these values would not be. On the basis of validation work done in Britain on the Guy's score[5] this would deprive about 5% of patients with infarcts of aspirin treatment, resulting in an increase of only about two preventable events per 1000 patients per three years. Delaying aspirin treatment for 30 days may also "result in an increase in some preventable events, but it is difficult to calculate how many and the number is probably not great. Until the results for the international stroke trial are available it is probably best to delay aspirin for 14 days anyway. The assumption that aspirin will cause rebleeding in all cases of haemorrhagic stroke is almost certainly pessimistic but is based on the axiom "first of all do no harm."

ROBERT F LOGAN
Consultant geriatrician
SUSAN M POULTON
Senior registrar
MARTIN P SEVERS
Consultant geriatrician
Department of Medicine for Elderly People,
Queen Alexandra Hospital,
Portsmouth PO6 3LY

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Adverse reactions to measles immunisation

EDITOR,—Richard Aickin and colleagues state that hypersensitivity reactions to measles vaccine in children with allergy to egg protein are mild and not related to the severity of the clinical reaction to egg.[1] Our data are not consistent with this.

We evaluated immediate adverse reactions after measles vaccination during a campaign against measles in the area of Parma, Italy, between November 1990 and June 1992. Children were immunised with a vaccine grown in human fibroblast culture (Moraten, Berna), which is recommended for children with allergy to eggs. After being immunised the children were observed for at least 30 minutes at the vaccine clinic. The doctors referred children with possible hypersensitivity reactions to the vaccine to the department of paediatrics.

Measles vaccine was given to 3300 children aged 13 months to 10 years. Three children were admitted to the department of paediatrics because of severe reactions a few minutes after administration of the vaccine (table). They were treated with subcutaneous adrenaline, intravenous hydrocortisone, nebulised salbutamol, and intramuscular promethazine. The symptoms resolved completely. All three children had a history of atopy (table). Results of skin prick tests and levels of specific IgE antibodies to the allergens listed in the table were positive. Food allergy was ascertained by controlled challenges.

Our data emphasise the potential of measles vaccine to cause appreciable adverse reactions in children with a history of severe multiple allergies, including allergy to egg. Differences between our population and that studied by Aickin and colleagues may explain the differences between our findings. As the measles vaccine in our study was not grown in chick embryo fibroblast culture, reactions may have been due to cross reactivity between constituents of the vaccine and either egg or cows' milk proteins.[2,3] We agree that "measles immunisation should be performed in a setting where any adverse reactions can be dealt with appropriately." Our results suggest, however, that this practice should be restricted in children with severe food allergy.

CARLO CAFFARELLI
Registrar
GIOVANNI CAVAGNI
Senior registrar
Clinica Pediatrica,
Università di Parma,
43100 Parma, Italy
FRANCA MARIA DERIU
Senior registrar
GIAN FRANCO ZAMBELLONI
Consultant
Servizio Materno-Infantile, USL 4,
Parma

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Reactions to measles vaccine and history of atopy in three children

Case No	Sex	Age at immunisation (years)	Reaction after immunisation	History of atopy: Allergens	History of atopy: Clinical reactions
1	M	4	Urticaria, angio-oedema, diffuse rash, wheezing, hypotonia	Egg	Vomiting, dyspnoea, cough, generalised urticaria
				Cows' milk, potato, wheat	Atopic eczema
				Trout	Generalised urticaria, atopic eczema
2	F	8	Pallor, vomiting, cough, wheezing, urticaria, angio-oedema	Egg	Vomiting, atopic eczema, swelling of mouth, generalised urticaria
				Cows' milk	Vomiting, rhinitis, wheezing, atopic eczema, angio-oedema, Swelling of mouth
				Mites, grasses	Rhinitis, asthma
3	M	4	Drooling, urticaria, dyspnoea, vomiting, abdominal pain, hypotension, hypotonia, pallor, sweating	Egg	Never previously ingested
				Cows' milk	Abdominal pain, pruritus, generalised urticaria, dyspnoea, atopic eczema
				Grasses	Asthma, rhinitis

Measles and rubella immunisation campaign

EDITOR,—In a letter to district general managers and district directors of public health the Department of Health has announced a measles and rubella immunisation campaign starting on 1 November.[1] It is aimed at all children aged 5 to 16 on the supposition that this will prevent an epidemic of measles next year. The evidence for this campaign has not been published. The campaign is unprecedented in terms of the number of immunisations required in the time allotted and in that family doctors have been excluded from the work unless given a contract from within their own health district; the department now says, however, that family doctors may be used for tracking down missed children (personal communication).

