combination of alopecia and failure of thymus and lymphoid tissue development, shows parallels with the nude mouse, the most widely used experimental model of immunodeficiency disease. The astonishing feature of AE is the relative ease with which the immunological and other disorders can be pharmacologically corrected. We believe that this may prove to be of the utmost importance for the understanding and treatment of both immune disorders and cancer.

What is the explanation for the immune disorders in AE? The regulation of cytoplasmic calcium concentration is probably crucial in the activation of lymphocytes.¹² We have shown that in both vascular smooth muscle and lymphocytes there is an antagonistic relationship between adenosine and prostaglandin(PG)-like substances.¹³ With an elevated adenosine:PG ratio release of intracellular calcium is reduced and cell activation fails. We have argued that this is the basis for the immunological failure in adenosine deaminase deficiency.¹³ In AE there is a failure of normal PG synthesis¹⁴ and in vitro clinically relevant concentrations of both zinc and penicillamine increase production of a substance with the characteristics of PGE₁.¹⁵ AE may therefore also be due to an elevated adenosine:PG ratio, this time due to PG deficiency rather than excess. Progress in cancer and immune disorders may depend on better understanding of the intracellular relationships between calcium, adenosine, and prostaglandins.

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IUDs dependent on copper for their contraceptive action is of dubious value." I do not think this can be accepted. Moreover, the clinical findings of Newton *et al*² were recently questioned by Dr I Sivin (6 August, p 387) and may not therefore provide the clinical confirmation implied. The devices studied by Gosden *et al*³ were removed from patients after being in utero for varying periods of time, and they found that some individuals laid down calcareous deposits more readily than others. The calcium deposit is porous and to what extent it reduces copper elution is not as yet readily known. With present clinical knowledge it appears that the continued elution rate is obviously sufficient for a contraceptive effect. This is supported to some extent in a recently published study by Larsson and Hamberger,⁴ in which they measured the concentration of copper in human uterine secretion during four years after insertion of a copper-containing IUD. In this clinical situation they found no significant reduction in concentration of copper in the uterine secretions during the first four years after insertion. Moreover, no pregnancy or increase in side effects was noted in these women.

Do these in-vitro studies have a great relevance to the clinical situation? In the final analysis, the proof of the pudding is in the eating; and I do not think anyone has yet satisfactorily shown, with any clinical study, that the pregnancy rate is significantly increased when copper IUDs have been left in utero for more than two years. Even the Food and Drug Administration accepts a three-year claim.

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- ³ Moyalhan, E J, *Lancet*, 1974, **2**, 399.
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- ⁷ Danbolt, N, and Closs, K, *Acta Dermato-Venerologica*, 1943, **23**, 127.
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- ¹⁰ Wells, B T, and Winkelmann, R K, *Archives of Dermatology*, 1961, **84**, 40.
- ¹¹ Neldner, K H, *et al*, *Archives of Dermatology*, 1974, **110**, 711.
- ¹² Berridge, M J, *Advances in Cyclic Nucleotide Research*, 1975, **6**, 1.
- ¹³ Ally, A I, *et al*, *Prostaglandins*, 1977, **14**, 109.
- ¹⁴ Evans, G W, and Johnson, P, *Lancet*, 1977, **1**, 52.
- ¹⁵ Horrobin, D F, *et al*, *British Medical Journal*, 1977, **2**, 190.

Release of copper from intrauterine contraceptive devices

SIR,—The paper by Dr E Chantler and others (30 July, p 288) would have been better entitled "Release of copper from copper-bearing contraceptive devices in vitro." The title at present gives an immediate impression that the devices tested had been in utero. It has been shown by Gibor *et al*¹ in 2788 women in a dose-related study that 200 mm² of copper on a device is an optimum surface area for contraception. Areas greater than this showed very little reduction in the pregnancy rate.

