situ a yield of 3.7 per 1,000 on initial screening fell to 0.63 per 1,000 on the second annual screening of the same women. For invasive carcinoma the corresponding figures were 2.8 and 0.52. This spontaneous reduction on rescreening reflects the expected difference between prevalence and incidence figures and should not be confused with a presumed favorable effect of any intervening medication in such studies. It would, of course, be expected that all women started on oral contraceptives would have been given the benefit of a prior pelvic examination and Papanicolaou smear. Hence, the findings in such a population of prescreened women cannot be compared with the findings in the population group from which they are initially selected.

The prolonged pathogenetic period for cancer of the cervix is estimated to be from 7 to 10 years on the basis of the difference in the age distribution of carcinoma *in situ* versus invasive carcinoma (*12*, *34*). Hence studies of the effect of any medication on this prolonged pathogenetic process should certainly exceed in duration this phase of the development of cervical cancer. Observations of this duration in significant numbers are not at hand.

Pincus and Garcia (*35*) have recently summarized their available data on the occurrence of invasive cervical cancer and certain associated cytological phenomena in a limited sample of women using either oral contraceptives, vaginal spermicides or intrauterine devices. They state: "The data give practically identical figures for the presence of carcinoma, anaplasia or negative tissues in the Enovid and vaginal contraceptive users." Also: "Obviously far more extensive data are required for definitive determination, but with an enlarged population for study we hope to have adequate information on carcinoma incidence." We agree that the data reported provide no sound statistical basis for assurance on this vital point.

More recently, Wied *et al.* (*35a*) among others have offered data indicating no significant effect of certain preparations on the course of initial cervical dysplasia over a 1 to 2 year period. Such data provide some assurance as to immediate effects on the initial phases of the pathogenetic process, but have only an indirect bearing on the ultimate response to chronic exposure to medication which may become apparent some years hence. Studies for much more sustained periods of time and after more prolonged exposure are clearly needed.

Statistical Considerations

A substantial change in the incidence of certain diseases such as cancer, may be difficult to detect even with very large samples. For example, in a study of breast cancer incidence with 4-year followup of women aged 20 to 39 years, a sample of about 15,000 to 20,000 women, or 60,000 to 80,000 person-years, would be required to have a reasonable (i.e., 90 percent) chance of detecting (at the 95 percent probability level) a two-fold increase in risk.

Changes in the incidence of cervical cancer could be detected with samples of about the same size; changes in the incidence of endometrial cancer would require samples about six to eight times as large as those for breast cancer. No studies approaching this magnitude have been reported. On the contrary, the initial approval of the administration of oral contraceptive agents for 4 years to young women was initially based on a 4-year experience in 400 cases properly documented with laboratory studies (*36*). Since duration of exposure is so critical a factor, only those women exposed for the actually approved period of 4 years provide any experience pertinent to this evaluation. Certainly, it is to be reasonably expected that a new public health practice would be predicated on a more soundly developed epidemiological basis.

Thrombophlebitis

Thrombophlebitis and thromboembolic phenomena following the use of oral contraceptive agents have been reported. Accordingly, in January of 1963 an "ad hoc" committee was established by the Commissioner of the Food and Drug Administration to determine if the use of one of the oral contraceptive preparations (Enovid) resulted in an increase in incidence of deaths from thromboembolic conditions.

This committee concluded that: "on the basis of the available data * * * no significant increase in the risk of thromboembolic death from the use of Enovid in this population group has been demonstrated" (*37*).

In concluding their report this Committee added: "Any firm reliance on the risks as calculated is tempered by the assumptions made. This Committee recommends that a carefully planned and