using the pill early because they had had a thromboembolic event). The users of products containing levonorgestrel and norethisterone might then comprise, in effect, a population of survivors who are less at risk of the condition under study. I understand that further analyses are in progress to test this hypothesis in various ways.

The same model, however, has important implications for prescribers now. A first time user could have an undiagnosed congenital or acquired abnormality of coagulation or fibrinolysis,² which would put her into what is believed to be the main minority group, in whom the small incremental changes caused by the pill are able to reach the threshold for a thrombosis. On the other hand, the established user of ethinyloestradiol (even if this is combined with a third generation progestogen) has, by her continuation with the drug for years without problems, shown her relative insusceptibility to venous thrombosis.

This argument means, firstly, that, should women taking third generation pills fail to respond to the current publicity, there is no pressing urgency to recall them for a discussion of the possibility of changing their brand. If it is logistically possible, however, it would be preferable medicolegally to contact those who are known to be predisposed to thrombosis (through obesity, for example). Secondly, might not the Committee on Safety of Medicines have used this same argument as the basis for a much less pressurised warning, recommending discussion of a possible change of prescription at women's next routine visit concerning the pill?

A useful additional point to make while counselling a woman who has taken the pill for several years is that, though her risk is never zero, as she has not had a venous thrombosis during these years she is particularly unlikely to have one. "The informed user should be the chooser."

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Committee's action has compromised continuing studies

EDITOR,—Douglas Carnall's report of the controversy over whether the third generation contraceptive pills are associated with an increased risk of thrombosis contains an error that illustrates how bias may arise in a case-control study such as that led by Professor Walter Spitzer.¹ Carnall states that the study "matches 980 users of the combined pill who have a cardiovascular event with 2200 controls." In fact, the study matched 870 women who developed the disease of interest—that is, cardiovascular events—with 2900 matched controls. A large percentage of these women were not taking or had never taken a combined pill.

Bias could have arisen in the study if recruiting physicians, with the best of intentions, actively recruited women using the pill who developed the disease of interest. We believe that this may have happened in some instances, which would artificially inflate the risk. We continue to check the data for bias. This possibility also illustrates the possible danger inherent in hasty action before careful review of the data. The action of the Committee on Safety of Medicines has clearly compromised important, continuing studies such as the one with which we are involved.

We urge that further action should not be taken until the peer reviewed data are available for scrutiny and regulatory bodies can agree on a single course of action for a problem that is clearly

worldwide. The ultimate decision must involve a balancing of the risks of thrombotic events with possible protection against myocardial infarction.

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Risk is highest during first months of use

EDITOR,—The well known association between use of oral contraceptives and venous thromboembolism received renewed interest when the results of three unpublished epidemiological studies suggested that the newer oral contraceptives containing third generation progestogens are associated with an increased risk of venous thromboembolism compared with the older oral contraceptives.^{1,2} Part of the explanation for this could be the shorter average duration of use of the newer oral contraceptives: if the risk of venous thromboembolism was highest during the first months of use it would be lower among women who had taken their oral contraceptive for longer than this without complications. To test this hypothesis we analysed spontaneous reports of adverse drug events received by NV Organon.

We looked at all spontaneous reports of venous thromboembolic events associated with the use of Marvelon (150 µg desogestrel and 30 µg ethinyloestradiol) and Mercilon (150 µg desogestrel and 20 µg ethinyloestradiol) entered into the product surveillance database up to 1 July 1995. We calculated (or estimated) the interval between the time when the contraceptive was started and the time when the event occurred. The figure shows the distribution of duration of use relating to the venous thromboembolic events (both drugs combined). Nearly half of the events occurred within the first six months of use.

The figure suggests a strong effect of duration of use on the risk of venous thromboembolism. Several limitations should be borne in mind. Firstly, the longer women have used oral contraceptives the less able they are to recall the date of

Reports of venous thromboembolic events as percentage of all adverse drug events associated with Marvelon and Mercilon (n=434) by duration of use (estimated total exposure is over 36 million woman years)

the start of treatment accurately. This, however, will lead to an underestimation of the effect as it will result in non-differential misclassification over the strata of duration of use. Secondly, the pattern of our findings should be contrasted with the overall distribution of duration of use of oral contraceptives in the general population. As the mean duration of use in the general practice research database study exceeded 16 months (H Jick *et al*, unpublished findings) high rates of early discontinuation cannot explain the sharp decrease in the rate of reporting over the first months of use shown in the figure. Thirdly, use of spontaneous reports could introduce bias since the tendency to report an event decreases with increasing duration of use. There is no reason to suspect, however, that doctors would be more likely to report a thrombotic event associated with short term than with long term use.

