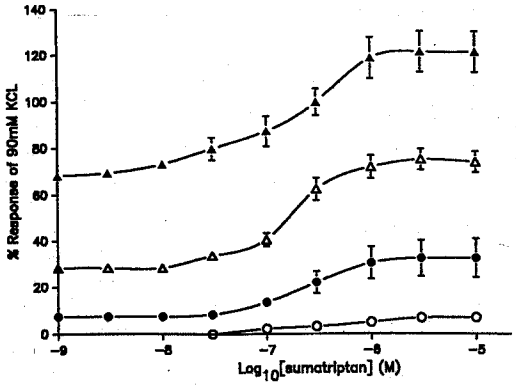

Contractile effect of sumatriptan in absence of U46619 (open circles, n=4), and in presence of EC_{10} concentration (filled circles, n=4), EC_{20} concentration (open triangles), or EC_{50} concentration (filled triangles) of U46619 on non-atherosclerotic epicardial coronary arteries.

Specimens were obtained from 4 patients aged 25, 29, 43, and 54 years, receiving heart transplantation for cardiomyopathy. Experiments were done in duplicate in vessels from each patient. (Initial response U46619 concentrations shown by different starting points for each curve on the y axis.) M = mol/L.

of abrogated nitric oxide release. These mechanisms could be of pathophysiological importance in vessels affected by atherosclerotic disease, since we have shown that areas immediately distal to atheromas are hyperreactive to sumatriptan.[1] The possibility exists that some patients receiving sumatriptan could have newly formed yet undetected atheroma, with an associated area of vascular hyperreactivity. Care should be taken when giving this drug to patients with coronary risk factors.

The physiological role of 5-HT_1-like receptors remains unclear, but in certain circumstances these receptors might mediate pathophysiological events in the coronary circulation.

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1. Chester AH, Martin GR, Bodelsson, et al. 5-hydroxytryptamine receptor profile in healthy and diseased human epicardial coronary arteries. *Cardiovasc Res* 1990; 24: 932–37.
2. Chester AH, Allen SP, Tadjkarimi S, Yacoub MH. Interaction between thromboxane A_2 and 5-hydroxytryptamine receptor subtypes in human coronary arteries. *Circulation* 1993; 87: 874–80.

SIR,—Dr Ottervanger and colleagues prudently advise caution in the use of sumatriptan in patients with chest pain or "tightness of the chest" after use of sumatriptan. As they mention, myocardial ischaemia and infarction have also been recorded after ergotamine,[1] an antimigraine drug that has been used for many decades. However, the fact that their particular patient had not shown signs of myocardial ischaemia after ergotamine, prompts us to put in a word of caution.

We compared the contractile effects in the human isolated coronary artery of sumatriptan and the non-selective 5-HT-receptor agonist ergotamine, and also of serotonin. The right coronary artery segments were obtained from 16 heart-beating organ donors who died of non-cardiac disorders (9 male, 7 female; aged 1–49 years). Hearts were provided by the Rotterdam Heart Valve Bank (Bio Implant Services Foundation/Eurotransplant Foundation) after removal of the aortic and pulmonary valves for homograft valve transplantation. Tension was recorded isometrically in organ baths containing oxygenated Kreb's solution. The EC_{50} and maximum effect (E_{max}) of the two antimigraine drugs and of serotonin show (table) that ergotamine was about 100 times more potent than sumatriptan. Moreover, the E_{max} of ergotamine was twice that of sumatriptan.

EC_{50} (nmol/L) AND E_{max} EXPRESSED AS PERCENTAGE OF MAXIMUM CONTRACTILE RESPONSE TO POTASSIUM, 100 mmol/L*

	EC_{50}	E_{max}	Recommended dose (mg)†
Serotonin	158 (33)	104 (9)	..
Ergotamine	4 (2)	43 (5)	0·125–0·5[2,3]
Sumatriptan	631 (128)	22 (5)	6[3,4]

*Mean (SE) shown, n=6–11, †subcutaneous.

The recommended dose of subcutaneously administered ergotamine is 10 to 48 times lower than for subuctaneous sumatriptan[2–4] (table). However, the 100-fold higher potency, combined with the 2-fold higher maximum effect, as well as the much longer duration of action of ergotamine, suggests that, in general, the cardiac liability of ergotamine is higher than that of sumatriptan. Both drugs are contraindicated in patients with known coronary artery disease. Possibly, the oral administration of sumatriptan—if feasible—would lead to a less rapid rise in plasma concentrations, which could be safer in patients who may be at risk from coronary side-effects.

