

CLINICAL EPIDEMIOLOGY: WHAT, WHO AND WHITHER

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Abstract:

Clinical epidemiology, the what, was introduced by John Paul in 1938 as a new basic science for preventive medicine. Its definition subsequently took on a more bedside tone, but continues to be adapted to the needs of its practitioners. *Clinical epidemiology*, the who, centers on Alvan Feinstein and the way that he led the field and nurtured so many of its practitioners. *Clinical epidemiology*, the whither, describes its more recent development and its impact on five evolutions and revolutions: in evidence generation, its rapid critical appraisal, its efficient storage and retrieval, evidence-based medicine, and evidence synthesis.

For someone who loved words (especially arcane “new” ones constructed from bits of “old” languages), Alvan Feinstein’s choice of “*clinical epidemiology*” to describe his thoughts and deeds was, uncharacteristically, both immediately pronounceable and transparent. Nonetheless, the term deserves (the Editor thinks) and rewards (I think) a brief etymological exploration of both the origins of its meaning and their changes with time. Its continuing evolution exposes the disutility of “essentialism,” the notion that words have a single, immutable meaning. On the contrary, the changes in the meaning of clinical epidemiology over the past 6 decades vigorously reinforce the “nominalist” view that definitions are best read from right-to-left.

In this essay, I shall summarize my understanding of the origins of clinical epidemiology before my time and describe its reintroduction and evolution after my arrival on the scene in 1963, with comments along the way on the central role Alvan Feinstein played in its continuing development and in the inspiration and mentoring of so many of its practitioners. I will integrate Alvan’s contributions with those of the other people, institutions, and journals that played major roles in the development of the field and its offspring.

I reckon that credit for the first appearance of clinical epidemiology in the medical literature goes to John Paul (1893-1971), an infectious disease internist who was appointed head of the Section of Preventive Medicine in Yale’s Department of Medicine in 1940. In his president’s address to the American Society for Clinical Investigation in 1938 (when it was still an organization with broad interests that included intact humans), he proposed clinical epidemiology as a “new basic science for *preventive* medicine” in which the exploration of relevant aspects of human ecology and public health began with the study of individual patients¹.

John Paul also gets the credit for the first use of the term clinical epidemiology as the title for both a book and a course for undergraduate medical students². Once again, it had a population rather than individual patient orientation in which he described the role of the clinical epidemiologist as being “like that of a detective visiting the scene of the crime” who then “branches out into the setting in which that individual became ill.” Thus the procedure in his course for 3rd and 4th year Yale medical students was to “start the student at the bedside and lead him gradually away from it.” [italics mine] This was in sharp contrast to the orientation of pioneers like William Silverman

and Thomas Chalmers who, although they didn't refer to themselves as clinical epidemiologists, exemplified its application in bedside neonatology³ and gastroenterology⁴.

The shift in the focus of clinical epidemiology from community ecology to individual patients and groups of patients took place in the 1960s, and I have long-attributed its Canadian branch to the combined influences of Nikita Khrushchev and Alvan Feinstein⁵. The former, by placing missiles in Cuba, precipitated the drafting of thousands of American junior clinicians into the armed forces and US Public Health Service, where we were torn from the bedside and forced to work in and think about public health ventures. Despondent over the interruption in my career as an academic nephrologist, I came upon Alvan's paper on Boolean algebra and clinical taxonomy⁶, and wrote him a fan letter. Thus began a relationship that led both of us to McMaster University in Canada (Alvan for 2 years and me for 27) and witnessed the development of clinical epidemiology in each of our respective countries and beyond.

My mentorship under Alvan began with a series of letters and conversations, often by no means cordial, in which we hammered out our separate (but overlapping) concepts of what clinical epidemiology ought to be and how it ought to be practiced. As I've described elsewhere, during his 2-year Visiting Professorship and ongoing stewardship of our McMaster efforts, Alvan "brought both science and intrepidity to our fledgling department (and did his best to make us presentable to the academic gentility)."⁷

With Alvan's encouragement, the first Clinical Epidemiology Research Unit in the new era was established at the State University of New York at Buffalo in 1966, followed shortly by the Department of Clinical Epidemiology and Biostatistics at McMaster in 1967⁸. In the prospectus for each of them I defined clinical epidemiology as "*the application, by a physician who provides direct patient care, of epidemiologic and biostatistical methods to the study of diagnostic and therapeutic processes in order to effect an improvement in health.*"⁹ Thus, at McMaster the external, public health orientation was set aside and replaced with a focus on individual patients and groups of patients in clinical, not community, settings.

