Editorial:
Aspirin and Coronary Deaths

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IN THIS ISSUE Hennekens, Karlson and Rosner report a lack of association between the frequent use of aspirin, defined as use \( \geq 4 \) days per week, and subsequent coronary heart disease (CHD) mortality. The experimental design was that of the retrospective, case-controlled study. The investigators surveyed the death certificates filed in two Florida counties over a 16-month period and identified those men whose death was attributed to CHD within 24 hours after the onset of symptoms. These men so identified are referred to as the "cases."

Systematically surveying households in the immediate neighborhood of each case, the investigators then identified a living, age-matched, male neighbor. These men were termed the "controls." Thus for each case there is an unidentifiable control, and each such pair was then examined as to whether there was a difference within the pair for the variable of interest.

By means of a standard questionnaire, the wives of the deceased cases and the living controls were interviewed to elicit information on the health habits of their husbands. One of the questions dealt with frequency of coffee use. Data have already been published from this survey revealing a lack of association between coffee use and CHD.1 In addition, the investigators obtained data on the frequency of aspirin use by the husbands. These data are the basis of the present report.

The authors very nicely address some of the limitations of retrospective studies. They identify the problem of "selection bias." For example, in this study the availability of wives for interviewing may be systematically different between the cases and the controls. Of the 1,019 wives of eligible patients, only 649 responded and were cooperative. Another 81 cases were excluded because of missing or unknown values. Thus the final data were based on 568 cases, or 56% of the original group. With such a large group excluded, one must question whether the data gathered on the 568 really represented the 1,019 in the original sample. Of course, there is no way of knowing; but certainly there is no basis to assume that aspirin usage was the same in the husbands whose wives were interviewed compared to those who weren't.

In randomized clinical trials, so many patients are excluded from the trial, either by specified criteria or by choice, that the applicability of the results are often questioned. However, there is an important distinction between the exclusions before randomization in a clinical trial and those in a retrospective study. Exclusions from the latter can affect the validity of the results for the groups compared, as well as the general applicability of the results to other populations. The exclusions from the randomized clinical trial in no way affect the validity of the comparison of the treated and control groups, but they can affect the general applicability.

The authors also address the potential problem of "observation bias." In the present study, the wives of the cases may systematically, and not randomly, either over- or under-report the true use of aspirin by their husbands and do so differently from the wives of the controls. This bias may be due to selective recall on the part of the wives or to a bias introduced by the interviewer. Although these biases may seem esoteric or improbable, they may be quite real and may lead to inaccurate conclusions.

Other problems also exist with retrospective case-control studies. In the present study, the cases and controls clearly chose on their own (or through their private physicians) whether they took aspirin and to what degree. Certainly, one does not elect to take a drug, even aspirin, without good reason, real or imagined. This decision to take the drug could be correlated with factors which in turn might be associated with an increased chance of dying of CHD.

In addition, by the very nature of the study, the data are generally historical. Thus, the wives in this study had to recall with what frequency their husbands took aspirin, and the accuracy of such recall is highly variable. Further, this variability can be easily biased by other life events, such as the recent loss of a loved one, or by the belief that aspirin may be harmful or helpful.

Another problem is the lack of a uniform dosage or dosage schedule of aspirin. Thus, the investigators must in many cases arbitrarily decide if a man has used aspirin regularly. For example, is the man who took aspirin every other weekend for six months for headaches and then took it daily for the week just before his death because of chest pain a regular aspirin user? Such decisions, even if made in an unbiased manner could lead to remarkably different results.

Given the limitations of the historical studies, do they have a place in scientific clinical investigation? I feel that they do, but one must be aware of their limitations to avoid the numerous pitfalls. As a step in the sequential development of scientific data, they can
provide the mechanism for the initial testing or development of hypotheses.

In addition, some disease-related problems cannot be studied using a randomized, prospective design since such studies may not be ethically or practically feasible. In such problems the case-control design or the cohort design (the non-randomized, concurrently controlled, prospective design) or the historically controlled design must be used. Examples of such problems are the study of the relationship between contraceptive pills and thromboembolic disease, or the relationship between cigarette smoking and CHD or lung cancer. In questions such as these, the approach is to strengthen the inferences from the non-randomized studies by using the same designs in vastly different populations and using multiple controls groups. If after many such studies, the relation tends to hold up and if other ancillary data (such as from animal studies) tend to support the hypothesis, we can have some assurance that the observed association may in fact be that of cause and effect.

However, the ultimate step in scientific clinical investigation, if at all feasible, must be prospective randomized clinical trials as initially set forth in the late 1940s and developed over the last quarter century. This technique, if properly applied, can remove the concerns of bias that plague non-randomized designs and can more easily lead directly to inferences regarding cause and effect. Thus, of interest to aspirin and its potential role in preventing subsequent CHD are three recent or ongoing randomized, prospective clinical trials. The report from the Coronary Drug Project Aspirin Study reveals a non-statistically significant, 30% lower mortality rate in the aspirin group as compared to the placebo group. The Aspirin Myocardial Infarction Study and the Persantin-Aspirin Reinfarction Study, both ongoing, are both due to be completed within the next year or two. We thus should consider the report in this issue by Hennekens et al. as an additional, but not final, piece of datum. We should await the reports of the ongoing prospective studies and weigh all of the data that will be available before reaching a final conclusion regarding the usefulness of aspirin in patients with CHD.

References
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