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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- ¹ Dillaha, C J, Lorincz, A L, and Aavik, O R, *Journal of the American Medical Association*, 1953, **152**, 509.
- ² Javett, S N, *Lancet*, 1963, **1**, 504.
- ³ Moyalhan, E J, *Lancet*, 1974, **2**, 399.
- ⁴ Neldner, K H, and Hambridge, K M, *New England Journal of Medicine*, 1975, **292**, 879.
- ⁵ Rodin, A E, and Goldman, A S, *American Journal of Clinical Pathology*, 1969, **51**, 315.
- ⁶ Julius, R, Schulkind, M, and Sprinkle, T, *Journal of Pediatrics*, 1973, **83**, 1007.
- ⁷ Danbolt, N, and Closs, K, *Acta Dermato-Venerologica*, 1943, **23**, 127.
- ⁸ Danbolt, N, *Acta Dermato-Venerologica*, 1956, **36**, 257.
- ⁹ Bloom, D, *New York State Medical Journal*, 1960, **60**, 3609.
- 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