menstrual syndrome might result from an overlap in symptoms. There could be no such overlap, however, to explain the link that we found between psychiatric state and the physical symptoms of the premenstrual syndrome. We know of no other source of contamination in our data. If, however, we had used the rating scale for the climacteric syndrome recommended by Drs Bell and Katona the findings would certainly have been contaminated by anxiety and depressive symptoms.

Drs Bell and Katona consider the association that we reported between vasomotor symptoms and psychiatric state to be "especially problematic." They attribute three statements to us (the first and third being incorrectly reported) and refer to "apparent inconsistencies" between them. We reported that psychiatric state was, firstly, associated with vasomotor symptoms in the two age groups 40-45 and 45-49, secondly, not associated with age, and, thirdly, not associated with menopausal state defined by the time scale mentioned above.

Our study is said by Drs Bell and Katona to have "methodological flaws in its design and data analysis." This is puzzling. Though they comment on our assessment procedures, they say nothing about the design of the study or the data analysis (apart from saying that no multivariate techniques were used to resolve inconsistencies that did not exist). In addition, they warn against the uncritical acceptance of our "implied conclusion that many gynaecological symptoms are psychiatric in origin." We implied no such conclusion. In discussing aetiology, we simply suggested that in psychiatrically vulnerable women gynaecological symptoms might induce emotional symptoms or that chronic difficulties might induce psychiatric disorders that could make women more likely to pay attention to gynaecological symptoms, or find them distressing, or regard them as abnormal. Do Drs Bell and Katona dispute these suggestions?

After careful consideration of their letter we conclude that their criticisms of our assessment methods, however strongly worded, are of no substance; that in our study highly significant associations were found between precisely defined gynaecological symptoms and standard measures of mental state and neuroticism; and that there is no reason to revise our aetiological suggestions.

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Acyclovir and pregnancy

SIR,—We agree with Dr C L S Leen and colleagues (31 January, p 308) that further data on the use of acyclovir in pregnancy are needed to determine whether it is harmless to the unborn child. As part of a more extensive epidemiological survey of all aspects of the clinical safety of the drug we are collecting information about pregnant women who have been exposed to acyclovir. Cases notified to the acyclovir in pregnancy registry before the outcome of pregnancy is known are followed up after delivery to ascertain neonatal outcome. This information is made available to doctors who have to advise patients on the relative risks and benefits of treatment or on the continuation of pregnancy after inadvertent exposure to the drug. Cases notified to us after the outcome is known are also reviewed descriptively but will not be used to calculate rates of abnormal outcomes because of the likelihood of selection bias.

Entries in the register have accumulated slowly over the past two years, and there are too few cases to warrant general publication or conclusions about the safety of the drug at any stage during pregnancy. The information is, however, reviewed by an independent advisory committee and summarised every few months, and these summaries will be made available in confidence to any health professional on request.

We depend on the continued cooperation of doctors who are responsible for cases suitable for inclusion in this study. Risk-benefit decisions concerning the wellbeing of the fetus should be based on firm ground, and until the results of formal epidemiological studies are known we hope to provide that base from an increasing number of prospectively notified cases in the register. Notifications of new exposures or requests for information should be made to one of us or to the medical director of the local Wellcome company.

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Oral acyclovir in acute herpes zoster

SIR,—Though we would not dispute the conclusions of Dr M W McKendrick and others (13 December, p 1529), their choice of placebo group makes it difficult to apply them in the spirit of scientific medicine.

When examining an analgesic effect it is reasonable to compare the trial drug with conventional analgesia, but it would seem that this was not done. This is surprising, particularly as acyclovir is a very expensive analgesic. The improvement in rash healing also seems to be in comparison with no treatment, although to design a trial otherwise would be difficult. Topical idoxuridine in dimethyl sulphoxide has been used for several years and is thought to be effective^{1,2}; it would have been useful to know if oral acyclovir was an improvement on this.

