Letters to the Editor

Oral contraceptives and mortality from venous thromboembolism

Sir—Vandenbroucke and colleagues (Aug 10, p 401)1 and Thomas (Aug 10, p 402)2 believe that the modest increase in mortality from venous thromboembolism (VTE) among young women that occurred between the mid-1980s and the early 1990s might have been due to the increased use of oral contraceptives (OCs) containing one of the newer progestagens (desogestrel or gestodene). We question their interpretation of the findings.

Death from VTE accounts for less than 1% of total mortality in women aged 15–44 years. Moreover, only a few deaths are not associated with trauma, surgery, or major illness. It follows that most of the 2-8 deaths per million women could not be associated with OCs. Because of its association with other illnesses the apparent frequency of death from VTE will be affected both by the preference of doctors (and coroners) when completing death certificates and by coding practices adopted by national statistical authorities. Investigators should be cautious in their interpretation of both absolute rates and secular trends in mortality.

Vandenbroucke and co-workers draw conclusions about the association between OC exposure and VTE from considerations of the secular trends in the death rates in 15–44 year olds estimated from a maximum of 20 deaths annually. In this age group about 60% of the VTE deaths will be in those over age 30, whereas about 70% of OC use is by women under this age. If any changes in mortality from VTE have been due to OCs they would be limited to women. The Dutch mortality rates indicate that the female to male ratio fell between 1985 and 1990 and remained stable thereafter. Thus, if the recent modest rise in female mortality was caused by changes in the patterns of OC use, then to explain the proportionately greater rise in males during the same period we would need to identify an agent that uniquely affects the male. In England and Wales, according to Thomas, the ratio between males and females aged 30–44 remained more or less stable and for neither sex is there a discernible secular trend. Mortality from VTE in males aged 15–29 is so low that year by year changes in mortality cannot be ascertainment. There seems to have been an increase in death rates among 15–29-year-old women between 1989 and 1990; between 1990 and 1992 rates were stable.

Since all combined OCs carry an increased risk of thromboembolic disease it is important to establish whether any trends are associated with overall usage before focusing on particular products. Between 1984 and 1990 the number of cycles used in the UK increased by 23–7% (from 31·6 to 39·1 million), and there was a modest increase in mortality from VTE among 15–29-year-old women (1·6 to 4·4 per million). Between 1990 and 1992 the number of cycles used increased by 11·2% (to 43·5 million), and there was no change in mortality. However, between 1990 and 1993 the proportion of OCs used that contained one of the suspect progestagens increased from 20·1% to 44·0%.* Multiple linear regression for the death rates amongst 15–29 year olds against total cycles and the proportion containing the newer progestagens gives a regression coefficient of 0·87, with an × coefficient for total use of +0·59 and that for the proportion of use of OCs containing newer progestagens of −0·09: the equivalent figures for 30–44 year olds are 0·15, +0·40, and −0·13. For the Netherlands, in women aged 15–44, the regression coefficient is 0·41 with an × coefficient for total OC use of 0·39 and that for the proportion containing newer progestagens being −0·02. Assuming that the principal determinant of VTE death were OC use these calculations indicate that the modest changes in VTE mortality could be accounted for in part by changes in the overall use of OCs, but that any such effect was limited by the introduction of OCs containing newer progestagens. This conclusion is consistent with the hypothesis that the newer products are safer than those they replaced.

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Sir—The debate on the safety of OCs is further confused by Vandenbroucke1 and colleagues1 and Thomas2 reports on mortality rates from VTE in the Netherlands and the UK. These investigators believe that their data support a hypothesis that third-generation OCs are associated with an increased frequency of VTE. Such a consideration would be relevant if bias could be excluded. Recent work indicates, however, the existence of biases,4,5 and suggests that earlier epidemiological studies were not able to adequately adjust for these biases. One of the initial studies4 also assessed mortality from cardiovascular disease and found no difference between users of preparations with second-generation and third-generation progestagens; this is not surprising because the frequency of VTE morbidity in OC users in that study was not higher than that of 15 years ago.

The data on which Vandenbroucke and colleagues base their conclusion fail to indicate any rise in mortality in the female group that was not present in the male group. Vandenbroucke is worried about the mortality rate in Dutch women during 1993 and 1994 compared with the end of the 1980s but does not comment on the unchanged female to male ratio in that period (1988, 2·1; 1989, 2·6; 1994, 1·9%). If anything, this ratio indicates a slight decrease in VTE mortality in women relative to men, which contradicts any concern over VTE in women using third-generation OCs. Moreover, the sudden increase in VTE mortality in 1993 and 1994 is unlikely to be related to the increasing use of third-generation OCs because changes in OC use in the Netherlands occurred much earlier. Third-generation pills were introduced in the early 1980s; by 1987 25% of OC users were taking a third-generation formulation. Since then there only has been a gradual increase, to 31·2% in 1991 and 36·8% in 1995 (data from a yearly population-based survey, unpublished). The data from Thomas provide merely erratic shifts in the female to male.
ratio and thus do not allow any interpretation.

The absence of a biological explanation of the differential VTE frequencies, the absence of confirmation by mortality data, and the increasing evidence of bias in the initial studies should end the efforts of scientists trying to revive a pill scare that should not have occurred in the first place, and that already has led to increasing unwanted pregnancy and abortion rates in several European countries.

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*Full data available from The Lancet or the author, on request

Sir—The latest eruption of epidemiology into modern medicine is again unjustifiable and may have negative consequences. Vandenbroucke and colleagues' and Thomas' suggest that third-generation OCs increase mortality from VTE in women—yet another example of disputable effects of epidemiology. Both groups base their interpretation on a slight increase in mortality from VTE in women in the past few years. However, they fail to explain the proportionally similar trends in men over the same period. In addition, it is not logical that suggested effects of third-generation OCs are observed years after (Dutch data) or before (UK data) they were widely used, whereas OC-associated VTE occurs mainly in women just starting on OCs.

