each year. It should be clear that this correction will not alter biases that will result if the patients lost to follow-up have disease rates different from those who remain. Moreover, the estimates do not take into consideration interest in more specific diagnoses, such as particular malformations, more specific age groups, or particular durations of oral contraceptive usage. If answers to detailed questions of this type are sought within a single study, considerably larger samples are required.

The first of the two major problems that make prospective studies difficult is the size of the samples required. The second consists of keeping losses to follow-up at a reasonably low level, and there is no single standard of what is meant by "reasonable." One must consider such factors as the characteristics of patients lost and of those remaining, the reasons for the losses, and the degree of observed effects in the members still followed. According to C. Tietze, MD (oral communication, November 1967), in a continuing cooperative study on the efficacy and acceptance of intrauterine devices, a rate of losses to follow-up in excess of 15% in the first year at any clinic was regarded as unsatisfactory.

It would be possible to study those who have used oral contraceptives for ten years by initiating a study several years from now when a reasonable number of long-term users are available. A sample of such persons taken at that time might be more representative than the residual members of a long-term study begun now. The disadvantages of this method are that one must rely on the recall of the subjects for contraceptive experience, no base line medical measurements ordinarily are obtained, and such persons represent the remainder of a group in which many others have discontinued use of oral contraceptives for reasons that may be medically significant.

Finding appropriate populations to launch prospective studies of this type is by no means easy. Prerequisites to a significant study include a well-motivated medical staff capable of developing data and records that are of research quality; a population that is large, cooperative, and convenient to follow; and capabilities in the fine arts of data collection and analysis.

Retrospective Studies

The value of retrospective studies of disease etiology has received considerable discussion.[17-19] Criticisms of this approach take two forms. The first involves the hazards of bias in the choice of study cases or controls, and in obtaining histories. Ideally, one should be able to identify the population from which study cases are drawn, and make comparisons with controls from the same population. For hospital admissions or cases from a physician's experience, two frequent sources of study populations, it is usually difficult to identify the population that is represented. Medical facilities vary in the types of cases attracted and in the class of persons attending. Because it is difficult to identify the parent population, controls are usually selected from the same source on the assumption that they will be representative of the persons free of disease in the population from which the cases are derived, whatever that population might be. Since it usually is not possible to verify the comparability of cases and controls, multiple comparison groups are often used as a safeguard.

Table 2.—Minimal Samples Required to Detect Differences in Disease Rates Between OC Users and Controls in Retrospective Study*

Proportion of Women in Population Who Are "Ever-Users"	No. of Cases and Controls Required
0.25	120
0.50	110
0.90	340

*By proportion of women who are "ever-users" of oral contraceptives (OC). This table is appropriate for studies of cancer, diabetes, thromboemboli, and malformations. It is computed for one-tailed significance tests at 0.05 level with power equal to 0.8.

Accurate dating of disease onset and contraceptive experience is significant in avoiding bias. It is important to know if the condition existed prior to the use of medications, if medications were contraindicated, or if their use was terminated with complaints or symptoms. In addition, the quality of recall of contraceptive experience must be evaluated with care, since there may be differences in the accuracy of reporting for persons with and without disease.

The second major criticism directed at retrospective studies is that there are limitations on the kinds of information they provide. Although the investigator is interested in the risks of disease in persons using oral contraceptives, retrospective studies, by their very nature, determine the frequency of oral contraceptive use in persons with disease. Unless the investigator has information on the proportion of the population using medication and the total incidence of the disease, the risk of disease for the oral contraceptive users and nonusers will not be provided by the study. On the other hand, when the incidence of the disease is low, the ratio of risks in these two groups can be inferred[20], which is often all that is required. This was demonstrated recently in the reports relating to retrospective British studies[7] in which a trebling of the risk of thromboembolism was the central most important statistic. Furthermore, it is under this condition of low disease incidence that the case-control method shows itself to best advantage, since studies can be conducted with small sample sizes whereas prospective studies require large populations.

Table 2 presents the numbers needed for case and control samples for retrospective studies. The algebra of the computations required for this Table is such that the same results obtain for all the dis-