Though there are sound theoretical reasons for thinking that oral acyclovir is useful when given in the first three days of rash, if the clinical response is no better than the response to conventional, supportive treatment its general use should not be encouraged, especially as the evidence suggests that it does not affect postherpetic neuralgia.

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AUTHORS' REPLY—We were surprised that Mr R J Marsh and Dr M Cooper questioned our inclusion of a placebo group and are uncertain what they mean by "the spirit of scientific medicine." They also state that topical idoxuridine is thought to be effective, but we would dispute that this has ever been confirmed adequately. Shingles is a variable disease, and in trials controlled adequately for this variability topical idoxuridine in dimethyl sulphoxide in the conventionally prescribed dose

(5% idoxuridine) was not shown to have any benefits.¹ The higher strength preparation has to be applied with lint for it to be of any use, which is impractical in an outpatient setting.

The controlled use of a specific analgesic drug, particularly in a domiciliary study, is neither practicable nor possible. The pain relief derived from different drugs varies between patients, as does preference for different drugs, in relation to patients' tolerance and the side effects experienced. Patients often need two or three changes of drug before optimum analgesia is achieved. In our study there was no significant difference in analgesic use between the acyclovir and placebo groups.

Drs Marsh and Cooper suggest that the clinical response to the antiviral acyclovir "is no better than the response to conventional, supportive treatment." This is exactly what we have been studying, and there is no doubt from our data that patients do respond to acyclovir, particularly those who have severe pain and who start treatment within 48 hours of the onset of the zoster eruption.

Though an effect on pain and rash healing has been shown in the acute illness, no effect on postherpetic neuralgia has been reported. This must be the ultimate goal in treating zoster, and we will soon be in a position to analyse the six month follow up of the many patients in our multicentre study. Only when all the data are available will we be able to provide more precise guidelines as to who is likely to benefit from treatment and how acyclovir should best be used in managing patients with zoster.

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Better reporting of adverse drug reactions

SIR,—Dr John Griffin (28 February, p 576) advocated a scheme of cohort identification that would enable the possible cause and likely number of any adverse reactions to be estimated more accurately. The sensitivity of the method would depend on the size of the cohort initially identified.

Although the introduction of yellow forms in the back of the *British National Formulary* and in FP10 prescription pads increased the notification of adverse drug reactions to the Committee on Safety of Medicines by 24%, from 12 500 to 15 500 yearly, the notification of adverse drug reactions still needs improvement, and any means whereby this can be achieved should be encouraged.

It has always seemed anomalous to me that the manufacturer of the medicine to which an adverse reaction occurs does not automatically receive the same detailed information from the doctor reporting the adverse drug reaction as the Committee on Safety of Medicines. Admittedly, the committee provides information in a tabulated, anonymised form for the pharmaceutical industry, but details of patients and of reporting doctors are not conveyed to manufacturers, and much of the other information given on the yellow card, including concomitant treatment, for example, is not available; it is, of course, ethically correct that details that might identify patients remain confidential. The overwhelming impression, however, from doctors with whom I have discussed this problem is that they would not object to details of the reporting doctor being sent to

the pharmaceutical company concerned. Nevertheless, the Department of Health and Social Security insists that the reporting doctor should remain anonymous when details of adverse reactions are passed to pharmaceutical companies, and any representations to allow the name of the doctor to be conveyed to the company have failed.

I suggest, therefore, that the yellow report form should be produced in triplicate rather than singly. The reporting doctor would then retain a copy of what he had reported. The top copy would still go to the Committee on Safety of Medicines, and the second copy, without the name of the patient, would go to the Association of the British Pharmaceutical Industry, which would act as a clearing house for forwarding to the relevant company. Just as the top copy is Freepost to the committee so the second copy would be Freepost to the association. The major advantage of producing a form in triplicate would be that the decision to send a second copy to the pharmaceutical company would remain with the reporting doctor. Obviously, I would hope that most second copies would indeed be sent to manufacturing companies. The introduction of the triplicate form and the cohort identification system would enhance the notification of adverse drug reactions and would make a system that is already probably better than any other in Europe the best in the world.