The campaign will produce considerable strains on purchasers, financially, and on providers, who are already fully committed. In a letter to consultants in communicable disease control the Department of Health suggests that the BCG campaign scheduled for the autumn could be postponed[2]—this at a time when tuberculosis is increasing considerably in many parts of Britain.

Would not the hypothetical epidemic be curtailed if the campaign had been arranged over a full academic year and had involved both community health services and family doctors, thus spreading the load to much more manageable proportions?

HARVEY GORDON
Consultant in communicable disease control
Community Health Service,
West Park Hospital,
Epsom,
Surrey KT19 8PB

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Cardioprotective effect of hormone replacement therapy

Is not due to a selection bias

EDITOR,—Ward F M Posthuma and colleagues have shown that many of the studies that report reductions in the risk of coronary disease among postmenopausal women using hormones also show decreases in cancer.[1] They claim that this implausible result shows a selection bias toward healthier women for hormone treatment and that the benefits in terms of heart disease must be considered to be suspect. In the exchange of correspondence they do not address the substantive arguments raised by Stevenson and Baum but instead accuse them of showing "ignorance of common medical reasoning."[2,3] Posthuma and colleagues, however, seem themselves to have ignored some common medical reasoning.

In their paper they talk about "total cancer within each study," but in many instances the studies were reporting the mortality from cancer rather than the incidence of cancer. This is an important distinction because, typically, patients who die of cancer have had the disease diagnosed previously. It is well known that many physicians refrain from giving hormones to postmenopausal women who have already been diagnosed as having cancer. Hence studies of mortality from cancer will naturally tend to show a spurious protective association of postmenopausal hormones unless women with cancer at the baseline have been excluded. This spurious association has nothing to do with the selection of women according to their risk of coronary disease.

A direct and more relevant approach would have been to assess the distribution of risk factors for coronary heart disease among users and non-users of oestrogen. Most studies that have made this comparison have indeed found that users tend to have a more favourable profile of risk factors. Because this is primarily a sociological rather than a biological association, however, the differences in the profiles of risk factors will vary widely according to the population studied. In particular, one would expect that in general population surveys the differences in the profiles of risk factors

Profiles of risk factors in users and non-users of oestrogen in two studies

	Current user*	Past user	Never used
Nurses' health study[4]			
Current smoker (%)	11·2	14·7	14·5
% With hypertension	23·2	25·0	21·8
% With diabetes	2·7	3·8	3·5
% With high serum cholesterol	9·9	11·2	7·6
% With parental myocardial infarction before age 60	10·6	10·0	9·3
% Taking vigorous physical activity ≥ once per week	48·2	43·1	42·4
% With body mass index ≥ 29 kg/m²	9·8	13·3	15·0
Lipid Research Clinics programme[5]*			
< High school education	16		25
% Smokers	33		31
% Taking regular exercise	12		10
% Drinking alcohol	82		79
Mean body mass index (kg/m²)	24·7		25·7
Mean age (years)	53·8		52·6
Mean systolic blood pressure (mm Hg)	129·0		127·7
Mean diastolic blood pressure (mm Hg)	79·9		79·5
Mean cholesterol	234·8		235·2

*In Lipid Research Clinics programme data for current and past users were combined.

would be greater than those in the relatively homogeneous populations from which much of our understanding of the epidemiology of hormones and heart disease derives. The table shows the distribution of risk factors for two large epidemiological studies that have provided data on oestrogen replacement therapy and heart disease; the differences in the profiles of risk factors are fairly modest. Moreover, adjustment for these differences has not materially altered the estimates of relative risk. Hence selection of healthier women for hormone treatment is unlikely to explain a major portion of the reduction in coronary heart disease.

MEIR STAMPFER
Professor epidemiology and nutrition
Harvard School of Public Health,
Boston, MA, USA

FRANCINE GRODSTEIN
Instructor in medicine
Channing Laboratory,
Department of Medicine,
Brigham and Women's Hospital,
Harvard Medical School,
Boston, MA 02115, USA

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Benefits women with established cardiovascular disease

EDITOR,—Ward F M Posthuma and colleagues postulate that the reported benefits of hormone replacement therapy in reducing the risk of cardiovascular disease in postmenopausal women may be due to unintended selection of relatively healthy women.[1] The implication of this is that, had sufficient women with cardiovascular disease been present at the start of the epidemiological studies, a result with a lower significance would have been obtained. It is relatively simple to analyse this hypothesis by using data that were only partially considered in their review.[2]

Sullivan *et al* presented findings from a cohort of 1822 women with cardiovascular disease documented angiographically.[2] Over 10 years the relative risk of death from cardiovascular disease fell by 89% among women using oestrogen compared with non-users. This implies that there is a greater benefit for postmenopausal women with established cardiovascular disease than for healthy women. It should also be remembered that premenopausal women with oestrogen deficiency resulting from a surgical or premature menopause have a risk of cardiovascular disease roughly three times that of women with normal oestrogen concentrations.

