My criticism should not be confused with "pharmaceutical industry bashing." The pharmaceutical companies in this country have made a vital difference in the quality of medical care provided through research and development of new and important products. These firms have a right to market their products to physicians, if done in an appropriate manner.

During the past year, my colleagues and I have begun writing letters to pharmaceutical companies who send out these gifts. It is our hope that if a sufficient number of physicians express their concern in this fashion, the pharmaceutical firms will cease with this illegitimate, noneducational form of marketing.

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Techniques of Meta-Analysis

To the Editor: As a physician who appreciates the value of meta-analysis, I was gratified to see two meta-analyses appear in the March-April 1993 issue.[1,2] Because meta-analyses can have such far-reaching implications, however, I believe that it is particularly important that they be properly conducted and reported. Therefore, I am writing to express some concerns about these two meta-analyses.

Although Hawley, et al.[2] attempted to locate unpublished studies, both meta-analyses could have fallen victim to publication bias. The use of only published studies might severely alter the conclusions of the body of literature. Minimally, both meta-analyses should have constructed a funnel graph[3] — plotting effect size against sample size — to seek visual evidence of publication bias.

In the study by Schneider, et al.[1] the description of the statistical methods used is scanty but suggests that these studies did not include control groups. In addition, at least some of the analyses are presented in such a way as to suggest that the subjects were pooled across studies rather than the effect sizes being pooled. A true meta-analysis involves pooling of study effect sizes rather then pooling of individual subjects. According to Feinstein,[4] the pooling of subjects is appropriate only if three criteria are met: (1) all data are from randomized clinical trials; (2) there is homogeneity of protocols including similar patients, treatment, and follow-up; and (3) individual study results are similar to each other. Based upon the heterogeneity of these studies, data pooling in this case would appear to be inappropriate. The authors cite Yusuf, et al.[5] for their methodologic adaptation of the Mantel-Haenszel methods. Yusuf, et al.[5], however, were conducting a meta-analysis using randomized trials. Hence, their methods might not be appropriate to this study.

The meta-analysis by Hawley, et al.[2] raises other concerns. I applaud the use of a quality assessment of the study protocols but question the wisdom of summing the ratings on individual study criteria. Horwitz and Feinstein[6] suggest that it is inappropriate to sum such methodologic assessments for deriving an overall study quality score in epidemiologic studies. In addition, when utilizing such subjective variables as quality assessment, it would be helpful to determine the interrater reliability for each criterion.

Although Hawley, et al.[2] are cautious about the relation between prepregnant contraceptive exposure and risk of breast cancer, they suggest that their meta-analysis supports such a relation. When interpreting a meta-analysis, however, it is important to remember that you are looking at relations among studies, not individuals. Hence, this meta-analysis has found a relation between the duration of prepregnant exposure in studies and their overall effect size, but it has not addressed the relation between individual durations of exposure and risk of breast cancer.

Sacks, et al.[7] previously reviewed the quality of a group of meta-analyses based upon criteria that they established. The concerns I have with these two meta-analyses are frequently seen in other meta-analyses. Sacks, et al.[7] found that only 7 percent of meta-analyses adequately describe their study protocol and only 5 percent presented measures of interobserver agreement on coding. In fact, only 2 percent of the meta-analyses adequately addressed the issue of publication bias.

Because both of these meta-analyses sought to explain conflicting results within a body of literature, it would have been particularly helpful if they had assessed the impact of different study characteristics and potential biases upon their outcomes. Unfortunately, neither meta-analysis appears to have explained the conflicting results within the literature. The potential for such an explanation is one of the strengths of meta-analyses as a technique. In conclusion, I am gratified to see an increasing number of meta-analyses appearing in the literature. Like Sacks, et al.,[7] I ask that the quality of conduct and presentation of meta-analytic results be improved.

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References

1. Schneider AP 2nd, Nelson DJ, Brown DD. In-hospital cardiopulmonary resuscitation. J Am Board Fam Pract 1993; 6:91-101.
2. Hawley W, Nuovo J, DeNeef CP, Carter P. Do oral contraceptive agents affect the risk of breast cancer? J Am Board Fam Pract 1993; 6:123-35.
3. Light R, Pillemer D. Summing up. Cambridge, MA: Harvard University Press, 1984.
4. Feinstein AR. Clinical epidemiology. Philadelphia: W.B. Saunders, 1985:518-9.
5. Yusuf S, Peto R, Lewis J, Collins R, Sleight P. Beta blockade during and after myocardial infarction. Prog Cardiovasc Dis 1985; 27:335-71.