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Primary pulmonary hypertension

SIR,—Drs Celia Oakley and A Rozkovec (10 January, p 122) regard long term prostacyclin infusion as an unnecessary, complicated, and dangerous treatment for primary pulmonary hypertension. We believe that we are the only group with experience of this form of treatment and that their conclusions are speculative.

The patients seen at Papworth have been referred for heart-lung transplantation. In those whose haemodynamic function deteriorates despite treatment with oral vasodilators, including nifedipine, and who fall into the poor prognosis group we use a prostacyclin infusion to buy time and improve the quality of life. Such patients have a pulmonary arterial blood oxygen saturation of less than 63% and only a 17% chance of surviving for three years.¹ Prostacyclin sustains these patients during the necessarily long time (up to two years) that they spend on the waiting list for the operation. For obvious reasons the number of patients so treated is very small, but our experience suggests that prostacyclin is no more complicated and dangerous to use than the previously ineffective oral vasodilators.²

The other point that needs clarification is Drs Oakley's and Rozkovec's belief that the gas transfer for carbon monoxide is always reduced in primary pulmonary hypertension, a belief not shared by others.^{3,5} It is fairly straightforward to explain why patients with pulmonary vascular disease, including pulmonary hypertension, may have a normal carbon monoxide transfer factor.⁴ If the capillaries are not directly affected by the obliterative or obstructive lesions they will contain red blood cells capable of taking up carbon monoxide. Filling of these capillaries depends on the various pressures acting on the pulmonary vascular bed and may be augmented by collateral blood flow from bronchial arteries.^{4,6} In addition, such patients also seem to have a normal ventilation to perfusion ratio,^{7,8} suggesting that many will indeed have a normal carbon monoxide transfer factor.

Finally, Drs Oakley's and Rozkovec's distinction between thromboembolic veno-occlusive disease and primary pulmonary hypertension according to the response to vasodilators is unfortunately spurious. It probably requires the detailed pathology of the patients' vascular disease to be correlated with premorbid or pretransplant physiological results. Such studies are only just beginning, and initial evidence suggests that all the pathological types of the syndrome show some degree of vasodilation with treatment.⁹ Studies of thromboembolic disease certainly indicate that pulmonary hypertension may be partially reversible with vasodilators.¹⁰

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**This correspondence is now closed.—ED, *BMJ*.

HIV transmitted by kissing

SIR,—Dr J W G Smith has responded (14 February, p 446) to my letter published in the *Guardian*, in which I challenged the Chief Medical Officer or any of the medical and scientific experts advising the government on the acquired immune deficiency syndrome (AIDS) to cite "even one published paper which gives detailed laboratory evidence that there is any cell-free infectious virus (human immunodeficiency virus or HIV) in semen; or cite even one published paper specifying the number of cells in semen containing either viral RNA, or pro-viral DNA, or both."

Although Dr Smith gave 16 references, he failed to cite a single relevant paper in response to the challenge, for the simple reason that no such paper exists. He cited two studies in support of his claim that HIV "can be detected fairly easily in semen from infected people."^{1,2} Only two people were described in the first study and one person in the second. In no case was any cell free virus detected in the semen, nor did spermatozoa contain any cell associated virus, nor could HIV antigen be detected in any lymphocytes found in the seminal fluid. Only after lymphocytes from semen had been cocultured for six to 11 days in the presence of other lymphoid cells and of T cell growth factor interleukin-2 were HIV antigens detected in any of them. These two studies, published in October 1984, proved no more than that at least one lymphocyte in a single specimen of semen from each of three men contained HIV proviral DNA. No viral RNA, or antigen, or any virion, could be detected until the semen had been subjected to prolonged, highly artificial laboratory conditions.

