have been shown so far. Given all this, why not vaccinate and try to vaccinate well?

The Health Council of Sweden has just recommended general vaccination with triple measles-mumps-rubella vaccine at the age of 18 months, as well as vaccination with triple vaccine of 12-year-old boys and girls. Belgium is expected to recommend shortly routine vaccination against measles and mumps at the age of 15 months, and vaccination of older children who have not had the vaccine or the disease. The Federal Republic of Germany (since 1976) and Canada have also joined the United States in recommending routine mumps vaccination of young children.

JAN DESMYTER

Rega Institute,
The University,
B-3000 Leuven, Belgium

- ¹ Hayden GF, Preblud SR, Orenstein WA, Conrad JL. *Pediatrics* 1978;**62**:965-9.
- ² Desmyter J, Krugman S. *Br Med J* 1980;**281**:1185-6.
- ³ Weibel RE, Bunyak EB, McLean AA, Hilleman MR. *Proc Soc Exp Biol Med* 1979;**162**:328-32.
- ⁴ Feldman HA. In: Evans AS, ed. *Viral infections of humans*. London: J Wiley and Sons, 1976:317-36.
- ⁵ Harasek G. *Wien Klin Wochenschr* 1978;**90**:7-10.
- ⁶ van der Veen J. *Ned Tijdschr Geneesk* 1979;**123**:714-5.

Long-term follow-up of mothers who received high doses of stilboestrol and ethisterone in pregnancy

SIR,—The report by Dr Valerie Beral and Linda Colwell (25 October, p 1098) linking oestrogen therapy during pregnancy with later appearance (after 18-22 years) of breast cancer prompted us to review studies on oral contraceptives. Most studies have found no increase of breast cancer in oral contraceptive users and perhaps even a decrease. A delayed appearance of breast cancer, such as that noted by these authors, might have been missed because younger women predominated in these investigations.

The table summarises data from case-control studies of breast cancer and categorises them according to "young" and "old" subgroups. Only those studies which presented the relevant information in terms of patients' ages are included. It should be noted that age categories differ among studies and that for two studies we assumed that premenopausal patients were younger than postmenopausal. The relative risks refer to breast cancer in women with any history of oral contraceptive use (ever use) compared with controls who have never used them. The study by Jick *et al*⁵ is an exception in that present and past users were evaluated separately.

The data in the table indicate an increased risk of breast cancer among women with a positive history of oral contraceptive use but only after they have passed into their fifth or sixth decade. Breast cancer is common in women in their later years; a small increase in risk would therefore mean a large increase in the absolute number of cases. Most oral contraceptive users have not yet reached the

critical age. Future studies should address this potential problem.

MICHAEL A VANCE

Pharmacology Section,
Northeastern University,
Boston, Mass 02115

WILLIAM R MILLINGTON

Division of Toxicology,
Johns Hopkins University
School of Hygiene and Public Health,
Baltimore, Maryland, USA

- ¹ Fasal E, Paffenbarger J. *J Nat Cancer Inst* 1975;**55**:767-73.
- ² Brinton LA, Williams RR, Hoover RN, Stegens NL, Feinleib M, Fraumeni JF. *J Nat Cancer Inst* 1979;**62**:37-44.
- ³ Vessey MP, Doll R, Jones K, McPherson K, Yeates D. *Br Med J* 1979;**ii**:1757-60.
- ⁴ Paffenbarger RS, Kampert JB, Chang H-G. *Am J Epidemiol* 1980;**112**:258-68.
- ⁵ Jick H, Walker AM, Watkins RN. *et al. Am J Epidemiol* 1980;**112**:577-85.

SIR,—Although the study of Dr Valerie Beral and Linda Colwell (25 October, p 1098) provides valuable data on long-term effects following administration of massive doses of stilboestrol and ethisterone to pregnant diabetics, the article is marred by an invalid comparison of the breast cancer risk found in their patients with that in postmenopausal women exposed to oestrogen therapy. We appreciate the pivot of their argument—that oestrogen exposure increases the risk of breast cancer and that the induction period may be as long as 18-20 years—but the comparison made in this paper is inappropriate for the following reasons.

Firstly, the pregnant diabetics were prescribed ethisterone and stilboestrol, a synthetic oestrogen, whereas climacteric women are usually treated with "natural oestrogens." Synthetic oestrogens are regarded as unsuitable for alleviating climacteric symptoms because of their more pronounced adverse effects on blood coagulation and lipid and lipoprotein concentrations, and they have been shown to be at least 70 and perhaps 100 times more potent than natural oestrogens on a weight-for-weight basis in the human female^{1,2} as Helgason *et al*¹ and Judd (at Round-table Conference on the Role of Progestins in Replacement Therapy, New York, 1979) have shown. Secondly, the daily dosage of stilboestrol in this study (0.5 mg) would be considered massive if given to postmenopausal women and the mean dose administered to the pregnant diabetics (16.3 g) would be equivalent to 119 years of cyclical or 89 years of continuous oestrogen use in postmenopausal women. Although commenting on differences in dosage Dr Beral and Ms Colwell failed to consider the relative potencies of synthetic and natural oestrogens; when these are taken into account the dosage of stilboestrol given to the pregnant diabetic becomes equivalent to many hundreds of years of postmenopausal oestrogen exposure.