In 1968 Alvan published his landmark series on clinical epidemiology in the Annals of Internal Medicine^{10, 11, 12}. It was a logical extension of his book, Clinical Judgment¹³, published the previous year, although the book did not employ the term *clinical epidemiology*. In the Annals series he defined the "territory" of *clinical epidemiology* as: "*the clinicostatistical study of diseased populations. The intellectual activities of this territory include the following: the occurrence rates and geographic distribution of disease; the patterns of natural and post-therapeutic events that constitute varying clinical courses in the diverse spectrum of disease; and the clinical appraisal of therapy. The contemplation and investigation of these or allied topics constitute a medical domain that can be called clinical epidemiology*"¹⁴. Thus, he cast a wider net, and included elements of classical "big E"^A epidemiology and public health. His inclusion of public health in his definition of clinical epidemiology was repeated 18 years later in his book of that name: "*clinical epidemiology represents the way in which classical epidemiology, traditionally oriented toward general strategies in the public health of community groups, has been enlarged to include clinical decisions in personal-encounter care for individual patients.*"¹⁵ (emphasis mine)

Over the next several years, Alvan led the development of clinical epidemiology in the US and throughout much of the world. A recurring theme and focus of his group at Yale was the careful observation and measurement of clinical phenomena (his term "clinimetrics"¹⁶) and Mary

^A In an effort to maintain my clinical skills while a graduate student at Harvard, I worked nights examining patients for William Kannel at the Framingham Study. When I first encountered Dr. William Castelli, a long-time Framingham investigator, he adopted the stance and voice of W.C. Fields and inquired: "Sonny, have you matriculated at Harvard in order to become one of those "big E" epidemiologists, or are actually going to get your hands dirty here in Framingham with us "little E" epidemiologists?"

Charlson's "comorbidity"¹⁷ came into common use), especially in the description and prediction of prognosis¹⁸ but also, with David Ransohoff, in diagnosis¹⁹. In Canada and the UK, the emphasis was directed rather more toward evaluating therapy, with major scientific attention devoted to improving the validity and credibility of the randomized clinical trial when applied to both groups²⁰ and individual patients²¹, and, once benefit was determined, toward compliance with efficacious health care²².

A Fellowship in clinical epidemiology had already begun at Yale and a degree-granting programme began at McMaster in 1970. Opportunities for clinicians to obtain education and training in clinical epidemiology gradually spread to other North American health sciences centres^B and to centres in Europe and the Far East. Combined training in clinical medicine and clinical epidemiology greatly expanded in the US in 1974 with the creation of the Robert Wood Johnson Clinical Scholars Program²³.

The first modern textbook in clinical epidemiology was written by Robert Fletcher, Suzanne Fletcher and Edward Wagner at the University of North Carolina, and came out in 1982²⁴. Now in its third edition, it continues to be a favoured introductory text. It was followed by ones from McMaster (now in its 2nd edition²⁵) and Yale²⁶ in 1985, Seattle in 1986 (now in its 2nd edition²⁷), and McGill²⁸ in 1988. Each has its own flavour and niche, and they are now available in several languages.

The internationalization of clinical epidemiology received a huge boost in 1980 when Kerr White and the Rockefeller Foundation initiated the International Clinical Epidemiology Network (INCLEN)²⁹. In this programme, young clinicians from low-income countries came for training in clinical epidemiology to "training Centres" at McMaster in Canada, Newcastle in Australia and the University of Pennsylvania. A key element of their career development was linkage to a mentor who spent part of each year working with them back at their home institutions. The organization now includes 64 medical institutions in 26 countries. Its most important accomplishments from my perspective have been the repeated redefinition of clinical epidemiology to suit local needs and the taking over of the training of clinical epidemiologists by regional centres in Africa, China, India, Latin America, and South East Asia.

