covariate can be ignored without concern for bias. If the responses in the two control groups are not similar, then care must be taken since there is evidence that the effect of exposure or treatment depends on variables not controlled for in the design and not measured for entry into the analysis.

How could this be done in the example of the study of stainless steel workers? Many times such studies contain comparisons with other workers in the same plant or with local, state or national population rates after adjusting for age. In comparisons within the same plant, cancer rates may be affected by substances in the environment other than nickel and chromium. The principle of control by systematic variation presented by Rosenbaum would lead to the formation of more than one control group distinguishable by different types and levels of exposure within the workplace environment, but not including nickel or chromium. For instance, one group could consist of office personnel. Another could consist of workers exposed to heat and dust in a plant that produces steel without nickel or chromium as ingredients.

In the example concerning the evaluation of burn care, the potential for survival may not be fully depicted by objective measures of the severity of the burn and by information on age and comorbidity that reflect the health and resilience of patients. Therefore it would be appropriate to include hospitals in the control, as well as treatment group, which treat a variety of types of patients. Possibilities include an inner city hospital that treats many indigent patients, a military hospital and a research hospital.

It may seen obvious that multiple control groups would be informative and desirable in these examples. Yet many observational studies use only one control group. Rosenbaum's review focuses attention on the benefit to be gained from multiple control groups and develops useful principles for their design and interpretation.

ADDITIONAL REFERENCES

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Comment

Norman Breslow

The major conclusions of this paper should come as no surprise to biostatisticians and epidemiologists involved in the applications of statistical methods and concepts to clinical and observational studies in public health and medicine. For the most part, the arguments lend mathematical precision to principles of study design and interpretation that are well-known and widely used. Few epidemiologists involved with cohort studies, for example, would take issue with the statement that "... if, after adjustment for (the covariables), the two control groups differ with respect to the response ... then ... at least one of the control groups is not comparable to the treated group." The principles of "control by systematic variation" and "bracketing" seem intuitively clear and are evidently well-established in the social science literature. Although it is reassuring to note that these principles are confirmed by the randomization paradigm developed by Rubin and Rosenbaum, it would perhaps be of even greater interest to see examples where the paradigm led to novel insights and new methods of study design and analysis. Recent work of Robins (1986) on causal inference in occupational cohort studies represents a start in this direction.

Turning specifically to the field of case-control studies, the major conclusion is that inference regarding the validity of a covariable-adjusted relative risk estimated for a particular exposure is strengthened if one can demonstrate equality in the covariable-adjusted odds ratios that contrast the exposures in two or more control groups. This confirms the insights of Hill (1971): "If a whole series of control groups, e.g., of patients with different diseases, gives much the same answer and only the one affected group differs, the evidence is clearly much stronger than if the affected group differs from merely one other group." In their pioneering work on lung cancer and smoking, Hill and Doll in fact utilized two control groups. One consisted of patients with diagnoses other than cancer who were

Norman Breslow is Professor and Chairman, Department of Biostatistics, University of Washington, Seattle, Washington 98195.