6. Horwitz RI, Feinstein AR. Methologic standards and contradictory results in case-control research. Am J Med 1979; 66:556-64.
7. Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC. Meta-analyses of randomized controlled trials. N Engl J Med 1987; 316:450-5.

The above letter was referred to the author of the article in question who offers the following reply:

To the Editor: I appreciate the letter by Dr. Katerndahl and his comments on measures to ensure publication of high-quality meta-analyses. I am puzzled by the specific concerns used by Dr. Katerndahl to imply that the report on oral contraceptives and breast cancer did not meet the definition of a high-quality meta-analysis. The technique for meta-analysis has become an extremely popular research methodology. A recent MEDLINE search revealed more than 1500 publications in 1992–93 employing this technique. I am in full agreement that it is in the best interest of all concerned to have authors make use of specific guidelines to limit the problems inherent in this research technique. The research design for the oral contraceptive project carefully followed guidelines recommended by L'abbe, Detsky, and O'Rourke.[1] Despite what was stated by Dr. Katerndahl, this included measures to describe a detailed study protocol, to minimize the potential for publication bias, and to develop and utilize properly a quality-assessment instrument. A substantial portion of the discussion was used to explain the nature of the conflicting results within this field of literature.

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References

1. L'abbe KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. Ann Intern Med 1987; 107:224-33.

In-Hospital Cardiopulmonary Resuscitation

To the Editor: I would like to comment on the Schneider, et al. exhaustive survey of the literature on in-hospital cardiopulmonary resuscitation (CPR). It is interesting to note that in general the results are similar to those of a previous meta-analysis, especially regarding the effect of increasing age on survival, despite differences in methodology between the two studies.[1]

I would differ, however, with the authors' interpretation of these results, especially their implication that if a subpopulation is found to have a 0.0 percent rate of survival following CPR, the finding "should be suspect and generally can be attributed to low numbers or special populations." While this statement is true in the strictest sense, in clinical practice an invasive therapy with a survival rate that has an upper bound of the 95 percent confidence interval (CI) of 2.0 percent would be considered by many to be consistent with clinical futility.

For example, in the meta-analysis mentioned above, 144 patients had a diagnosis of metastatic cancer at the time of resuscitation. The survival rate was 0.0 percent, with an upper bound of the 95 percent CI of 2.1 percent.[2] It is unlikely that many patients would choose to undergo an invasive, painful therapy with a survival rate under 2.1 percent, especially when my research shows that the cost per survivor approaches $250,000, and the average survivor lives approximately 3 years.

It is also important to note that both the composition of the inpatient population and the techniques of resuscitation have changed dramatically in the past 30 years and that older studies are of questionable applicability to the modern clinical setting. In addition, the paucity of strict inclusion and exclusion criteria meant that dissimilar studies were pooled, a questionable technique. Finally, I am curious why the Mantel-Haenszel statistic was not used more widely throughout the analysis, rather than the simple pooling of data; this technique is preferred for combining 2×2 tables across studies in a meta-analysis.[3]

Certainly CPR should not be abandoned; it is a valuable and appropriate medical intervention for many patients. I believe, however, that it should be possible to single out subpopulations of patients who are poor responders to CPR, using predictive instruments, artificial intelligence, and such meta-analytic techniques as pooling the raw data from similar studies. In this way, CPR can be applied where it will do the most benefit and the least harm.

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References

1. Ebell MH. Prearrest predictors of survival following in-hospital cardiopulmonary resuscitation: a meta-analysis. J Fam Pract 1992; 34:551-8.
2. Breslow NE, Day NE. Statistical methods in cancer research. Volume 1: the analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980.
3. Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC. Meta-analysis of randomized controlled trials. N Engl J Med 1987; 316:450-5.

The above letters of Dr. Ebell and Dr. Katerndahl were referred to the author of the article in question, who offers the following reply:

To the Editor: Dr. Ebell and Dr. Katerndahl raise a number of important issues. I would agree with Dr. Ebell that cardiopulmonary resuscitation (CPR) for a patient with metastatic cancer would in general be clinically extraordinary (e.g., a young parent showing a favorable response to treatment of advanced