The dissemination of clinical epidemiology to other high-income countries proceeded at different paces and with varying enthusiasm. It was quickly adopted in the Netherlands, with nearly simultaneous developments in Amsterdam (led by Harry Buller at the Academic Medical Centre), Leyden (led by Jan Vandenbroucke at the University Medical Centre), and Maastricht (led by Andre Knottnerus at the Faculty of Medicine, with a special focus on primary care research). Early on, Alessandro Liberati established a Clinical Epidemiology Unit at the Mario Negri Institute in Milan, and Les Irwig, Steven Leeder and Paul Glasziou led its development at the Universities of Sydney, Newcastle and Queensland in Australia. Its champions in the UK were mostly clinicians like Peter Sleight and Charles Warlow, and its expansion there was often resisted by the new Faculty of Community Medicine. Other countries like Germany, Spain and South Africa were still dominated by "clinical authorities" who resisted the egalitarianism inherent in clinical epidemiology, and (with the exception of a few hospital-based clinical epidemiology units such as Francisco Pozo's in Madrid) it was not until the evidence-based medicine movement that the rapid, widespread adoption of these ideas occurred in such countries^C.

^B For example, by 2001, 15 of the 16 Canadian medical schools offered graduate training in clinical-practice research methods.

^C I am certain that I have not done justice to the development of clinical epidemiology outside North America. Some of this deficit will be corrected in a forth-coming book (J. Daly, Evidence-Based Medicine and the Search for Certainty in Clinical Care, New York and Berkeley: The Milbank Memorial Fund and the University of California Press), and I hope that readers will inform us about the development in their countries through Letters to the Editor.

In the meanwhile, Alvan was making clinical epidemiology a respectable undertaking for North American academic clinicians. The most prestigious annual meetings of North American academic medicine were the American Federation for Clinical Research^D, the American Society for Clinical Investigation^E, and the Association of American Physicians^F. There was no place on their programmes for clinical epidemiologists, so we borrowed an unused meeting room from them and held our own Sydenham Society meetings^G to discuss the methods and findings of clinical epidemiology. By 1972, Alvan's negotiating skills and political connections had led to the introduction of sections on Clinical Epidemiology at each of the societies, where they soon became their fastest-growing scientific sessions. Alvan also managed the election of the first young clinical epidemiologists to these organizations, where they now comprise an impressive proportion of the membership.

Clinical epidemiology has not been without its detractors³⁰, especially among more traditional epidemiology departments who perceived (often correctly) their loss of resources and bright young minds to this new discipline. Perhaps the most radical and articulate of these is Walter Holland who, in 1983, urged us to abandon the term *clinical epidemiology* altogether³¹. While acknowledging its usefulness over the previous 15 years^H, he now found it a divisive term that conferred "respectability" only on those epidemiologists who practiced medicine, created the impression that one form of teaching (using epidemiology for solving clinical problems) was more appropriate than another (mastering classical epidemiological methods), and fashioned students' perceptions of the priorities and needs of societies.

I replied to Walter Holland's criticisms, first by emphasizing that the distinction between clinical and non-clinical epidemiologists was on a nominal, not ordinal, scale³², and suggested that his other criticisms were not only true, but to be applauded: clinical epidemiology was a better way to teach medical students, and clinical epidemiology was reshaping the perceptions of not only medical students (who began to see it as a relevant basic science) but entire faculties (departments of clinical epidemiology were growing in number and size; clinical departments were carrying out more and better "clinical-practice" research³³), and learned societies were acknowledging the relevance of clinical epidemiology to "clinical research" in ways that classical epidemiology had been unable to achieve,

Having established itself, gained formal recognition at universities, granting agencies, and learned societies, and populated academic departments and research groups around the world, the field of clinical epidemiology became increasingly able to emphasize its similarities to, rather than its differences from, classical public health epidemiology and the related sciences of economics, political science, psychology, and sociology. As pointed out by Walter Spitzer³⁴, all of these disciplines^I carry out and collaborate in studies of "*diagnostic and therapeutic processes in order to effect an improvement in health*,³⁵" and the term's usefulness nowadays is perhaps

^D The young squirts.

^E The young turks.

^F The old farts.

