

physicians to use thromboembolic diagnoses with increasing frequency. Furthermore, since pulmonary embolism is primarily an autopsy diagnosis,¹² changes in autopsy rates which follow a pattern in trend by age, sex, or color similar to that for oral contraceptive use would also distort trends in mortality for ICD 460-8. Since the ICD 460-8 category accounts for only a small proportion of deaths of US women 15-44 (1.2 per cent in 1965), an increasing tendency for physicians to use these diagnoses could cause large increases in the 460-8 category along with imperceptible decreases in a variety of other categories. If knowledge that a patient used oral contraceptives increases the likelihood of an autopsy and the diagnosis of pulmonary embolism, case-control studies would also be affected.

The ICD category 460-8 is particularly susceptible to a second kind of distortion, possible changes in the tendency to be selected as the underlying cause of death when several diagnoses are listed on a death certificate. US multiple-cause mortality data for 1955 indicate that there were seven times as many diagnoses of 460-8 listed on the death certificates of 15-44-year-olds as were coded as the underlying cause of death.⁶

Even if biases are not occurring in mortality statistics for the underlying causes being considered, studies which depend on temporal correlations cannot distinguish among agents which have similar distributions in the population. This especially concerns thromboembolism, whose determinants are poorly understood.⁵

The strength of determinants for thromboembolism can be inferred from the marked geographic variation in the prevalence of thrombosis among autopsied deaths.^{13,14} The powerful factors responsible for this geographic variation may also be increasing in US females in recent years at the same time that

oral contraceptive usage is increasing. For example, cigarette smoking, which has some influence on blood clotting,¹⁵ has increased more rapidly in US females than in US males in recent years.¹⁶

Another such example is suggested by experimental work indicating that pulmonary embolism may be a relatively normal clinical occurrence which becomes pathological only in the presence of cardiac or respiratory diseases.^{12,17} Increasing mortality from pulmonary embolism among younger women, therefore, could result from a relatively greater recent increase in the prevalence of pulmonary disease among females, which in turn may be a result of the relatively greater increase in cigarette smoking in women than in men during recent years. The large amount of unreported chronic respiratory disease present at death, particularly among females, makes it difficult to interpret the relatively greater increases for females in the United States in their rate of death from chronic respiratory diseases.¹⁸

Inman and Vessey⁴ reported a case-control study of deaths in the year 1966 in England, Wales, and Northern Ireland, where thrombosis or embolism of the pulmonary, cerebral, or coronary vessels (or other synonymous terms) were mentioned on either the first or second part of the certificate. They found a strong relation between the use of oral contraceptives and death from pulmonary embolism or cerebral thrombosis in the absence of predisposing conditions. For coronary thrombosis, their results were suggestive but not statistically significant.

They studied 26 deaths from pulmonary embolism without known predisposing conditions, too few to permit detailed examination for such characteristics as age and parity. They present a breakdown of the pulmonary embolism deaths, however, that leads them to conclude "that the excess of users of oral