among users of third-generation OCs tend to be within normal ranges, the observation of APC-resistance may explain why this property does not benefit the user population. Fourth, the observation of one isolated event might not be sufficient and may produce a fallacy similar to the one regarding the relation of beta blockers and cholesterol metabolism. Fifth, we would expect to find a profound difference in VTE distribution when comparing users of second-generation with third-generation OCs. A stratification of the cases in the Transnational Study shows that this is not so. But, finally, the first results of an ongoing population-based study conducted on 822 Bavarian women in whom ProC global and APC COA tests were done show the expected differences in APC-resistance related to factor V Leiden mutation, but no differences related to OC use (Scharmann W, Heinemann LAJ, unpublished).

The most important aspect to consider, however, is the impact on the population. Your commentators lead us astray when they divide the world of difference between second-generation and third-generation pills. However, this is now shifted to the true magnitude of increased risk of venous thrombosis in third-generation pill users would be more than offset by the benefit in a reduced incidence of MI. In addition, although more difficult to quantify, third-generation pills are generally perceived as better tolerated and with fewer nuisance side-effects such as acne and hirsutism. These benefits should not be ignored because of a possible slight increase (even if real) in a rare and very rarely fatal condition.

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**Authors’ reply**

Sir—Your correspondents seem not to doubt any more that there is some reality in the association between third-generation contraceptives and an increased risk of venous thrombosis. We are grateful for this important progress in comparison with previous rounds of discussion in The Lancet. The argument is now shifting to the true magnitude of the risk, the explanatory strength of the new coagulation findings, and the balance of risks and benefits.

The discussion about the magnitude of the risk still uses the “recency of introduction” argument. This has now been shown to be a matter of subgroup analysis. That the haemostatic study to which we refer was not randomised is unimportant. The mere mentioning of an unqualified theoretical bias that has not been shown to affect the results serves little purpose. The philosopher Hume has stated that causal statements do not follow from observations, but from inference. It is extremely unlikely that general practitioners who prescribed third-generation and second-generation contraceptives selected the women so as to prescribe one brand to those with an unknown haemostatic abnormality. The relevance of the haemostatic test is shown in its correspondence with the level of risk due to the factor V Leiden mutation, and in the interaction with that mutation. The recent calculation of the balance of arterial benefits and venous risks1, 2 shows that very little risk remains, either with second-generation or third-generation contraceptives, after simple screening for arterial risk factors. Finally, Lidegaard and Milsom, in their earlier commentary (to which they refer), wrote that there was no difference in risk of cerebrovascular accident between second-generation and third-generation contraceptives, which was later corroborated in an analysis from the WHO study. This finding opens the possibility that views are also converging on this issue. With the uncertainties, we refrained from speculation about the arterial risk in our commentary. By contrast with your correspondents, we also refrained from specific recommendations to the authorities, but only mentioned that steps were necessary.

Several of your correspondents tell us that the tone and style of our commentary does not make a useful contribution to the debate. However, what else can one express, apart from deep amazement, when claims of “biases” are repeated long after it has been shown that they do not lead to any alteration of the estimates? In the recent exchange of views about silicone breast implants and autoimmune disease, The Lancet took the uncommon but highly interesting step of asking the contributors to state their possible “conflicts of interest”; perhaps this habit should be continued.

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**Musculoskeletal side-effects of varicella**

Sin—Burke and Chambers (Mar 22, p 818)\(^1\) describe a recent increase in musculoskeletal complications of varicella requiring surgery caused by group-A β-haemolytic streptococcus. As mentioned in this commentary, the recent increase of invasive group-A streptococcal disease worldwide may be due to a change in the epidemiology of group-A streptococcal disease, with an increase in the proportion of strains with M types associated with greater virulence. Although it is likely that changes in bacterial virulence are an important factor, host factors may also have contributed to the changing epidemiology of group-A streptococcal disease. It has been suggested that changes in strain-specific population immunity with time are responsible for the emergence of new strains.\(^2\)

Certain individuals are known to be at increased risk of invasive group-A streptococcal disease. Traditionally, this disease has been associated with the elderly and patients with debilitating illness. In addition, it has been suggested that there may be genetic predisposing factors, such as MHC class II type or T-cell receptor V\(γ\) repertoire.\(^3\) At a more practical level, there has also been increasing recognition of the possible link between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and the development of invasive group-A streptococcal disease. Traditionally, NSAIDs may mask the cardinal signs of inflammation that may otherwise lead to early recognition and treatment of invasive disease.

At present, it is not possible to be certain if the link between the use of NSAIDs and invasive group-A streptococcal disease is causal. This association may simply reflect the greater use of NSAIDs in patients with severe disease. NSAIDs are increasingly being proposed as first-line antipyretic drugs in both adults and children.\(^4\) In the light of the documented increase in invasive group-A streptococcal disease and the hypothetical link between the use of NSAIDs and this disease, it may be prudent to avoid the widespread use of NSAIDs as antipyretics in patients in whom the diagnosis is uncertain and particularly in those with varicella.