incidence, duration, and intensity of attacks on a diary card and they were assessed weekly in this department, when haematological, biochemical, and urine analyses were also carried out. Analgesic drugs were restricted as much as possible during the trial, their eventual use being noted on the diary cards. One patient discontinued the study owing to the development of nausea and vomiting; otherwise no significant side effects have so far been observed. The mean number of attacks ranged from 2 to 17 per week during cimetidine and from 2 to 13 during placebo medication.

Four of the nine patients improved on cimetidine medication compared with placebo, whereas one remained unchanged and four deteriorated. Statistical analysis of the results has so far not shown cimetidine to be superior to placebo ($P < 0.2$, null hypothesis).

From these preliminary results it therefore seems unlikely that histamine H₂ receptors alone are responsible for the symptomatology of cluster headache. Confirmation of these findings, however, will not exclude a possible therapeutic role for a combined H₁-H₂ receptor antagonist preparation in the treatment of cluster headache.

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¹ Sjaastad, O, in *Vasoactive Substances Relevant to Migraine*, (ed S Diamond *et al*), p 45. Springfield, Thomas, 1975.

² Edvinsson, L, and Ownam, C, in *Proceedings of the Bergen Migraine Symposium, Sandoz-Information*, 1975, suppl. 1, p 32.

³ Saxena, P R, in *Proceedings of the Bergen Migraine Symposium, Sandoz-Information*, 1975, suppl. 1, p 68.

Economy in prescribing

SIR,—The Department of Health and Social Security has requested that general practitioners should prune their prescribing in such a way as to ensure a reduction of £70m in the next year. How is this to be achieved? The majority of doctors realise that in keeping with every commodity the cost of the drugs tends to rise. There are few cheap medicines, only the expensive and the very costly.

I feel sure that substantial sums could be saved if patients were made to respect drugs at a financial level. The majority regard their medicines as costing from nothing to 20p per item whatever the nature or amount supplied, and as a consequence abuses are numerous and varied. One answer to the problem would be for all patients to pay a percentage of the cost of the retail price of the drugs dispensed, the percentage varying to cater for the elderly and the young. Scaled on the percentage basis the patients' outlay need not be excessive, but realisation of the actual cost of the drug would possibly breed a greater respect in many ways.

The method could be employed easily as the dispensing chemist with a pocket calculator could work out the arithmetic, and in view of the fact that most modern widely used drugs are so very easily dispensed, often by an electronic tablet counting machine, the pharmacist could really earn the dispensing fee, which in itself is a percentage based on the prescription cost.

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Nicotine chewing gum

SIR,—Dr M A H Russell and his colleagues (14 August, p 391) have attempted to ascertain to what extent, if any, nicotine gum can be substituted for cigarette smoking with satisfaction to the smoker.

Chewing nicotine gum doubtless results in buccal and alimentary absorption of nicotine dissolved in saliva—as did chewing tobacco,

which was common at the beginning of the century. Some 66% of cigarette smokers, however, inhale the smoke, as I did myself for 12 years. Inhalation of cigarette smoke results in almost immediate appeasement of the inhaler's usually urgent craving for nicotine. Here, *vaporised* nicotine is inhaled and absorption through the pulmonary alveoli is almost immediate. Buccal and alimentary absorption of nicotine *in solution*, on the other hand, is very much slower and much less satisfying to the craving cigarette inhaler. This, I suggest, explains why Dr Russell and his colleagues found merely a "modest inhibitory effect on smoking behaviour" when nicotine was introduced "from another source."

Slowness of absorption doubtless also explains the absence of any pleasure when nicotine is absorbed through unbroken skin. I painted an area 3 × 2 in of the flexor surface of my forearm, previously washed with hot soapy water and dried, with 5% nicotine solution at a time when I was partially addicted to nicotine. No pleasure was experienced, but seven minutes after the painting I experienced nausea, headache, and faintness which persisted for over an hour.^{1,2}

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9 Julian Road,
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¹ Johnston, L M, *Lancet*, 1942, 2, 742.

² Johnston, L M, *The Disease of Tobacco Smoking and Its Cure*, pp 29-35. London, Johnson Publications, 1957. (Copies available from the author at the above address.)

Requests for references

SIR,—In the context of the recent correspondence about the security of references (24 July, p 236, and 14 August, p 424) another aspect that has slipped badly lately is the casual photocopying and distribution of confidential references. I protested to the personnel department of a London teaching hospital about this in April. This week I was handed an uncovered sheaf of information about the two vocational training scheme doctors who are rotating to this hospital next month. This included confidential references from consultants which had been photocopied.

In former times a request for a reference would be accompanied by an assurance that it would *not* be copied or distributed but would simply be read out at the appointments committee. Please could this admirable practice be reinstated?

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Development of RhD antibodies after kidney transplantation

SIR,—Mr M G Kenwright and others (17 July, p 151) report a case in which anti-RhD developed after kidney transplantation. It was thought to be a case of primary response due to "residual" red cells in the kidney. An earlier communication¹ in 1973 reported three cases of anti-RhD production after renal transplantation, but each of these was thought to be a secondary response. These grafts survived for quite lengthy periods in spite of the presence of anti-RhD, the longest being for seven years, when the patient died.

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