of women exposed to these drugs for many years are needed to investigate this problem, the only exception being cancer of the cervix where studies of the rates of progression from dysplasia to carcinoma in situ may be made on the assumption that such progression rates are indicators of carcinogenesis. This approach has been attempted both for study of the intra-uterine device[8] and oral contraceptives.[9]

The third set of problems is the potential development of certain metabolic diseases, such as diabetes, and the fourth is the possible relationship between oral contraceptives and the occurrence of congenital malformation in children conceived during or after cessation of medication.

The purpose of this paper is to discuss some of the difficulties that are met in studying these problems, and point out the advantages and limitations of particular approaches. Whereas the focus will be on study of the oral contraceptives, much of what will be said is relevant to the study of other methods of contraception as well.

General Problems

There are two principal approaches to the study of an association between an agent and events such as disease or adverse reactions. One is referred to as the prospective method, in which samples of persons with and without the agent are kept under surveillance for the purpose of observing the rate at which the event occurs. The other is called the retrospective or case-control method, in which individuals with the disease and appropriate controls are compared to discover the proportion of each group exposed to the agent. For example, a prospective study of the role of oral contraceptives as a carcinogen would require the observation of samples of users and nonusers for several years, and comparisons of the proportion in which cancer developed in each group. A retrospective study would require selecting a sample of cancer cases and carefully chosen controls and obtaining information from each on previous use of the medication.

Each of these methods has been used to advantage. The relationship between rubella and malformation was clearly demonstrated by a case-control study[10]; the agents contributing to an increased risk of heart disease were studied prospectively in the Framingham Heart Study.[11] In the case of cigarettes and lung cancer, both methods have been used. The early studies were largely the case-control type and suggested relationships which were later verified by prospective studies.[12]

There are circumstances that favor one or the other of these two methods that we will describe. Certain problems related to oral contraceptives beset both methods, however. For instance, the technology of oral contraceptives is constantly changing. There are two categories of drugs now available for use: the combined formulation, which is a mixture of estrogen and a progestin, taken together for 20 days with an interruption in order to permit withdrawal bleeding, and the sequential formulation, which involves the ingestion of an estrogen for the first 15 days of the cycle and a progestin for the last five days. A third formulation is now under development and shows great promise although it is not yet available for general use. It involves the ingestion of remarkably small doses of a progestin daily without interruption. Women so treated generally ovulate but, for reasons not yet understood, do not become pregnant. It is likely that this formulation may in time essentially replace the former ones.

The results of the study of one formulation may not be applicable to the others, due to the fact that effects may be dependent on dose, ingredients, and time. In addition, since formulations and schedules undoubtedly will continue to change, studies must be flexible in their design, ie, capable of adapting to a changing agent. Research programs should be thought of as systems of patient surveillance to provide early warning of possibly adverse effects.

Other problems include the changes of state that occur in persons under study. Women will interrupt use of a drug for a planned pregnancy, because of side effects, or for other reasons, and women who were not using them may start, thus altering the control group. Analysis of such checkered exposure data presents a considerable challenge. Beyond this, the use of pills is not observable. The practice of obtaining medications from family planning clinics for the purpose of selling them is well known by administrators of such clinics and epidemiologists know that respondents to interviews or questionnaires often provide responses that are designed to give a good impression, or please the physician, or avoid conflict. This is not to say that good data cannot be obtained from respondents, only that one should be concerned about the validity of responses.

The last problem common to all studies of oral contraceptives is that the investigator is usually confronted with all the biases that come with self-selection. Use of pills varies with religion, economic level, education, race, and age, to say nothing of variables of which we are unaware, and particular care is required that differences in disease rates related to these factors are not erroneously attributed to use of the oral contraceptive. Whereas one study has been initiated in which women are randomly assigned to oral contraceptives or vaginal contraceptives as controls, according to D. Rutstein, MD (oral communication, June 1967), randomization is not normally acceptable to patients. Even if attempted, the procedure is blind neither for the women nor for the examining physicians. Furthermore, where patients have preferences in the method of contraception, they may not be content with the one allocated to them, so that losses may occur at a high rate, or at differential rates from the study and control groups.