In their discussion Dr Chantler and his colleagues use the findings of in-vivo trials to substantiate their in-vitro studies and come to the conclusion that "the long-term use of

- ¹ Gibor, Y, *et al*, *Journal of Reproductive Medicine*, 1973, **11**, 209.
- ² Newton, J, *et al*, *British Medical Journal*, 1977, **1**, 197.
- ³ Gosden, C, Ross, A, and Loudon, N B, *British Medical Journal*, 1977, **1**, 202.
- ⁴ Larsson, B, and Hamberger, L, *Fertility and Sterility*, 1977, **21**, 624.

Effect of oestrogens on postmenopausal bone loss

SIR,—Professor B E C Nordin's group have confirmed the view that oestrogen therapy prevents postmenopausal loss (Dr A Horsman and others, 24 September, p 789). This has previously been suggested by at least two prospective trials¹⁻³ and one non-interventionist Canadian study.⁴ The evidence provided by these centres was considered at a meeting of the Endocrinology and Metabolism Advisory Committee of the Food and Drug Administration in February of this year. This committee concluded that substantial evidence existed that oestrogens were effective in the prevention of bone loss in postmenopausal women, a conclusion with which Dr Horsman and his colleagues happily concur. In addition to showing the beneficial effects of oestrogen Heaney and Recker⁴ also demonstrated that calcium therapy results in partial prevention of bone loss, a result with which this most recent paper also agrees.

We think that if a critical committee of the FDA has accepted that oestrogens prevent bone loss in postmenopausal women it is likely that they are indeed effective. At least one authoritative textbook states categorically that Koch's postulates for the causation of disease

are satisfied: "Estrogen deficiency causes; estrogen prophylaxis prevents it; and estrogen replacement stops progression of the disease."⁵

What is needed is information about the effect of such oestrogen replacement on the complications of bone loss characterised by fractures. Additional prospective trials are required to obtain the minimum effective dose of both the synthetic oestrogens and those unhappily called "natural" oestrogens. Attention has to be focused also on the various progestogens and any effect they may have on bone, both by themselves and in combination with oestrogen. This is particularly important since the majority of postmenopausal women who are going to be provided with oestrogen will have intact uteri and should be prescribed a progestogen at least cyclically to induce endometrial shedding and prevent abnormal hyperplasia and possible neoplastic change. This will continue to be so unless we find an oestrogen or a dose of oestrogen which is effective so far as bone loss is concerned but fails to stimulate endometrial growth.

This most recent contribution quotes our original publication¹ demonstrating the effect of mestranol given to oophorectomised women and correctly quotes our conclusion from that paper that therapy delayed until six years after oophorectomy is ineffective. However, our data have since been updated and many of these patients followed up for five years.² In this subsequent publication, not quoted by Dr Horsman and his colleagues, we have demonstrated that our original failure to show a significant effect in that group of patients in whom therapy had been delayed for six years was due to the small number of patients and the short follow-up period. We have no doubt that oestrogen therapy is effective in preventing bone loss when prescribed at any stage in the postmenopausal era; moreover, when treatment is delayed we have demonstrated a significant increase in bone mineral content (estimated by a photon absorptiometric technique), which corresponds to their conclusion that oestrogen "may have stimulated subperiosteal bone apposition."

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- ¹ Aitken, J M, Hart, D M, and Lindsay, R, *British Medical Journal*, 1973, **2**, 515.
- ² Lindsay, R, *et al*, *Lancet*, 1976, **1**, 1038.
- ³ Heaney, R P, and Recker, R R, *Clinical Research*, 1975, **23**, 535.
- ⁴ Meema, S, Bunker, M L, and Meema, N E, *Archives of Internal Medicine*, 1975, **135**, 1436.
- ⁵ Gordan, G S, and Vaughan, C V, *Clinical Management of the Osteoporoses*. Acton, Mass, Publishing Sciences Group Inc, 1976.