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1. Galer BS, Lipton RB, Solomona S, et al. Myocardial ischemia related to ergot alkaloids: a case report and literature review. *Headache* 1991; 31: 446–50.
2. Perrin VL. Clinical pharmacokinetics of ergotamine in migraine and cluster headache. *Clin Pharmacokin* 1985; 10: 334–52.
3. Farmacotherapeutisch Kompas 1992. Amstelveen, The Netherlands: Ziekenfondsraad, 1992: 288–301.
4. The Subcutaneous Sumatriptan International Study Group. Treatment of migraine attacks with sumatriptan. *N Engl J Med* 1991; 325: 316–21.

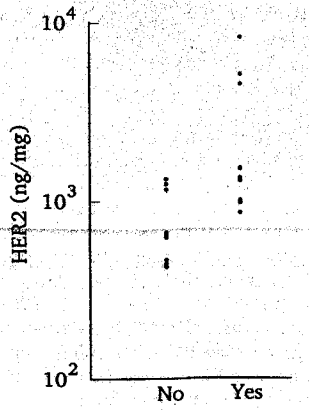
Tumour *HER2* protein in breast cancer and family history

SIR,—The *HER2* gene, located on the long arm of chromosome 17, codes for a protein with the characteristics of a growth factor receptor.[1,2] The ligand may belong to a family of proteins called heregulins.[3] *HER2* protein overexpression in breast cancers is associated with poor prognosis.[4] Moreover, *HER2* overexpression is positively correlated with inflammatory tumours, higher tumour mitotic activity, high tumour grade, large tumour size, and young age. *HER2* overexpression is negatively correlated with tumour oestrogen and progesterone receptor content.[5] We report that high tumour *HER2* protein is also associated with a family history of breast cancer.

We measured *HER2* protein in 20 women who had breast cancers excised in our centre. *HER2* protein in the tumours was measured by enzyme-linked immunosorbent assay (ELISA)[6] which, being quantitative, may be preferable to immunohistochemistry or western blotting, which are semiquantitative.[6] All assays were done by Dianon Systems, Stratford, Connecticut.

HER2 concentrations were significantly higher in women with a family history of breast cancer ($p=0·0025$, two-tailed Mann-Whitney U, figure). The 10 women with family history were predominantly post-menopausal (mean age 64·4 [SE 3·1] *vs* 57 [4·7] for the other 10; not significantly different, *t*-test). There was no significant difference in tumour DNA index between the two groups (1·13 [0·08] *vs* 1·28 [0·12]). Of the 10 women with a family history of breast cancer, 4 had a first-degree relative with the disease (mother or sister); the other 6 had a second-degree relative with breast cancer (aunts, cousins, or a niece).

A familial breast-ovarian cancer gene, BRCA1, has been localised to the long arm of chromosome 17.[7,8] This gene, associated with breast cancer in women under age 45, is not the *HER2* gene.[2] In addition, there is evidence implicating at least two genes on the short arm of chromosome 17 in breast cancer carcinogenesis.[9]



***HER2* protein in tumours of women with and without family history of breast cancer.**

Mean (SE): 742 (113) and 2607 (776) ng/mg, respectively; n = 10 per group.

The association of family history of breast cancer and raised tumour *HER2* protein suggests that another gene, linked to post-menopausal familial breast cancer, may reside on the long arm of chromosome 17. Since there are few mutations of the *HER2* gene in breast cancer,[5] the gene in question might lie in a nearby region of the chromosome which affects *HER2* expression. It would be worthwhile to try to correlate the high *HER2* concentrations and family history with a chromosome 17 marker. Linkage studies with the marker might then further localise the gene.

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1. Hoffman M. New clue found to oncogene's role in breast cancer. *Science* 1992; 256: 1129.
2. Roberts L. Zeroing in on a breast cancer susceptibility gene. *Science* 1993; 259: 622–25.
3. Holmes WE. Sliwkowski M, Akita RW, et al. Identification of heregulin, a specific activator of p185-erbB2. *Science* 1992; 256: 1205–10.
4. Paik S, Burkhard E, Lippman ME. Clinical significance of erbB2 protein overexpression. In: Dickson RB, Lippman ME, eds. Genes, oncogenes, and hormones. Advances in cellular and molecular biology of breast cancer. Boston: Kluwer Academic, 1992: 181–91.
5. Lofts FJ, Gullick WJ. c-erbB2 amplification and overexpression in human tumors. In: Dickson RB, Lippman ME, eds. Genes, oncogenes, and hormones. Advances in cellular and molecular biology of breast cancer. Boston: Kluwer Academic, 1992: 161–79.
6. Carney WP, Hamer PJ, Petit D, et al. Detection and quantitation of the human neu oncoprotein. *J Tumor Marker Oncol* 1991; 6: 53–72.
7. Hall JM, Lee MK, Newman B, et al. Linkage of early-onset familial breast cancer to chromosome 17q21. *Science* 1990; 250: 1684–89.
8. Narod S, Feunteun J, Lynch HT, et al. Familial breast-ovarian cancer locus on chromosome 17q12–q23. *Lancet* 1991; 338: 82–83.
9. Coles C, Thompson AM, Elder PA, et al. Evidence implicating at least two genes on chromosome 17p in breast carcinogenesis. *Lancet* 1990; 336: 761–63.

