thromboembolic disease, fundamental metabolic changes, and potential carcinogenesis.

An etiologic relation between oral contraceptives and an increase in thromboembolic disorders has been disclosed by several groups of investigators using retrospective methods of inquiry. In 1967, The Royal College of General Practitioners in Great Britain undertook interviews of young women who were recorded as having had vascular disease. By comparing patients with superficial thrombophlebitis with a suitably matched series of controls, it could be shown that the risk of developing thrombophlebitis was tripled in women who used the oral contraceptives. In another study Vessey and Doll investigated young women admitted to several hospitals in Northwest London with a diagnosis of idiopathic thrombophlebitis. These patients were also matched with suitable controls. A third study involved all the deaths that occurred in England, Wales, and Northern Ireland during 1966 in women of reproductive age and whose death certificates referred to thrombosis or embolism of the pulmonary, cerebral or coronary vessels. In summary, these studies showed that the chance of hospitalization from thromboembolic disease was about one in 2,000 among users of oral contraceptives, as compared to one in 20,000 for nonusers. Similarly, the mortality rate was estimated at 1.5 per 100,000 users age 20 to 34, and 3.9 per 100,000 users age 35 to 44. Since the publication of these results Vessey and Doll have continued their retrospective study to include a larger group of patients matched with controls. The results of this last study confirmed the previous investigations.

In the meantime, Drs. Sartwell, Masi, and colleagues conducted a retropective study of cases of thromboembolism, and an equal number of matched controls in 5 large cities in the United States. The risk of thromboembolism to women using hormonal contraceptives was estimated by indirect methods to be 4.4 times as that of the nonuser. The excess risk did not persist after cessation of use, nor did prolonged continuation of use enhance the risk. No striking differences among contraceptive products were found except for an excess of the use of seqeuntial compounds among the cases, as compared to control. The findings of the American study are in general agreement with those previously reported from Great Britain.

These studies together establish an etiologic relation between thromboembolic disorders and the use of oral contraceptives. Quantitatively they suggest that the mortality from thromboembolic disease attributable to oral contraceptives is about 3 per 100,000 women per year adding slightly less than 3 percent to the total age specific mortality in users of these drugs.

The hormonal contraceptives produce numerous metabolic changes affecting many organs, for example, the liver, the thyroid, and the adrenal. They also affect some of the body's homeostatic mechanisms; they change salt and water metabolism and occasionally induce hypertension. Recently histologic changes in the blood vessels of some women have been described. In many areas where alternation in function or structure has been noted there is very little basic information regarding the metabolism of the oral contraceptives. For example, little is known of the effects of oral contraception on renal function.

Fears that oral contraceptives might limit the growth, if prescribed for young girls, have proved foundless. These fears were based on observations that large doses of estrogen hasten epiphyseal closure. These observations, however, were based on very large doses of estrogen administered prior to the growth spurt, which occurs somewhere between 10 and 12 years in the United States. It is unlikely that oral contraceptives would be used this early.

The labeling of the oral contraceptives includes a warning to use these drugs with caution in very young girls. This warning is based on an uncertainty about the use of anovulants at the onset of reproductive life. Their effect, however, is probably no more permanent than the suppression of ovulation by a pregnancy.

There is no evidence at this time that any of these drug-induced metabolic alterations pose serious hazards to health. The systemic effects of these drugs, however, are so fundamental and widespread, that continued medical surveillance and investigation is required.

Much indirect evidence suggests that the steriod hormones, particularly estrogen, may be carcinogenic in man. These data are derived from experiments on laboratory animals in which estrogen in particular appeared to cause cancer in 5 species. Although all physical and chemical elements that are carcinogenic in man produce malignant tumors in experimental animals also, evidence of the