Tietze's syndrome

SIR,—In contrast to Dr G V Gill's report of Tietze's syndrome in Zambia (20 August, p 499) I have found this syndrome to be quite common in Finland. I see about two to three cases a month in a district hospital of 200 beds and covering a population of 80 000 people.

In Finland, where coronary heart disease is common and where people are very sensitive about their thoracic pains, most patients with Tietze's syndrome present themselves in the emergency room believing that they have a heart attack. Careful palpation of the thoracic

cage usually reveals the true cause of the pain. The syndrome is not always self-limiting and may incapacitate the patient for months. The best treatment is a local injection of a corticosteroid plus an anaesthetic like lignocaine. Often one injection is enough to relieve the symptoms. Sometimes the injection must be repeated. Oral anti-inflammatory drugs have a very limited value in the treatment of Tietze's syndrome.

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Teaching first aid to children

SIR,—Dr D D'Auria (24 September, p 835) asks about educating children in first aid and he cites the splendid example of Norway, where this teaching has been done for many years. Safety and accident prevention should also be taught as part of the same package.

Unfortunately no national plan in the UK is yet forthcoming from any official source to require the teaching of safety and first aid in all schools, in spite of the obvious humanitarian and other reasons for doing so. However, an editorial and an article in *Burns*^{1,2} on teaching safety, accident prevention, and first aid in schools shows what can and could be achieved.

Do the hours devoted to literature, mathematics, languages, physical education, and the arts show that these subjects are, to the official mind, more important than the preservation of the lives and limbs of our children? It would seem imperative that all children should be enabled to survive free from injury so that they may enjoy the benefits of these other subjects. Or is the absence of interest and teaching simply a matter of lethargy and lack of compassion in our society?

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¹ Gardner, A W, and Foster, S, *Burns*, 1976, 2, 203.
² Gardner, A W, and Foster, S, *Burns*, 1976, 2, 204.

Place of chlormethiazole in treatment of alcoholics

SIR,—The risks of indiscriminate use of chlormethiazole should be widely known and, as stressed by Dr J J Bradley (17 September, p 774), Dr Joan M Horder's warning (3 September, p 614) is very timely. However, in contrast to Dr Horder's opening statement, chlormethiazole is not an antidepressant "widely used in the treatment of depression" and her concluding sentence, "In the depressed alcoholic it would seem wiser to avoid the drug altogether," misses the point.

Chlormethiazole is held in Sweden and Germany to be the best drug for the treatment of severe alcohol withdrawal syndromes, including delirium tremens. Experience in the routine use of this drug at the Alcoholism Unit at St Bernard's Hospital¹ over the past 13 years have fully confirmed that for such purposes it is an extremely valuable and safe drug. It is, however, not a "treatment for alcoholism"; as a rule it should not be used except under hospital conditions or (except in delirium tremens) for longer than about six to seven days because of the risks of psychological and, more rarely, physical dependence.^{1,2} Prolonged use in alcoholic patients outside hospital of course also carries the risks of

potentiation and of overdose, as rightly described by Dr Horder. Reactive depression in alcoholics during the alcohol withdrawal phase is very common (being present to a severe or moderate degree, for example, in 53% of over 100 patients in our 1965 controlled trial of chlormethiazole¹); under hospital conditions the drug can certainly be used for depressed alcoholics in the withdrawal phase.

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¹ Glatt, M M, George, H R, and Frisch, E P, *British Medical Journal*, 1965, 2, 401.

² Glatt, M M, "Alcoholism—A Social Disease," Teach Yourself Books. London, English University Press, 1976.

Surgical treatment of trigeminal neuralgia

SIR,—We are surprised that your leading article (17 September, p 718) makes no mention of peripheral branch injection or division as part of the surgical treatment of trigeminal neuralgia.

