rate of 38% at the end of 12 months deserves serious consideration, it is disquieting to read that seven out of the 47 abstainers in the "active" gum group were still chewing the gum, taking in an average of 11·4 mg of nicotine daily. This represents 15% of abstainers with what appears to be continuing nicotine dependence. At our walk-in Advisory Centre (Latimer House, 40/48 Hanson Street, London W1) we have been approached by several people using the gum, because their doctor is proposing to discontinue prescribing and they fear that the result will be a recurrence of desire to smoke which they will find very difficult to resist.

Whether doubts thrown up by a recent report on blood levels of nicotine metabolites in pipe smokers[1] on the accepted view[2] that nicotine shares with carbon monoxide a major role in causation of arterial disease are confirmed or not, substitution of one dependence for another is not an ideal result. The decision whether to prescribe the gum must, of course, rest with the patient's own doctor, but I suggest that it should not be considered until other approaches have been tried: not only general counselling on the lines of the Health Education Council booklet *So You Want to Stop Smoking*, combined perhaps with such adjuncts as a dummy cigarette, but also more intensive programmes like the five-day plan first developed in this country by the British Temperance Society.

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[1] Wald NJ, Idle M, Boreham J, Bailey A, Vunakis HV. *Lancet* 1981;ii:775.
[2] Royal College of Physicians. *Smoking or Health*. Tunbridge Wells: Pitman Medical, 1977.

SIR,—Having read with interest the accounts by Mr M J Jarvis and others (21 August, p 537) of trials of nicotine chewing-gum, I feel that I may be able to make a contribution by recounting my own experience as a user.

I have used 2 mg nicotine chewing-gum (Nicorette) since November 1980 (about 21 months up to the time of writing) with success in as much as I was able to stop smoking completely at the outset and have not since been in danger of relapsing. It is true that I was, and still am, strongly motivated by fear of the consequences of smoking.

Unfortunately though not a very heavy smoker (17-20 a day) I had developed a strong dependence on cigarettes, and this was soon supplanted by a corresponding dependence on the gum. According to my records, over the period up to February 1982 (15 months) my consumption showed no overall tendency to decrease, although there was a curious demiannual rhythm peaking at 10·4 pieces daily in March and September and falling to six daily in June and January.

Despairing of giving up the gum painlessly by simply using fewer pieces, I decided to try reducing the dose by dividing the pieces. This approach has been very successful, although I have found that in order to avoid noticeable effects apart from perhaps increased appetite I have had to reduce the dose in steps of two-thirds, halving it being too severe.

Over the past six months I have worked through doses of two-thirds, a half, one-third, a quarter, one-sixth, and am now on one-ninth. I have found that I quickly become accustomed to the smaller pieces and that I do not tend to compensate by using more pieces at each stage. As a consequence, I am now using the equivalent of less than one piece of gum a day, whereas a year ago I would have considered four a day an achievement.

The method may appear pedantic, but it has enabled me to enjoy the benefits of cutting back on nicotine without any of the usual stresses, thereby making the process self-reinforcing.

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Warfarin and albumin

SIR,—The report by the Royal College of Pathologists on drug interaction with anticoagulants (24 July, p 274) lists hypoalbuminaemia among the physical states that will potentiate coumarin-type drugs. The best known of these, warfarin, circulates as an albumin-bound (98% in equilibrium with the 2% free) pharmacologically active drug. Interaction with other albumin-bound drugs displaces this equilibrium through competition for binding sites on the protein, and hypoalbuminaemia mimics this effect by offering fewer binding sites.

The effect of an albumin variant (as in alloalbuminaemia, bisalbuminaemia) will be less predictable: the alloalbumin may bind either warfarin or its competing drugs differently from the albumin-A normally present, and this virtual hyper- or hypoalbuminaemia will be reflected in unexpectedly low or high prothrombin activities. In-vitro tests by Wilding *et al*[1] have shown that a European alloalbumin bound more warfarin than albumin-A, and two varians found in Amerindians (where bisalbuminaemia is common) bound less. The differences would be large enough to account for clinical effects.

The condition is rare in Europeans, and the reason for the unexpected prothrombin time will easily be missed. Total warfarin concentrations will show no significant change.

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[1] Wilding G, Blumberg BS, Vesell ES. *Science* 1977; **195**:991-4.