A second fundamental flaw in Posthuma and colleagues' paper is that the authors chose total cancer as being a disease that is "unlikely to be influenced by oestrogen." This assumption may be unsound. Fotsis *et al* showed that 2-methoxyoestradiol, an endogenous oestrogen metabolite, is a potent inhibitor of the proliferation and migration of endothelial cells and an inhibitor of angiogenesis both in vitro and in vivo.[3] Angiogenesis is essential for successful tumour growth, and the antiangiogenic properties of interferon alfa have been shown to be promising in the treatment of haemangiomas.[4] Such findings in no way confirm a protective effect against cancer in oestrogen users after the menopause but may go some way to explaining the absence of the much predicted increase in breast cancer in such women. More fundamentally, it shows that one must be careful about making assertions about the impossibility of an observed effect.

Although the degree of protection that oestrogen replacement therapy offers against cardiovascular disease may be subject to selection bias favouring healthy subjects, whether this results in an overestimate or an underestimate of the true benefit cannot be stated with certainty. It remains to be elucidated whether oestrogen replacement therapy may also reduce the risk of all cancers in postmenopausal women through an effect on angiogenesis.

DAVID SPIERS
Head of British cardiovascular research and development
E Merck Pharmaceuticals,
Alton,
Hampshire GU34 1HG

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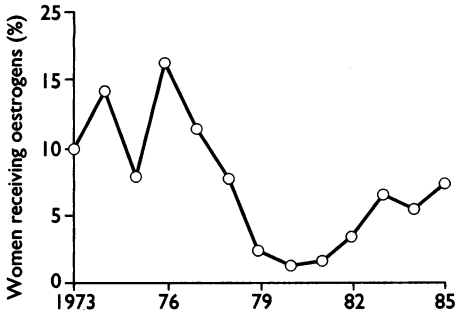
Authors' reply

EDITOR,—For reasons other than David Spiers suggests, the paper by Sullivan *et al* clarifies the subject. The figure, based on their data, shows the percentage of women using oestrogens at the time of cardiac catheterisation for each year of the study. The downward trend in the late 1970s indicates that the prescription of oestrogens was omitted in patients with signs and symptoms of coronary artery disease. The authors ascribed this reluctance to prescribe oestrogens to the increased frequency of myocardial infarction observed in men receiving oestrogens for secondary prevention. Most probably, oestrogen replacement therapy was stopped in patients who developed coronary artery disease and continued only in those with a favourable course. This differential prescription may explain why the effect of use of oestrogen was not significant when the data were analysed by treatment received at the time of



Percentage of women receiving oestrogen replacement therapy at time of diagnostic coronary angiography (data from Sullivan et al's study[1])

angiography. It also explains the lower mortality in women who subsequently used oestrogens.[1]

Even more fundamental than making assertions about the (im)possibility of an effect is weighing arguments for a plausible biological explanation.[2] Here we have to consider the possible beneficial effect of 2-methoxyoestradiol as an antiangiogenic compound not only for haemangiomas but, as stated in the original paper, also for rheumatoid arthritis, psoriasis, and diabetic retinopathy. As 2-methoxyoestradiol is an endogenous oestrogen metabolite the concentrations are probably higher in women. 2-Methoxyoestradiol is unlikely to have an important action because in most of these diseases neither sex predominates, whereas rheumatoid arthritis is almost exclusively a disease of women. On the other hand, recent Swedish evidence has led to the conclusion that the high oestrogen concentrations associated with pregnancy have a long term protective effect against breast cancer by inducing differentiation of normal mammary stem cells but increase the risk by stimulating the growth of cells that have undergone the early stages of malignant transformation.[3]

Now we know that the observational studies on cardiovascular diseases have been subject to selection of healthy subjects we should realise that their results are difficult to interpret.[4,5] They give us clues for further development of scientific ideas on the relation between sex hormones and cardiovascular disease. An inference about preventive measures is a step too far.

WARD F M POSTHUMA
Resident in internal medicine
RUDI G J WESTENDORP
Lecturer
JAN P VANDENBROUCKE
Professor
Department of Clinical Epidemiology,
Leiden University Hospital,
PO Box 9600,
2300 RC Leiden,
Netherlands

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Supervision registers for mentally ill people

EDITOR,—Glynn Harrison and Peter Bartlett set out several anxieties concerning the implementation of supervision registers for mentally ill people.[1] In particular, they question the clarity of the Department of Health's guidance about which patients should be included on the registers.