In the two and a half years since these two papers were published no further detailed laboratory study of

the presence of HIV in semen has been published. Professor Jay Levy (personal communication) has detected HIV in the semen of only 10% of more than 50 men who had HIV in their blood. He has already published the finding that HIV can be detected in semen only if the lymphocytes in it "are cultured under optimal laboratory conditions"; usually none can be found.

Understanding of the pathogenesis and transmission of a viral disease requires knowledge of the quantity of virus shed into bodily fluids, the duration and variability of shedding, the balance between cell free infectious virions and cell associated virus, the stability of the virus in the environment, and the route of entry into the host. This well established principle has been neglected by many experimental and medical scientists who, like Dr Smith and other members of the government's expert advisory group on AIDS, have accepted uncritically the hypothesis that "HIV is transmitted primarily by sexual intercourse." Many have been so certain of the validity of this flawed hypothesis that they have assumed that experimental studies support it, even though they do not.

Nineteen experimental scientists said in *Nature*: "High titres of cell free infectious virions can be obtained from AIDS patients' semen."^{3,4} The papers in *Science* cited in support of this fact showed that no cell free infectious virion had been found in semen.^{1,2} Eight medical and experimental scientists wrote in the *Lancet* that HIV "circulates as cell free virus in . . . seminal fluid."⁵ They adduced as evidence the paper in *Science*, in which the authors reported that "because of the toxic effects of semen on target cells used for these isolations, it is unclear whether there is also cell free (HIV) in seminal plasma."²

Dr Robert Gallo, in a paper delivered to a plenary session of the second international conference on AIDS in Paris in June 1986, said: "We think that semen is a particularly rich source of virus," although he gave no scientific evidence to substantiate these thoughts. The BBC's Radio 1 programme *Play Safe—AIDS and You* (13 December 1986) asserted that "virus is present in semen in very high concentrations." Sir Donald Acheson, Chief Medical Officer; Dr Anthony Pinching, a member of the government's advisory group on AIDS; and Dr John Dawson, head of the scientific division of the BMA, were the medical experts speaking on the programme.

As to the infectivity of saliva, Dr Smith wrote: "The difficulty in determining the relevance of such *in vitro* studies is evident in the reference⁶ quoted by Dr Seale on virus in saliva. The method of culture employed in that study could not have differentiated between cell free and cell associated virus." The relevant words in the text of the Groopman study are: "Saliva samples were diluted to a final volume of 2 ml in complete growth medium, incubated for 2 hours at 37°C, and centrifuged at 1000 g for 10 minutes at 4°C. Pelleted materials were fixed for electron microscopy, and supernatant fluids were filtered (0.45 µm) and used for transmitting virus to fresh peripheral blood lymphocytes."⁶ Similar words were used in the caption to table I in the paper. Groopman and his colleagues make it crystal clear that cell free infectious virions were obtained directly from the saliva of eight of 18 men who had antibodies to HIV in their blood. Furthermore, figures 1c and 1d are electron micrographs of "mature virus particles . . . obtained from the saliva of patient No 8."

There are three essential properties that a parasitic microbe must have in its interaction with the human host if the disease it causes is to be transmitted characteristically by sexual intercourse. Firstly, the microbe must be shed in large quantities in genital secretions and not in other body fluids. Secondly, it must be able to enter a person only through the genitalia. Thirdly, it must perish within a few minutes outside the body. If any of these properties is missing the microbe may be transmitted by various means in addition to sexual intercourse. A major flaw in the hypothesis that HIV is transmitted primarily by sexual intercourse is that none of the pathogenic properties essential to make it so is present.

When HIV is indeed transmitted during sexual intercourse nobody knows if it is usually passed on in saliva, or in the serum from minor abrasions, or in genital secretions, or in some other way. Consequently, there are good reasons to doubt the claim made by experts advising the government