^G Alvan, Tom Chalmers, and I organized the meetings, and Harold Conn kept us solvent.

^H Indeed, his own department bore that name for several years, in part because the inclusion of "clinical" in its title afforded higher salaries to its members. True to his convictions, he removed the word from the name of his department.

^I Indeed, one recent "clinical epidemiology" text was written by two biostatisticians: Knapp RG, Miller MC III: *Clinical Epidemiology and Biostatistics*. Baltimore: Williams & Wilkins, 1992.

greater in describing the “clinical epidemiologist” as the sort of academic clinician who, along with collaborators from an array of disciplines, carries out this sort research.

Clinical epidemiology has not evolved in a vacuum, and much of its growth, strength and continuing evolution are the result of its leadership and participation in five other parallel evolutions (some of them revolutions) in evidence generation, evidence appraisal, evidence retrieval, evidence application, and evidence synthesis. Although a wide spectrum of clinical journals have published the concepts, methods and results of clinical epidemiological research, and The Journal of Clinical Epidemiology has been a natural home for the discipline, some individual general medical journals stand out in fostering the field and its recent evolutions. In the 1970’s the Journal of Clinical Pharmacology and Therapeutics turned Donald Mainland’s “Notes from a Laboratory of Medical Statistics” over to Alvan for his landmark series in “Clinical Biostatistics.” In the 1980’s the Canadian Medical Association Journal hosted series on “How to Read Clinical Journals” and “How to Interpret Diagnostic Data” from Brian Haynes, Peter Tugwell, and our group at McMaster. In the 1990’s, Drummond Rennie at the Journal of the American Medical Association and I collaborated in starting the “Rational Clinical Examination” series, currently edited by David Simel, that hosted reviews of the accuracy and precision of the clinical history and examination from clinical epidemiologists such as Alan Detsky, Richard Deyo, John Williams, Steven Grover, David Naylor, Sonia Anand, and Akbar Panju. Drummond went on to host the bell-weather series of “Users’ Guides to the Medical Literature” led by Gordon Guyatt, and they collated the latter into a major text. Throughout this era, Ed Huth, followed by Robert and Suzanne Fletcher, Frank Davidoff and now Harold Sox have led Annals of Internal Medicine to champion the field, beginning with Alvan’s 1968 papers on clinical epidemiology, including series such as the one on systematic reviews edited by Cynthia Mulrow and Deborah Cook³⁶, and culminating in Brian Haynes’s creation of the ACP Journal Club and Evidence-Based Medicine series of journals of secondary publication. In the latter it was joined by the British Medical Journal, whose leadership, especially Richard Smith and Alexandra Williamson, helped explain our new world ideas about clinical epidemiology and evidence-based medicine to the old world, and nurtured their maturation and relevance for Europe and beyond.

Clinical epidemiology has played a central or major role in five recent evolutions (some say revolutions) in health care: in evidence generation, its rapid critical appraisal, its efficient storage and retrieval, evidence-based medicine, and evidence synthesis. The evolution in evidence generation since 1970, although most easily documented in the growth in reports of and about the randomized trial (with more of them published in the single year 2000 than in the decade 1965-75), is paralleled by similar, although less spectacular, increases in the numbers and sophistication of reports about diagnosis, prognosis, and the appropriateness and quality of clinical care. Clinical epidemiologists are providing leadership in both the generation and continuing methodological development of this burgeoning body of clinically-relevant evidence.

The price to be paid for this vast increase in relevant evidence was an increasing difficulty in finding it, retrieving it, and keeping up-to-date with it. Although I doubt that the busy front line clinician was able to keep up to date even in the 60’s, by 1972 there were about 4M articles published in the biomedical literature per year (in all languages)³⁷. Restricting one’s reading to just the journals that provide the content that is sound and relevant for internal medicine requires reading 33 articles every day of the year³⁸. The dramatic decline in general medical knowledge after certification that was documented by a group of clinical epidemiologists at the University of Washington made it impossible to ignore this growing problem³⁹. A second problem became evident when this growing body of evidence was subjected to the critical appraisal of its validity: the majority of it was found wanting. These two situations combined to place clinicians at increasing risks of “drowning in doubtful data.” The parallel evolutions in the rapid critical appraisal of evidence (for its validity and potential clinical usefulness) and in the efficient storage and rapid retrieval of evidence combined to rescue clinicians who were striving to track down the evidence than might help their patients. Although several clinical epidemiologists, as well as library scientists, statisticians, and qualitative researchers made vital contributions to these parallel evolutions, it was Brian Haynes who rolled up his sleeves, provided both intellectual and

