

thromboembolism was similar. No such information is provided for the coronary and cerebral thrombosis.

There is much to learn from their methodology. Histories of chronic diseases that alter sexual practices or the probability of contraceptive prescription are a real problem in case-control studies of oral contraceptive effects. Parity presents an interesting example of the problems that arise. Parity affects oral contraceptive use, which argues for matching it, but oral contraceptive use affects parity, which argues against matching it.

The two studies for venous thromboembolism and pulmonary embolism suggest a relative risk of about eight times for women using the oral contraceptive compared to women who are not. Ryder and Westoff [3] estimate 15 per cent of the U. S. married population in 1965 of reproductive age were using the oral contraceptive. These two pieces of information lead one to expect a large impact on mortality rates. Table IV illustrates how this could work.

TABLE IV

IF NO INCREASED RISK	DEATHS
15 Users die at rate 8 R	15 R
85 Non-Users at Rate R	85 R
100 Population	100 R
IF RELATIVE RISK OF 8	DEATHS
15 Users die at rate 8 R	120 R
85 Non-Users at Rate R	85 R
100 Population	205 R

If the oral contraceptive users experienced no increased risks, the total number of deaths that would be seen in a population of 100, 15 of whom were using the drug, would be equal to 100 R. If the women who used the medication had a risk of death 8 times that of other women, then a total of 205 R deaths would occur.

It is important that such large changes in mortality are conceivable because the analysis of mortality trends is not a sensitive technique. There are significant limitations to the analysis of mortality data. These include a) the inherent difficulty in selecting an underlying cause, especially when more than one disease process is present, b)

the complex of factors that lead to unreliable death certificate diagnosis such as certifiers who are unfamiliar with the medical history of the decedent, c) the bias that physicians may bring to the diagnosis of a condition in a young woman who has been using oral contraceptives, and d) changes in other factors occurring simultaneously that may also affect mortality data.

Markush and Seigel [2] reviewed mortality trends from several rubrics of the *International Classification of Disease*, notably ICD categories 420, arteriosclerotic heart disease including coronary disease; 332, cerebral embolism and thrombosis; and 460-468, diseases of veins and other diseases of the circulatory system. The number of deaths in each of these categories is given in Table V.

We attempted to determine whether death rates from these causes in recent years in women of reproductive age have been greater than one would expect. Estimates of expected rates were derived from a) the experience of women in the years prior to the marketing of oral contraceptives, 1957-1961, and b) the experience of men in recent years 1962-1966. Table VI shows the differences between the observed annual per cent change in mortality (by age, for whites and non-whites) and the per cent change estimated from each of these comparison groups. Entries that are positive signify that the observed rates are increasing relative to the expected rate of change; those that are negative indicate a rate of change in recent years that is less than would be expected. Neither ICD 332 nor ICD 420 shows a consistent pattern of relative increases in women of reproductive age. For ICD 460-468, on the other hand, each five-year age group from 20 to 45 shows some relative increase (with one exception), both in white and non-white. Outside these ages, moreover, negative changes occur. Furthermore the increases are not trivial.

The mortality data were also used to estimate the relative risk of death from ICD 460-468 [4] for women in each age group. These are given in Table VII. By relative risk we mean the ratio of mortality rates in