Guest Editorial

Selection Bias in Clinical Research: The Land Outside the Tower

Stephen H. Gehlbach, MD
University, Alabama

It is not surprising that academic medical centers produce much of the research that guides clinical practice. Academic centers have a tradition of inquiry in which "organized curiosity" is an expectation. These centers attract professionals who are skilled in the techniques of investigation, and they furnish the personnel and technologic support needed to nourish research. From their hospitals and clinics come large patient populations with diseases that are the grist of clinical investigation.

Clinicians use the latest findings of academe to make better diagnoses, increase their understanding of the natural history of disease, and provide patients with novel treatments. It seems a most efficient system. The concentration of resources enhances productivity and quality. The ready availability of patients means that sizable samples may be collected easily and results obtained rapidly.

There are recent revelations, however, that the fruits of the ivory towers may not be palatable to those in the surrounding countryside. Some of the very resources that make academic centers fertile limit the value of their produce. Their large, accessible patient populations are a liability as well as a strength. Patients who find their way to research and teaching hospitals are special cases. They have unusual or recalcitrant forms of disease; they have coexisting conditions that complicate management. They have puzzled or frustrated referring physicians; they are sicker, or poorer, or less cooperative. They are not representative of their communities nor typical of the patients most physicians care for.

The patients of medical centers are a filtered lot. Most have already seen a primary physician, and many will have been to community specialists or evaluated in local hospitals. Some represent a disadvantaged portion of the population for whom private medical care is not easily available. Frequently their economic difficulties are compounded by complex social and medical problems. The well-known study by White et al[1] depicts this

From the University of Alabama School of Medicine, Tuscaloosa Program, University, Alabama. Requests for reprints should be addressed to Dr. Stephen H. Gehlbach, Department of Pediatrics, College of Community Health Sciences, PO Box 6291, University, AL 35486.

selection process as a pyramid where, for every 1,000 individuals in a community, 250 consult a physician within a given month, 9 are hospitalized in community hospitals, but only 1 reaches the referral center.

Evidence is growing that this selection process introduces a serious bias into research and hampers our ability to generalize medical center results to general patient populations. In 1980 Ellenberg and Nelson[2] published a review of research on the question of future nonfebrile convulsions in children who had experienced febrile seizures. How likely is it that children with "febrile fits" will become "epileptics"? The authors analyzed 24 studies that followed groups of children who had febrile seizures and categorized the research according to the source of patients evaluated. "Clinic-based studies" followed patients who were gathered from hospital clinics or specialty referral units. "Population-based studies" followed children who came from a general population, such as a large prepaid health plan or a community sample.

The prognosis for children varied dramatically with the study setting used. The risk of epilepsy calculated from the clinic-based studies was as high as 65 percent when patients were drawn from a developmental evaluation center. The median estimate for the 18 clinic-based studies evaluated was 17 percent. In contrast, when the six population-based studies were reviewed, the variability was much less. Estimated rates of nonfebrile seizures ranged from 1.5 to 4.6 percent with a median of only 3 percent. Ellenberg and Nelson conclude that "studies from clinic-based populations may overestimate the frequency of unfavorable sequelae" and that it may be inappropriate to generalize from "the potentially biased experience of the specialty clinic to practitioners who care for patients with the full spectrum of a given disorder."

The paper by Williamson in this issue of the *Journal*[3] presents further evidence of the effects of selection bias. In his study the question concerns the causes and appropriate evaluation of lymphadenopathy. How often do enlarged peripheral lymph nodes signify an important medical problem? How aggressive should a physician be in evaluating lymphadenopathy? In reviewing the literature, Williamson finds that previous studies suggest lymphadenopathy carries ominous implications.

Sinclair et al[4] report that among 85 of 135 patients with enlarged, superficial lymph nodes who had "diagnostic biopsies," there were 50 cases of lymphoma, 14 of carcinoma, and 6 of tuberculosis. Lake and Oski[5] reviewed 75 childhood cases of lymphadenopathy and found that 17 percent had lymphoreticular neoplasms and 7 percent had tuberculosis. Knight et al[6] also studied peripheral adenopathy in children and found that 13 percent of 239 cases reviewed had malignancies and 32 percent had granulomatous disease of some type. Alarming results! But these studies all come from medical centers and include only patients with adenopathy that caused sufficient concern to warrant a biopsy.

Williamson's findings should be reassuring to primary care clinicians. In his review of 249 cases of lymphadenopathy seen in a family medicine center during a five-year period, few serious diseases were discovered. There were only two cancers and one case of tuberculosis. Only 3 percent of these patients required lymph node biopsy. Notwithstanding some differences in the methods of diagnosis and follow-up of cases in these studies, selection bias appears to have painted an overly pessimistic picture.

The news is also encouraging for those in the business of primary care research. The mandate for good research on unselected patient populations is compelling. Medical centers, with all their resources, simply cannot provide much of the important data needed by clinicians who practice in the land outside the tower.

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