

issue of Feb 4 contained good news. The hopeful message was not found in the entirely predictable response by Kickbusch (p 325), a member of Nakajima's staff, to a previous *Lancet* editorial. Rather, in the news section, McGregor (p 312) reports that at the January WHO Executive Board meeting a decision was taken to develop and propose a new global health charter. This new charter, intended to be promulgated in late 1997, offers enormous promise, especially if several critical conditions are met.

First, clarity and coherence in the analysis of global health problems, challenges, and possible solutions is essential. Although criticising the shortcomings of progress in realising the Alma-Ata Declaration (1976) is easy, a genuinely new and creative path forward will be more difficult to define. Global health is inextricably connected with global social, economic, and political realities. Since WHO was created, much has been learned about the biological and societal basis of health. A new vision can be built on the solid foundation of the preamble to the WHO constitution, with an updating to take account of such key elements as the insights for health arising from the modern human rights movement. A clear path forward must be both far-reaching and sufficiently concrete to mobilise the human and financial resources that protecting and promoting global health requires and merits. Then, as form follows function, organisational restructuring can ensue.

Second, it is essential to recognise the strength and importance of the non-governmental organisations (NGOs) in health assessment, policy development, and assurance of services. Half a century ago, when WHO was created, NGOs were far fewer and less important; today, as shown by the Cairo conference on population, they are numerous and essential. Therefore, NGOs should not only be consulted, but also should become centrally involved in the development of a new health charter. Everyone knows that the United Nations (UN) and other official agencies can either give lip service to NGOs or take them seriously, and the difference will be critical and obvious.

Third, the new global charter has to take account of the emerging realities in the UN's involvement in health matters. Again, since WHO was created, and even more recently, many other parts of the UN system have (fortunately) interpreted their mandates to include health. For example, awareness of the importance of investment in people and on the linkage between health and development have led the World Bank and the UN Development Program to invest and focus increasingly on health, along with the more obvious UN participants such as UN Children's Fund, UN Population Fund, UN Educational, Scientific and Cultural Organisation. Yet WHO's entire budget is quite small compared with the resources of the World Bank or the UN Development Program. WHO needs to clarify its role within the UN system. How WHO organises these consultations and relations could determine the credibility of the new health charter.

Finally, the preamble to the WHO constitution highlights the importance of "informed opinion and active cooperation on the part of the public". The development of a new health charter is an historic opportunity to inform and educate the

## Ethics of n-of-1 trials

SIR—We agree with Irwig et al (Feb 25, p 469) that medical research committee approval is unnecessary for n-of-1 trials when the treatment and its indication for use are not new. We believe, however, that it is premature to call for n-of-1 trials to be encouraged by health-care systems and for facilities to be made available to carry out n-of-1 trials in daily clinical practice. Experience so far with n-of-1 trials has been uncontrolled.<sup>1-3</sup> Comparison of outcomes, including economic costs, between groups of patients randomised to receive treatment by n-of-1 trials or by standard practice (an open, before-after test of therapy) is needed to show whether n-of-1 trials are a cost-effective alternative to current clinical practice. In this respect, they are no different from other new interventions. Randomised controlled studies of n-of-1 trials versus standard practice are feasible.<sup>4</sup> Pending results of further such investigations, widespread use of n-of-1 trials cannot be advocated.

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- 1 Guyatt G, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. The n-of-1 randomized controlled trial: clinical usefulness. *Ann Intern Med* 1990; **112**: 293-99.
- 2 Larson EB, Ellsworth AJ, Oas J. Randomized clinical trials in single patients during a 2-year period. *JAMA* 1993; **270**: 2708-12.
- 3 March L, Irwig L, Schwarz J, Simpson J, Chock C, Brooks P. N of 1 trials comparing a non-steroidal anti-inflammatory drug with paracetamol in osteoarthritis. *BMJ* 1994; **309**: 1041-45.
- 4 Mahon JL, Laupacis A, Donner A, Wood T. A randomized trial of N of 1 trials versus conventional therapy. *Clin Res* 1993; **4**: 180A.

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## Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer

SIR—Dowsett and colleagues (Feb 25, p 525) argue that the high response rate that we reported (Jan 7, p 29) to the specific antioestrogen ICI 182780 should be interpreted with care since patients were selected as likely to respond after failure of tamoxifen. In a similarly selected group of patients they report a high response rate to newer aromatase inhibitors. We have seen a response rate of 63% in similar patients (n=57) given the progestagen megestrol acetate. Thus, we agree that the patients are generally responsive. The selection was made because we were unsure of the potential activity of a specific antioestrogen after failure of a partial agonist antioestrogen. Our study showed a high response rate and a prolonged response duration. The median response duration on megestrol acetate was 14 months, whereas in the small group of patients given ICI 182780 the median duration of response has not yet been reached after 22 months. When used to treat human mammary tumours growing in nude mice, ICI 182780 resulted in cessation of tumour growth for periods about twice as long as tamoxifen (Osborne CK, personal communication). Our data suggest that ICI 182780 might

disease after 28 months of treatment. In practice, few clinicians change treatment when metastatic disease is classed as no change.

