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AUTHORS' REPLY,—We are grateful to Dr Hinchley, Dr Kubba, and Dr Szarewski and her colleagues for their interest in our paper.

We believe that induced oestrogen deficiency is the most plausible explanation of our findings, but we recognise the limitations of population studies of this nature and concur with the view that sequential studies of women starting and finishing long term DMPA use are necessary to prove or disprove our hypothesis. Many of the factors suggested by Dr Hinchley have no demonstrable influence on the bone density of premenopausal women. For the record, only four of the 30 premenopausal controls were taking combined oral contraceptives and the parity of the DMPA users ranged from 0 to 4, with a median of two births. In response to the points raised by Dr Kubba, the median duration of exposure to DMPA in our subjects (10 years) is quite clearly stated in our paper, as is the observation that the differences in bone density between DMPA users and premenopausal controls persisted even when pairs discordant for cigarette smoking were eliminated. Dr Szarewski reminds us that DMPA may be partially protective against postmenopausal osteoporosis. Our point is that the net effect of DMPA on bone when administered to women with established oestrogen deficiency may not be the same as when DMPA induces oestrogen deficiency.

We agree that DMPA remains a valuable and effective contraceptive option. Our current recommendations are that women with more than one risk factor for osteoporosis (family history, underweight, cigarette smoking, European or Asian origin) should have bone mineral density measurements undertaken if they are considering DMPA use on a continuing basis. Those in the lower third of the normal range (for Europeans) are advised to consider other contraceptive methods. As Dr Szarewski indicates there is a dilemma for women who have used DMPA long term and are approaching the age of the natural menopause. We agree that it would be appropriate for these women too to be offered bone mineral density measurements.

TIM CUNDY
IAN R REID

Auckland Hospital,
Auckland,
New Zealand

HELEN ROBERTS

Family Planning Association of New Zealand,
Auckland,
New Zealand

SIR,—In their paper on bone density in women receiving depot medroxyprogesterone acetate for contraception Dr Tim Cundy and colleagues rightly state that increases in serum alkaline phosphatase activity and urine hydroxyproline excretion are recognised features of the menopause that reverse with oestrogen replacement therapy.[1] In common with results of calcium kinetic,[2] histomorphometric,[3] and animal studies,[4] such observations suggest that the menopause is associated with increased rates of turnover of bone. This increase is thought to be largely responsible for the accelerated bone loss that follows the menopause, and inhibition of bone turnover is held to be the principal mechanism by which oestrogen exerts its protective effect on bone mass.

Despite a reduction in both oestrogen concentration and bone mineral density no effect of treatment with medroxyprogesterone on bone turnover was found. Though the authors suggest that this might simply reflect the insensitivity of measurements of serum alkaline phosphatase activity and urine hydroxyproline excretion at low values, an alternative explanation might be that such treatment had little effect on bone turnover but instead led to reduced bone formation. Reduced bone formation could be a result of an inhibitory action of medroxyprogesterone, but this seems unlikely in view of previous observations that progesterone stimulates bone formation.[5] An alternative explanation might be that reduced concentrations of oestrogen after treatment with medroxyprogesterone led to loss of oestrogen mediated stimulation of bone formation.

Unfortunately, clinical studies investigating the effect of oestrogen on bone formation in postmenopausal women have been hampered by the indirect increase in bone formation that follows the menopause secondary to a rise in bone turnover. In a recent study of adult female rats that had undergone oophorectomy and had been given bisphosphonates to prevent increased bone turnover we found that oestrogen exerted a strong dose dependent stimulatory effect on bone formation (unpublished findings). This suggests that bone formation would be adversely affected by a significant reduction in oestrogen concentrations, as occurs after treatment with medroxyprogesterone.

J H TOBIAS

Department of Rheumatology

J CHOW
T J CHAMBERS

Department of Histopathology,
St George's Hospital Medical School,
London SW17 0RE

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Prenatal screening for Down's syndrome

SIR,—Recent reports have devoted much attention to the cost effectiveness of screening for Down's syndrome with the so called "triple test," which includes as a marker maternal serum unconjugated oestriol.[1-5] We previously reported retrospective data showing that unconjugated oestriol does not contribute to detection efficiency in Down's syndrome screening.[6,7] We have now further assessed the contribution of unconjugated oestriol in a prospective screening. Specifically, the addition of unconjugated oestriol to our screening protocol, which includes maternal serum α fetoprotein, free β human chorionic gonadotrophin, and maternal age, increases false positive rates. Free β human chorionic gonadotrophin is used in our protocol because it has been shown to be superior to intact human chorionic gonadotrophin.[8,9]

We prospectively studied 1410 pregnant women undergoing routine maternal serum screening. All patients' samples were evaluated for unconjugated oestriol, α fetoprotein, and free β human chorionic gonadotrophin, and patient specific risk for Down's syndrome was calculated as previously described.[8]

The table shows that including unconjugated oestriol resulted in a 2·2% increase in the rate of initially positive results in the 1410 samples evaluated prospectively.

As the table shows, an additional 85 800 American and 17 160 British patients would experience initial positive results if unconjugated oestriol is added to the Down's syndrome screening protocol. This seems to represent costly and unnecessary emotional, clinical, and financial burdens.

JAMES N MACRI
RAMANA V KASTURI
EDWARD J COOK
DAVID A KRANTZ

Research Division,
NTD Laboratories Inc,
Carle Place,
New York 11514, United States

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SIR,—My major concern in commenting on the commercial launch of the triple plus test[1] was not that the neutrophil alkaline phosphatase study on which it is founded[2] was retrospective but that the proportion of Down's syndrome to non-affected pregnancies and the maternal ages sampled in that study were not representative of population characteristics. The response by Professor Howard S Cuckle and his colleagues, that no association between neutrophil alkaline phosphatase activity and age was found, does not remove this concern.[3] The lack of association between neutrophil alkaline phosphatase activity and maternal age in the non-Down's syndrome cases cannot be evaluated without more detailed information on the age range sampled (88% are described only as being under 37 years) and is in any case not directly relevant to the argument. In affected cases, 79% of women were 38 years or over. The restricted age range of this sample, in conjunction with the bias (in opposite directions) in the two samples, greatly limits the possibility of any age effect emerging. From this study, it cannot safely be concluded that neutrophil alkaline phosphatase activity will be raised in affected pregnancies at all maternal age levels.

Women of 38 and over account for only a minority (31%) of Down's syndrome births. Collecting neutrophil alkaline phosphatase data—

Inclusion of unconjugated oestriol in Down's syndrome screening protocol

Components of screening protocol	No at risk (n=1410)	Initially positive (%)	Initially positive results*: United States	United Kingdom
α Fetoprotein, free β human chorionic gonadotrophin	75	5·3	206 700	41 340
α Fetoprotein, free β human chorionic gonadotrophin, unconjugated oestriol	106	7·5	292 500	58 500

*Based on a potential nationwide screening population of 3 900 000 in United States, 780 000 in United Kingdom.