Our findings are consistent with an effect of duration of use: the risk of venous thromboembolism is higher during the first months of use. A consequence of this could be that when short term use of a certain type of oral contraceptive is overrepresented in a dataset the risk of venous thromboembolism associated with that type of contraceptive will be overestimated if appropriate adjustment is not made.

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Studies implicate only gestodene and desogestrel

EDITOR,—The Committee on Safety of Medicines' advice to the profession on combined oral contraceptives led to two editorials^{1,2} and three other items.³⁻⁵ All the authors, apart from Naomi Craft,⁵ incorrectly reported the committee's warning as extending to all "third generation" or "newer" combined oral contraceptives, whereas these two terms do not appear in the committee's letter. The committee's warning related only to desogestrel and gestodene. In addition, the committee recommended that "No change in prescribing practice is required for any other combined oral contraceptive."

Janssen-Cilag markets Cilest, a combined oral contraceptive that contains the third generation progestogen norgestimate. I hope that my letter corrects any confusion that readers may have about Cilest's position.

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Committee's action will undermine further research and development

EDITOR,—We deplore the failure of the Committee on Safety of Medicines and its chairman, Professor Michael Rawlins, to understand the issues raised by their hasty and ill considered advice to doctors not to prescribe oral contraceptives containing the

progestogens desogestrel and gestodene.¹ Rawlins claims that the committee has to take on the responsibilities of peer reviewers with regard to unpublished information.² In this it presumes to act as both judge and jury, a single role that the United States Food and Drug Administration rightly refuses to assume. Presented with similar problems, the administration embarks on detailed public hearings, with the eventual publication of a comprehensive report.³ The necessity for such consultation is evident in the dissent from John Guillebaud, with his great experience of oral contraceptive prescribing⁴; Clifford Kay, who directed the Royal College of General Practitioners' classic investigation into the safety of oral contraceptives⁵; and W O Spitzer, whose transnational study was used by the Committee on Safety of Medicines in reaching its decision.⁶

In justifying the committee's decision Rawlins dismisses the methodological problems in the recent studies of venous thromboembolism in women using the pill yet attempts to undermine the importance to be attached to the accumulating data on stroke and myocardial infarction.² He also denigrates the importance of changes in lipoprotein concentrations induced by oral contraceptives, on the basis of a review that hardly discusses this issue. The risks of stroke and myocardial infarction are a critical consideration. Women of childbearing age are 15 times more likely to die of arterial disease than of venous thromboembolic disease, and the third generation pills were introduced specifically to reduce the risks of arterial disease in women using oral contraceptives. This is acknowledged in the fact that the European Committee for Proprietary Medicinal Products is to defer a decision on the safety of the third generation pills.

Unfortunately, the precipitate action of the Committee on Safety of Medicines may have seriously damaged our chances of learning just what effect the new pills have on arterial disease. More importantly still, it may also have irrevocably undermined any further research and development on oral contraceptives by the pharmaceutical industry. What justification can there be for such work if it is to be rendered irrelevant overnight by a single rush to judgment?

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Was Committee on Safety of Medicines' advice arrived at lawfully?

EDITOR,—Michael Rawlins seeks to defend the Committee on Safety of Medicines' recent advice on third generation oral contraceptives.¹ Prescribers should be aware that the committee's published advice may not have been arrived at lawfully because of questions regarding process and whether the advice was disproportionate and beyond the committee's authority.

Consideration of the issue seems to have been hasty and not based on all relevant data. Spitzer *et al*'s analysis was made available on 9 October and Jick *et al*'s manuscript on 11 October, and

members of the committee were given 30 minutes to consider the data on 13 October.² Rawlins's refutation of "undue haste" is unconvincing. Furthermore, Rawlins suggests that there are three relevant studies. That is incorrect. Farmer *et al* published a study recently,³ and have subsequently conducted further relevant analyses. The committee does not seem to have considered these data.