Methaemoglobinaemia due to monolinuron—not paraquat

SIR,—I was interested to read the report of methaemoglobinaemia and haemolysis after ingestion of Gramonol (10% paraquat) (15 May, p 1445) since I too have encountered these problems with this paraquat formulation.

A 63-year-old woman drank a cupful of Gramonol and within nine hours was noted to be an unusual colour. Her haemoglobin was then 11·8 g/dl, reticulocyte count 0·9%, and the blood film was normal. Forty-three hours after ingestion her skin was a deep slate-blue colour and her total haemoglobin was 8·8 g/dl, of which 36% was methaemoglobin and 7% sulphaemoglobin. The reticulocyte count had risen to 5%, Heinz bodies were present, and Schum's test was positive. Methylene blue (50 mg intravenously) reduced the methaemoglobin concentration to 12%. Over the next five days the haemoglobin fell to 6·4 g/dl, the reticulocyte count rose to a maximum of 8·8%, and 19 normoblasts/100 white cells together with immature myelocytes appeared in the blood film. As was our practice at the time she was treated by haemodialysis on several occasions in an attempt to remove paraquat, although much later measurement of the plasma paraquat concentration (0·1 mg/l 15 hours after ingestion) indicated that she was not at serious risk.[1] Fortunately she recovered completely.

I have reviewed the records of 71 patients with paraquat poisoning managed in this unit since 1968, and this is the only one in whom methaemoglobinaemia was noticed. She is also the only one who ingested Gramonol. To the best of my knowledge methaemoglobinaemia has not been reported after ingestion of other paraquat formulations, and I believe Dr Ng and his colleagues are wrong in attributing it to paraquat in their case.

The other active constituent of Gramonol is monolinuron (140 g/l), which together with monuron, linuron, and diuron belongs to the substituted urea herbicides. Nothing is known of the acute toxicity of these compounds in humans,[2] but studies in animals suggest that they are metabolised to aniline derivatives and giving monolinuron alone has produced methaemoglobinaemia in cats and dogs.[3] The propensity of aniline and its derivatives for causing methaemoglobinaemia and haemolysis is well documented.[2] Although it is encouraging to have found a remediable cause of cyanosis in "paraquat" poisoning it seems that Dr Ng and his colleagues have recorded the first case of toxicity of monolinuron in man rather than a new feature of paraquat poisoning.

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[1] Proudfoot AT, Stewart MJ, Levitt T, Widdop B. *Lancet* 1979;ii:330.
[2] Gosselin RE, Hodge HC, Smith RP, Gleason MN. *Clinical toxicology of commercial products*. 4th ed. Baltimore: Williams and Wilkins, 1976.
[3] Maier-Bode H, Hartel K. *Residue Rev* 1981;**77**:3.

Interaction between flurbiprofen and coumarins

SIR,—Recently our monitoring centre received two reports suggesting a serious clinical interaction between the coumarin anticoagulant acenocoumarol (Sintrom) and flurbiprofen (Froben), a propionic acid non-steroidal anti-inflammatory agent. This interaction was not listed by the Standing Advisory Committee for Haematology of the Royal College of Pathologists (24 July, p 274).

Case 1—A 64-year-old man, stably anticoagulated for several years with acenocoumarol (13 mg weekly; varying daily dose) was treated with flurbiprofen (150 mg daily) because of a painful cervical syndrome. After three days he developed haematomas and melaena. The Thrombotest time[1] before the use of flurbiprofen was 158 s (therapeutic standard: 105-180 s). During the period of bleeding the Thrombotest time was 13·5 min. Both drugs were discontinued and the patient was successfully treated with intravenous vitamin K_1. After three and a half weeks he was again anticoagulated with the usual dose.

Case 2—A 41-year-old woman, also stably anticoagulated for several years with acenocoumarol (41 mg weekly; varying daily dose), was treated with flurbiprofen (300 mg daily) because of painful thrombophlebitis. Two days later she developed haematomas and haematuria. The Thrombotest time before the start of flurbiprofen was 127 s. At the time of the haemorrhagic complications the Thrombotest time was 200 s. She was successfully treated with intravenous vitamin K_1, and both drugs were discontinued. Six weeks later she was again stabilised with the same amount of acenocoumarol.