Thirdly, the authors' inference that a causal relationship exists between postmenopausal oestrogen use and breast cancer is not sup-

ported by the published data and only three of the 12 relevant studies have reported a positive association. The study of Hoover *et al*,³ which is quoted in a highly selective and unrepresentative manner, reported an increase in risk but no dose-dependent relationship was found. The other two studies suggesting a causal relationship are those of Casagrande *et al*,³ in which only 47 patients were scrutinised, and Ross *et al*,⁴ which, like most of the other epidemiological surveys, suffers from a lack of adjustment for surveillance and protopathic bias.⁵ Whether Dr Beral and Ms Colwell also implicate ethisterone, a progestin, in the genesis of breast cancer is unclear. We are not aware of any human studies suggesting an oncogenic role for progestin and it is more likely that they would exert an inhibitory effect on the breast analogous to that on the endometrium.⁶ Pregnant diabetics receiving massive doses of stilboestrol and ethisterone may be at an increased risk of developing breast cancer, but it would be unwise to extrapolate these conclusions to postmenopausal women receiving oestrogen therapy.

G LANE
NICK SIDDLE
M WHITEHEAD

Department of Obstetrics and Gynaecology,
King's College Hospital Medical School,
London SE5 8RX

- ¹ Helgason S, Damber M-G, von Schoultz B, Stigbrand T. (in press).
- ² Hoover R, Gray LA, Cole P, McMahon B. *N Engl J Med* 1976;**295**:401.
- ³ Casagrande J, Gerkins J, Henderson BE, Mack T, Pike MC. *J Nat Cancer Inst* 1976;**56**:839.
- ⁴ Ross RK, Paganini-Hill A, Gerkins VR, Mack TM, Pfeiffer R, Arthur M, Henderson BE. *JAMA* 1980;**243**:1635-9.
- ⁵ Horowitz RI, Feinstein AR. In: Pasetto N, Paoletti R, Ambrus JL, eds. *The menopause and postmenopause*. Lancashire: MTP Press, 1979:195-205.
- ⁶ Whitehead MI, King RJB, Campbell S. In: *Proceedings of IX world congress of obstetrics and gynaecology*. Amsterdam: Excerpta Medica, 1980: 61-5.

* * We sent this letter to the authors, and Dr Beral replies below.—Ed, *BMJ*.

SIR,—We agree with Dr Lane and his colleagues that the evidence linking menopausal oestrogen use and breast cancer is contradictory.

Our findings, together with those from Chicago,¹ offer strong evidence that when given during pregnancy high doses of stilboestrol (with or without progestogens) increase the risk of breast cancer. Furthermore, long latent periods seem to be involved. It therefore seems reasonable to suggest that if menopausal oestrogens affect breast cancer risk long latent periods may also be involved. At the time of preparing our report only Hoover *et al*² had considered that the risk of breast cancer following menopausal oestrogen use may be altered after relatively long latent periods. They noted an increased risk of breast cancer 15 years after exposure to oestrogens. Clearly more information on menopausal oestrogens—and on "natural oestrogens" in particular—is needed; but the possibility that very long latent periods may be involved must be taken into account.

VALERIE BERAL

Department of Medical Statistics
and Epidemiology,
London School of Hygiene and
Tropical Medicine,
London WC1E 7HT

- ¹ Bibbo M, Haenszel WM, Wied GL, Hubby M, Herbst AL. *N Engl J Med* 1978;**298**:763-7.
- ² Hoover R, Gray LA, Cole P, McMahon B. *N Engl J Med* 1976;**295**:401-5.

Relative risk of breast cancer in women with a history of contraceptive use compared with controls in published studies

Reference	Definition (y)		No of cases		Relative risk		
	Young	Old	Young	Old	Young	Old	OC use
1	15-39	40-49	104	348	0.72	1.31	Ever
2	pre	post	126	160	0.80	1.66	Ever
3	16-40	46-50	301	115	0.8	2.4	Ever
4	pre	post	768	1090	1.09	1.24	Ever
5	31-45	46-55	31	24	1.2	3.2	Past
5	31-45	46-55	23	26	0.8	8.0	Present

Pre = premenopausal; post = postmenopausal; OC = oral contraceptive.