Dowsett and colleagues suggest that treatment with ICI 182780 is conceptually similar to that with aromatase inhibitors in that both treatments produce "pure deprivation of the oestrogenic signal". In as much that, as we have argued,<sup>2</sup> all endocrine therapies for breast cancer probably act directly or indirectly by reducing the oestrogenic signal in tumour cells, this comment could be correct. However, ICI 182780 and aromatase inhibitors have different mechanisms of action. The ability of ICI 182780 to bind tightly to the oestrogen receptor (much more so than tamoxifen) and to downregulate the receptor might afford the specific antioestrogen a therapeutic advantage over other forms of endocrine therapy. Our results suggest that this hypothesis is worth pursuing.

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- 1 Howell A, MacIntosh J, Jones M, Redford J, Wagstaff J, Sellwood RA. The definition of the 'No change' category in patients treated with endocrine therapy and chemotherapy for advanced carcinoma of the breast. *Eur J Cancer Clin Oncol* 1988; **24**: 1567-72.
- 2 Howell A, DeFriend DJ, Anderson E. Mechanisms of response and resistance to endocrine therapy for breast cancer and the development of new treatments. *Rev Endocr Rel Cancer* 1993; **43**: 1-17.

## Vitamin-D-receptor-gene polymorphism and bone loss

SIR—Polymorphisms of the vitamin-D-receptor (VDR) gene have been linked with bone mineral density (BMD) in twin studies from both Australia<sup>1</sup> and the UK.<sup>2</sup> Ferrari and colleagues (Feb 18, p 423) report in a study of 64 elderly women (and 8 men) that the annual rate of change in spinal BMD over 18 months was small (+0.47%) and not significantly different from zero, but differed between VDR genotypes. They suggest that a similar genetic effect may also influence BMD changes in younger women. We have examined this potential relation in a larger group of healthy women soon after the menopause; these women should be experiencing greater rates of bone loss due to relative oestrogen deficiency.

296 women within 5 years of the menopause were recruited from two population-based cohort volunteer groups. All were free of bone disorders and did not receive hormone replacement therapy or other medication known to affect bone throughout the study period 1988-93. BMD was measured at the lumbar spine and femoral neck by dual photon absorptiometry (Novo-BMC Lab 22a) at 0, 12, 24, and 48 months in 141 women and by dual-energy absorptiometry (Hologic QDR-1000) at 0, 12, 24, and 48 months in 155 women. Coefficients of variation from repeat measurements on healthy volunteers were 0.8% at the spine

Mean (SE) bone loss (% per year)			
Lumbar spine	-1.31 (0.14)	-1.09 (0.17)	-1.01 (0.30)
Femoral neck	-0.48 (0.36)	-1.00 (0.20)	-1.00 (0.46)

Table: **Relation of vitamin D receptor genotypes, demographic variables, and bone loss in 195 women**

and 1.6% at the hip for both techniques. Rates of change in BMD for each individual subject were calculated by least-squares regression analysis. DNA was extracted from leucocytes, PCR used to amplify a 740 bp DNA sequence, and the *TaqI* restriction enzyme used to detect VDR alleles. The genotypes were coded as TT, Tt, and tt; the tt genotype is equivalent to the previously reported BB genotype.<sup>1</sup>

Full results (three or more scans and VDR genotype) are available for 195 women. Genotype frequencies were as expected from other populations. There were no significant differences in anthropometric or menopausal characteristics between the genotype groups (table). There was no difference in the rate of change in BMD from hip or spine between the VDR genotypes (analysis of variance,  $p=0.55$  and  $p=0.37$ ). For the total group the 95% CI for rate of change in BMD were -1.32 to -0.88% per year at the spine, and -1.08 to -0.45% per year at the hip. The proportion of women with spinal bone loss below the lower 95% CI of -1.32% per year (as used by Ferrari et al) was similar in the three groups: 35/71 (TT), 38/96 (Tt), and 10/28 (tt). The same was true of losses at the femoral neck.

By contrast with Ferrari and colleagues' findings, in a larger and longer-duration study we have found no association between VDR genotype and bone loss from lumbar spine or femoral neck. We believe that the VDR gene acts predominantly to determine peak bone mass and that other genes are likely to be involved in the regulation of bone loss after the menopause.

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- 1 Morrison NA, Qi JC, Tokita A, et al. Prediction of bone density from vitamin D receptor alleles. *Nature* 1994; **367**: 284-87.
- 2 Spector TD, Keen RW, Arden NK, et al. Vitamin D receptor gene (VDR) alleles and bone density in postmenopausal women: a UK twin study. *J Bone Min Res* 1994; **9**: S143.

SIR—Ferrari and his colleagues conclude that the variability in the response of bone mass to calcium intake and vitamin D supplementation may be predicted by analysis of VDR-gene polymorphisms. We investigated the effects of 1  $\alpha$ (OH) $D_3$  (0.5  $\mu$ g per day) with or without calcium supplementation (as calcium lactate of 1.5 g per day) on lumbar-spine mineral density in 31 Japanese adults (4 men, 27 postmenopausal women; mean age 68.3 [SE 1.4] years), in whom lumbar-spine mineral density (L2-4) was lower than in age and sex matched Japanese controls. BMD of L2-4 was measured with dual energy X-ray absorptiometry (DPX, Lunar Co)<sup>1</sup> before and after (mean 8.0 [SE 0.7]