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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1 Carnall D. Controversy rages over new contraceptive data. *BMJ* 1995;311:1117-8. (28 October.)

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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1 Guillebaud J. Advising women on which pill to take. *BMJ* 1995;311:1111-2. (28 October.)

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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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4 Spitzer WO. Data from transnational study of oral contraceptives have been misused. *BMJ* 1995;311:1162. (28 October.)

5 Craft N. Clots of trouble. *BMJ* 1995;311:1172-3. (28 October.)

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