organizational leadership, formed the teams, and endured a decade of inattention from granting bodies to bring these evolutionary streams together in powerful and clinically-relevant ways^{40,41}. The example he set by reducing the internal medicine literature to just the 2% that was both valid and clinically relevant in the ACP Journal Club⁴² introduced the revolution that today provides front line clinicians in a number of clinical fields with manageable chunks of up-to-date, reliable evidence, right at the bedside⁴³.

As more and more clinicians, armed with the strategies and tactics of clinical epidemiology, cared for more and more patients, they began to evolve the final, vital link between evidence and direct patient care. Building on the prior evolutions, and manifest in clinically useful measures such as Andreas Laupacis's NNT (the Number of patients a clinician would Need to Treat in order to prevent one more bad outcome)⁴⁴, and often incorporating the patient's own values and expectations as in Sharon Straus's LHH (the Likelihood that a treatment would Help vs. Harm the patient's achievement of their health objectives)⁴⁵, the revolution of Evidence-Based Medicine was introduced by Gordon Guyatt⁴⁶. Since its first mention in 1992, its ideas about the use (rather than just critical appraisal) of evidence in patient care and in health professional education have spread worldwide and have been adopted not only by a broad array of clinical disciplines (most recently in a new sort of house officers' guide edited by Christopher Ball and Robert Phillips⁴⁷) but also by health care planners and evaluators.

Simultaneous with these other evolutions and revolutions, and both supporting and building upon them, has been the evidence-synthesis evolution of strategies and tactics for assembling and systematically reviewing the totality of evidence about the effects of health care. Generated from revelations such as Cynthia Mulrow's exposure of the sad state of the medical review article⁴⁸, and cautionary notes about subgroup analyses from Andrew Oxman and Gordon Guyatt⁴⁹, this evolution is epitomized in the Cochrane Collaboration⁵⁰, a worldwide collaboration of patients, clinicians and methodologists who prepare, maintain and promote the accessibility of systematic reviews of the effects of healthcare interventions. Conceived and led by Iain Chalmers, and with invaluable support from Muir Gray, this work has been characterized as equal in importance to the human genome project⁵¹. Although the conceptualization, operation, and ramifications of this evidence-synthesis evolution extend far beyond clinical epidemiology, the contributions of clinical epidemiologists to its success are, in my view, their greatest accomplishment since the term was introduced 65 years ago.

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Potential Competing Interests:

(NOTE: given the revelations in the paper from Alfredo Morabia, I'd like the following statement to appear in its entirety):

Dave Sackett has been wined, dined, supported, transported, and paid to speak by countless pharmaceutical firms for over 40 years, beginning with two research fellowships and interest-free loans that allowed him to stay to finish medical school. Dozens of his randomised trials have been supported in part (but never in whole) by pharmaceutical firms, who never received or analysed primary data and never had veto power over any reports, presentations, or publications of the results. He has twice worked as a paid consultant to advise pharmaceutical firms whether their products caused lethal side-effects; on both occasions he told them "yes." He has testified as an unpaid expert witness for a stroke victim who successfully sued a manufacturer of oral contraceptives, and as a paid expert in preparing a class-action suit against a manufacturer of prosthetic heart valves. He was paid by a pharmaceutical firm to develop "levels of evidence" for determining the causation of adverse drug reactions. His wife inherited and sold stock in a

pharmaceutical company. While head of a division of medicine he enforced the banning of drug-detail personnel from clinical teaching units (despite the threat of withdrawal of drug industry funding for resident research projects). He received the Pharmaceutical Manufacturers' Association of Canada Medal of Honour (and cash) for "Contributions to Medical Science in Canada" for the decade 1984-94. One of his recent awards (the 2001 Senior Investigator Award of the Canadian Society of Internal Medicine) was sponsored by Merck Frosst Canada.

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