The committee's advice may not be proportionate. The statement in the "Dear Doctor" letter that third generation oral contraceptives should "only be used by women who are intolerant of other combined oral contraceptives"⁴ does not seem to be supported by the totality of data available to the committee.

The statutory framework within which the committee exists provides only for its giving advice to the licensing authority. As the committee disseminated advice unconnected to regulatory action it is arguable that it was acting beyond its authority.

Rawlins has set an unenviable precedent since the committee's advice was not accompanied by licensing action affecting the licensed products referred to in the "Dear Doctor" letter. The licensing authority has a statutory duty to take licensing action on issues of drug safety. Thus in the continuing absence of regulatory action one must conclude that the authority considers that there is no concern over safety. To use Rawlins's phrase, the position is "frankly absurd." If there is a credible concern over safety the licensing authority should take appropriate licensing action. If the concern is not credible then the committee's advice should be withdrawn. Rawlins was generous enough to "apologise unreservedly" about the manner in which the advice was disseminated. In the continuing absence of licensing action showing confidence in the committee's advice it seems that further apologies are to be expected.

Recent events suggest that regulatory consideration of issues concerning drug safety in Britain falls short of acceptable standards. An independent inquiry should examine the failures of safeguards in the regulatory system. Improved quality assurance procedures are needed, perhaps including guidelines on good pharmacovigilance. British patients and doctors should not again be subjected to scares over drug safety that arise from processes that seem unlikely fully to have met relevant scientific and legal standards.

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Placebo effects

Psychological, sociological, and general practice research may elucidate effects

EDITOR,—While I agree with E Ernst and K L Resch that the benefit of an intervention is based on "the optimisation of both the specific treatment effect and the true placebo effect," I question their conclusion that the best way to research the complexity of the true placebo effect is to include an untreated control group in placebo controlled trials.¹

The controlled trial is responsible for the concept of the placebo effect, but there is no evidence that it is the best research method to elucidate the

concept. We might instead look to psychological research, which shows people's need to make sense of their illness, gain some control over it, and build hope and self esteem²; to sociological research, which describes how people canvass opinion from many sources before making decisions about treatment options³; and to general practice research into the therapeutic relationship⁴ and the importance of sharing lay and medical understanding in the consultation.⁵ This sort of research, most of which uses qualitative methods, allows us to take a broader view of the factors that optimise a given intervention. It suggests that interpersonal relations and communication are of prime importance in health care.

Once we have this wide perspective, which goes well beyond that of biomedical medicine, it is possible and necessary to design pragmatic trials to learn how to maximise these central therapeutic skills that make up the placebo effect. Complementary medicine, because it challenges the scientific paradigm and insists on treating each patient as an individual, undoubtedly has much to teach us in this. However, a research programme that is limited to placebo controlled trials is unlikely to be fruitful.

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Concept of placebo should be discarded

EDITOR,—E Ernst and K L Resch state that the true placebo effect can be measured in trials that compare an untreated group with a placebo group.¹ They assume that non-specific effects other than the true placebo effect produce the same response in the two arms of a trial. This assumption may not, however, be true. Some effects, such as increased skill of an investigator and white coat hypertension, which the authors call "other time effects," could well be different in the two groups. Furthermore, unless the outcome was survival it would be difficult to measure the effect in the untreated group without interference with the patients.

Thus it may not be justified to speak of a true placebo effect.² One could speak of placebo maximising and placebo minimising groups rather than placebo groups and untreated groups.³ It might, however, be preferable to discard the placebo concept altogether since defining it in a consistent way that distinguishes it from so called specific treatment effects seems impossible.² One should therefore focus on the choice of outcome measure and the magnitude of the effect rather than on interventions that are difficult to define.² As an example, when compared with usual obstetric care, the presence of a support person during labour has dramatic effects on the use of analgesics, anaesthesia, episiotomy, and caesarean section and the incidence of severe postpartum depression.⁴ Thus, what one chooses to call such an intervention is unimportant.

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