Vandenbroucke and Thomas' interpretations are even more surprising since the suggested increase in mortality from VTE cannot be related to the use of OCs. The frequency of OC-associated VTE did not increase in the time of their investigation, as evident from cohort studies. In the early 1980s four cases of VTE were recorded in 10,000 OC users' per year, whereas OC-associated VTE in 10,000 OC users'' per year were found in the recent cohort studies from the early 1990s, when third-generation OCs were available.

An increasing number of new publications on the OC and VTE issue point out that the observed difference in frequency of VTE between OCs of the second and third generation may result from biases and confounders rather than a biological effect. As pointed out by Thomas, "death certificate diagnoses may not be accurate, changes in mortality with time may reflect changes in other risk factors, and there may be diagnostic bias".

These considerations re-emphasise the need for critical evaluation of epidemiological data and their clinical relevance. Will we ever learn from this and previous pill scares?

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Authors' reply

Sir—Discussion about the time trend in venous thromboembolism was started to point to a discrepancy: it has been said that no increase had been demonstrated among young women, whereas an increase would have been expected if third-generation contraceptives carried twice the risk. On checking data for two countries, we found increases in mortality. Whether this is accepted as further evidence for the association between venous thrombosis and third-generation contraceptives depends on one's previous beliefs. Nevertheless, it becomes difficult to use the mortality data as an argument against the epidemiological studies.

Your correspondents propose that the data should be analysed proportionally, without explaining why rise and fall of diseases ought to be proportional in men and women. If proportional, the absolute increase among women remains larger than among men. The British data reported by Thomas do not fit the proportionality argument: mortality from venous thrombosis among young men shows no sign of change, whereas there is a continuous increase among young women.

Farmer and Lewis try to solve an equation with too many unknowns: it is impossible to calculate the relative mortality between two subgroups only from total mortality and the proportions of the subgroups without making an assumption on mortality in one of the groups. In their regression analysis, they use two explanatory variables (total use of contraceptives and percentage of third generation) that are strongly interdependent (correlations of 0·95 and 0·99), which leads to unstable estimations. The instability of their estimates is demonstrated by very large p values (which we recalculated). Moreover, plotting the data shows that the increase in the use of third-generation contraceptives strongly violates the linearity assumption of the regression analysis. The use of a linearising transformation in the Dutch data (squaring), clearly improves the fit of the model and the picture completely reverses: the coefficient of third-generation use now becomes positive (with a smaller p value) and that of total use becomes negative. We do not need this reanalysis to maintain that the mortality data are in line with the epidemiological studies.

We are amazed by the continuing insistence that bias and confounding explain the epidemiological studies. The starter bias argument is answered by looking separately at first-time users in the WHO, the Transnational, and the UK-General Practice Research Database (GPRD) study, and during the first year of use in a reanalysis of the WHO study.2 The referral bias argument is answered by the observation that the percentage of diagnosis did not influence the results in the WHO and the UK-GPRD study. The prescribing bias argument is answered by the observation that patients with major underlying disease were excluded (so that most cases are either idiopathic or linked to unpredictable intercurrent events like trauma or immobilisation), and by the adjustment...
is significantly higher, with preparations containing desogestrel or gestodene.1, 2, 3

Your correspondents play down the problem by referring to the doubling in mortality in young women as a "slight" or "modest" increase; van Lunsen refers to an “absence of confirmation by mortality data”. Three separate case-control studies (including one of which Lewis is a co-author) and a cohort study indicate an increased risk of thromboembolism with preparations containing desogestrel or gestodene. Since their introduction mortality from this cause has increased in younger women. I believe this is ample justification for the concern I expressed previously.

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Coordination of poliomyelitis immunisation programme in China’s border areas

Sir—Since the World Health Organization adopted a goal to eradicate poliomyelitis by the year 2000, the number of reported cases has gradually decreased. Well-organised AFP (acute flaccid paralysis) surveillance systems with laboratory networks and supplementary immunisation programmes, including national immunisation days, designed to promote oral poliovirus vaccine (OPV) immunisation, have greatly contributed to this decrease.3

Of the four wild poliovirus strains isolated in China between 1995 and April, 1996, all occurred in Yunnan Province, in four children with paralytic polio. They lived in Myanmar and were seen at the De Hong Prefectural Hospital (table). Isolates were confirmed as wild strains by the PCR-RFLP.1 Yunnan Province, which is in southwestern China, shares 4060 km of its border with Myanmar, Laos, and Vietnam.

Three national immunisation days were held in China between 1993 and 1996, with more than 90% coverage reported. Myanmar conducted its first such programme in February and March of 1996. Despite these efforts, the border areas remained susceptible to outbreaks of polio. These areas have transient populations that often move across the border. The four patients who were paralyzed came to China to see the doctor, although they were residents of Myanmar. Investigations at nine hospitals in De Hong Prefecture revealed that they provided medical services to 22 062 patients from Myanmar in 1995.

Even though races, culture, and languages are fairly uniform in these areas, it is difficult for health authorities to

<table>
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<th>Case</th>
<th>Age</th>
<th>Residence</th>
<th>OPV</th>
<th>Paralytic onset</th>
<th>Poliovirus Isolated</th>
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<tr>
<td>1</td>
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<td>2</td>
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<tr>
<td>3</td>
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<td>4</td>
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<td>None</td>
<td>Apr 1, 1996</td>
<td>Type III, wild</td>
</tr>
</tbody>
</table>

OPV, oral polio vaccine.

Table: Four patients from whom wild polioviruses were isolated in China (Jan, 1996–Aug, 1996)