For several years now we have adopted this method as the first line of surgical management in those patients whose pain is no longer controlled by medical means and is essentially confined to one division of the trigeminal. In accepting the ultimate inevitability of pain recurrence we have nevertheless found that prolonged periods of remission are obtainable by injection, either with local anaesthetic or alcohol, or subsequent neurectomy. The success of the method depends firstly upon meticulous mapping of the distribution of the patient's pain so that, secondly, an anatomically accurate injection may be made. In the face of recurrent pain the injection can be repeated, often in the privacy and comfort of the patient's home, or appropriate neurectomy performed of one or more peripheral branches.

Before recourse is made to the destructive procedures on the ganglion or sensory root, with their inherent morbidity and mortality, we suggest that the simpler and safer peripheral procedures be tried.

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Intravenous diazepam and Cyclimorph

SIR,—Dr A S Gardiner (10 September, p 701) attributes amateur status and inferior results to those who use intravenous diazepam and Cyclimorph as a substitute for general anaesthesia. I invite him to consider the example of the patient with a dislocated shoulder admitted to the casualty department after a recent meal who is presented with the alternatives of waiting several hours for general anaesthesia or having an immediate injection of diazepam and Cyclimorph followed by painless reduction of the dislocation. I also invite him to visit my fracture clinic and see fractures remanipulated immediately during the course of the clinic rather than enduring anxious waiting for the next anaesthetic session.

I am delighted to read the letter from Mr P

Sykes (24 September, p 832) and to learn that he can perform the most complicated dental extractions under intravenous diazepam and pentazocine. This confirms my expectations that the use of intravenous diazepam with or without intravenous analgesics will obviate the need for general anaesthesia in dentistry and thus eliminate the recurring tragedies of deaths in the dental chair. Mr Sykes claims that intravenous pentazocine is virtually non-nauseating. This is rather surprising in view of the reports which suggest that the emetic side effects of pentazocine are about half those of pethidine and plain morphine.^{1,2} Moreover, pentazocine is known to have a higher incidence of other side effects such as dizziness and light-headedness. When I started using Cyclimorph I thought that it was virtually non-emetic until I made careful follow-up inquiries as to what happened after the patient got home. I then discovered that in some cases the emetic effects of morphine outlasted the antiemetic effects of cyclizine. A comparative trial of intravenous diazepam with Cyclimorph and with pentazocine is clearly indicated.

I am surprised that Mr Sykes has not found much increase in tolerance to intravenous diazepam in patients taking long-term benzodiazepine medication. Last week, for example, I injected 80 mg of diazepam before getting adequate sedation in such a patient who required remanipulation of relapsed Colles fractures. However, I agree that adequate sedation can usually be obtained and there appears to be no danger in larger doses providing these are carefully titrated.

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¹ Mowat, J, *British Medical Journal*, 1970, 2, 757.

² Morrison, J D, et al, *British Journal of Anaesthesia*, 1969, 41, 987.

Barbiturates and fractures

SIR,—Drs J B and Elspeth T MacDonald (1 October, p 891) have not fully taken up the main point I was making in my letter (10 September, p 699), perhaps because I expressed myself badly.

It is to be expected that any hypnotic would increase the risk of falls and hence of femoral fractures in the elderly, especially in those whose balance is already impaired. The figures in their paper (20 August, p 483) support this, though the authors drew attention particularly to the association of barbiturate hypnotics and nocturnal fractures. Their figures, however, suggest that non-barbiturates are more prone to cause fractures than barbiturates and show an altogether unexpected difference in the two groups between night and day fractures.

Time distribution of fractures

	10 pm-6 am	Daytime	Total
Barbiturate hypnotic fractures ..	91	12	103
Non-barbiturate hypnotic fractures ..	5	216	221
Non-hypnotic fractures ..	2	64	66

I agree that hypnotics will not be prescribed as often in the elderly generally as in those referred to a geriatric clinic, but when they are prescribed it would be reasonable to expect the prescribing pattern to be similar to that in the geriatric clinic referrals in the same locality.