Editorial

How Do I Know Thee...? Let Me Count the Ways. The Varieties of Medical Evidence

Buchanan and Kean in an accompanying editorial[1] argue that the current approach to evidence based medicine relies too heavily on the randomized controlled trial (RCT). They proceed to outline some of the weaknesses of RCT and conclude that they "believe in a critical approach to medicine with emphasis on questioning every fact and idea and researching the evidence for them." In fact this approach takes a major leap from the RCT to the clinician's evaluation of an individual patient as the best way of acquiring new knowledge in medicine. However, there are more ways to derive knowledge in medicine than the RCT or individual expert opinion. The US Preventive Services Task Force in its report in 1996[2] suggested that there were gradings for types of evidence that could qualify as evidence based medicine and that these grades depended on the research design. They suggested that the highest grade was reserved for evidence obtained from at least one properly randomized controlled trial. However, they also suggested that the next level of best evidence was obtained from well designed controlled trials without randomization, from well designed cohort or case control studies, and from multiple time series, with or without intervention. Finally, the least reliable grade of medical evidence for describing new knowledge are the opinions of respected authorities based on clinical experience, descriptive studies or case reports, or reports of expert committees. Buchanan and Kean have described some of the drawbacks of conducting RCT, especially in circumstances where they may not be ethical or deal only with a very specific subgroup of patients that may not represent the spectrum of disease seen in the ordinary clinic. It is under such circumstances that other methods of deriving new evidence based knowledge are useful and important.

In two recent articles in *The New England Journal of Medicine*, Benson, *et al*[3] and Concato, *et al*[4] conclude that modern day observational studies can give results similar to RCT. These reports should reopen the debate on the relative merits of RCT versus well done clinical observational cohort studies, which has has been relatively silent since the early 1980s when Sachs, *et al*[5] reported the supremacy of randomized versus historical controls for clinical trials. In contrast, in the same era Feinstein in a series of 4 articles[6-9] extolled the virtues of "clinical practice research" when the proper methodologies were applied to this kind of research. This, he felt, would "require major attention to the events and observations that occur in the ordinary circumstances of clinical practice," as well as rigorous attention to reproducible forms of clinical measurement — his proposed science of "clinimetrics" — and the appropriate handling of these acquired measures with proper statistical analyses. Modern observational studies have accomplished this and produce data that are similar to the randomized controlled trials as described by Benson[3] and Concato[4].

Thus there is no single way to advance medical knowledge. Where possible in terms of available patients, adequate finances, and the ethical appropriateness, the RCT should be used to assess new therapeutic agents. However, there are other important medical questions that cannot be answered by RCT, including outcomes of disease and its therapies, risk factors for specific outcomes, prognostic factors for outcomes, clinical laboratory correlations (which will help physicians guide their therapy), and confirmation in clinical practice, with its heterogeneous population, of results of RCT performed in a homogeneous population. There are instances where RCT would be difficult, impossible, or unethical for the reasons stated above. For all these situations longterm observational cohort studies appropriately performed would be the best approach.

Modern observational cohort studies differ from those reported in the 1970s and early 1980s since the earlier studies primarily used historical controls. Currently, in well followed longterm observational cohort studies it is possible to do a cohort control study or a case control study using patients followed in the same clinic in the same era. There are good meta-analysis methodologies today to allow for better pooling of data, and current statistical handling of the data can correct for differences among patients at inclusion.

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In rheumatology, observational cohort studies have been used increasingly in the last 3 decades to address important issues. We have mined our longterm observational cohort study in systemic lupus erythematosus (SLE)[10] to address questions not yet answered or not answerable by RCT trials. In the area of *outcomes*, our observational cohort study gave rise to the concept of the bimodal mortality pattern in SLE[11]. This has opened the area of atherosclerosis as a late manifestation of SLE and may eventually give insight into the inflammatory-immunological mechanisms underlying the pathogenesis of idiopathic atherosclerosis. Further, it has changed the approach to the treatment of SLE in that risk factor monitoring and therapy is now an integral component of lupus treatment[12.] In the area of *therapy,* we have used cohort studies to describe the role of methotrexate[13] in antimalarial resistant lupus arthritis, prior to the publication of any RCT of methotrexate in SLE, as well as the role of antimalarials[14] in skin lupus in cigarette smokers versus nonsmokers. We used a case control design to study the safety of hormone replacement therapy in postmenopausal women with SLE[15]. We evaluated *risk factors* for the development of coronary artery disease in SLE in a cohort study[16], and *prognostic factors* for mortality in a similar cohort study[17]. *Clinical laboratory correlations studies* in our cohort have given rise to the concept of the serologically active, clinically quiescent patient with SLE[18] and thus modifying approaches to therapy in this disease.

In other words, in an era of evidence based medicine, there are many ways of "knowing." RCT or the critical observations of an experienced clinician are not the sole roads to medical knowledge. To promote either as such would distort the truth. Every question in medicine should be addressed by the medium most suited to give valid answers.

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