Fetal nutrition and cardiovascular disease in adult life

SIR,—Professor Barker and colleagues' findings (April 10, p 938) indicate that babies small at birth or during infancy have increased rates of cardiovascular disease and diabetes as adults.

Living in juxtaposition with Africans, traditionally living and transitional, we are uncertain how much of their health/ill-health is regulated by genetic and environmental factors, dietary and non-dietary. African village children, equally poor and eating the same limited range of foodstuffs, show wide ranges in various indices (anthropometrical, biochemical, haematological, faecal pH), which are not fully explained by carefully assessed dietary intakes. Doubtless, factors of genetic origin, of very early childhood experience, and of differing individual reactivity to environmental factors are in operation.

In African countries, low birthweight is twice as common as in western populations. 15% or more of infants lie below the 5th centile of growth, as indicated by US National Children's Health Study reference standards[1]—reaching 25–40% in preschool and schoolchildren.[2] Nevertheless, these conditions seem to inhibit subsequent cardiovascular disease. In black South African adults, coronary heart disease (CHD) is absent in rural dwellers, and remains rare in urban dwellers, despite the facts that a quarter have raised cholesterol concentrations, over half the men smoke, and hypertension frequency is higher than in the white population.[3] However, with the slight rise in socioeconomic status and its sequelae, the prevalence of diabetes, by contrast with its near absence in the past, is as high in elderly rural blacks as in whites.[4] In both populations the poor and less poor are affected.

Historically, in western populations up to the turn of the century, most people were very poor. Undoubtedly, low birthweight and malnutrition diseases such as rickets were far more common than now. Yet until the 1920s CHD was very uncommon: in the UK it was regarded as "a rare disease in hospitals".[5] Similarly, in the USA, when Paul Dudley White was young (in the 1920s), records at Massachusetts General Hospital did not reveal "more than a rare case of CHD" among poor people, although cases did occur among the well-to-do.[6] We therefore suggest that adverse factors at birth and immediately after manifest their long-term pathogenicity, with respect to CHD and diabetes, principally in a westernised setting—higher energy high-fat diets, smoking practice, and diminished physical activity.

What can we do toward clarification? Unfortunately, no anthropometric data at infancy are available for middle-aged black adults. As second best, we are seeking to learn from individual black patients with CHD and diabetes to what extent their early family life was very poor, average, or better off.

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1. Yach D, Coetzee N, Hugo-Hamman CT, Fisher SA, Kibel MA. Identifying children at risk in peri-urban Cape Town. *S Afr J Epidemiol Infect* 1990; 5: 6–8.
2. Walker ARP, Walker BF, Walker AJ. Slower growth and other deficits in South African black schoolchildren aged 12 years: is dietary supplementation mandatory? *Int Clin Nutr Rev* 1989; 9: 76–83.
3. Walker ARP, Walker BF. Coronary disease in blacks in underdeveloped populations. *Am Heart J* 1985; 109: 1410.
4. Walker ARP, Walker BF. Diabetes prevalence in elderly rural blacks in South Africa. *S Afr J Food Sci Nutr* 1991; 3: 68–71.
5. McCrae T. Osler's principles and practice of medicine. London: Appleton, 1912: 836.
6. White PD. The cardiologist enlists the epidemiologist. *Am J Public Health* 1957; 47: 1–3.

SIR,—Professor Barker and colleagues, in their review of the effects of fetal nutrition on cardiovascular disease in adult life, risk seriously misleading clinicians and other non-specialists about the effects of maternal undernutrition in pregnancy. Their long-term, retrospective, epidemiological studies are a valuable stimulus to further reflection, but I believe that their ideas on possible physiological mechanisms may be misconceived and counterproductive.

Intrauterine growth retardation may be mainly caused by maternal undernutrition and excessive physical labour, as well as closely spaced pregnancies and disease, in parts of the developing world, but there is no evidence that the same is true in industrialised countries such as the UK. The test is whether supplementary feeding of pregnant women in the UK increases birthweight, and it does not. Smallness for dates for our women has a multitude of causes, many of them unknown, and there are many known non-nutritional factors in the environment related to lifestyle—but undernutrition is not known to be among them.[1]

Even in communities in which undernutrition is a contributing factor, this factor can only be shown to operate in the last trimester, and has not been shown in man in early embryonic life or in mid-pregnancy. It is not helpful to assert that embryonic and trophoblast growth are influenced by the concentration of nutrients,