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On the new clinical fashion in epidemiology

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The clinical application of the principles of epidemiological research has become fashionable. Three recent textbooks carry the words 'Clinical Epidemiology' in their titles (Feinstein, 1985; Sackett, Haynes & Tugwell, 1985; Weiss, 1986), and a venerable journal has recently changed its name to this effect (Feinstein & Spitzer, 1988). Deans of medical schools, Government Health Officials and editorialists pay tribute to the new science which is expected to steer the medical profession of the third millennium.

Usually, there is some looseness as to the meaning of the words, and some people wonder about the origins of this new creature. Still others wonder what clinical epidemiologists actually do and what qualities they should have. This paper will try to answer these questions.

The demarcation of the field of clinical epidemiology

The author sides with those who see 'clinical epidemiology' first and foremost as a research discipline within clinical science. Therefore, it must be demarcated from practice-oriented applications such as decision analysis, cost benefit analysis, technology assessment, and also from medical audit and quality assurance.

Clinical epidemiology aims to bring the principles of epidemiological investigation into research on patient populations; research of the type described as 'clinical science' by Sir Thomas Lewis (1934). The clinical epidemiologist aims to support medical colleagues who want to investigate aetiology, diagnosis, prognosis and therapy, in as far as it involves counting patients and making comparisons of counts between groups of patients. To paraphrase Feinstein (1985), it is research in which the unit of measurement is the patient, not the patient's white blood cells or nucleotides. Thus clinical epidemiology is considered to differ from its parent discipline, general epidemiology, which is concerned with disease occurrence in general populations. The distinction is not always a sharp one; around the turn of the century, Sir James MacKenzie already professed that the true study of the natural history of diseases necessitated also the study of their origin in the healthy population (MacKenzie, 1919).

More clearly, clinical epidemiology distinguishes itself from two other areas of professional activity, which have lately become fashionable. Firstly, it is distinct from the area of decision analysis, cost benefit analysis and technology assessment. Medical decision analysis consists of the application of principles of general decision analysis to the problems of medicine: medical management of individual patients as well as broader decisions on the health care of populations (Weinstein & Fineberg, 1980). Its aim is to maximize gains in life years, eventually quality-

adjusted. Medical decision analysis tries to disentangle the complexities of such decisions into separate steps by drawing decision trees (Weinstein & Fineberg, 1980). Thereby, it makes use of *existing* medical scientific knowledge which it tries to rearrange along the decision tree, in order to arrive at new, and better, decision patterns for the *future*. Cost efficiency and cost benefit analyses are an extension of decision analysis in which financial gains or losses are weighted along the different decision strategies. They have most appeal to third-party payers, such as insurance and government bodies. Medical decision analysis by itself, trying to restructure the sometimes bewildering areas of diagnostic and therapeutic possibilities, has most appeal within the medical profession.

Secondly, clinical epidemiology is distinct from the area of medical audit and quality assurance in health care (Donabedian, 1980). Again, issues of quality comprise both the micro environment and the macro environment in health care. The latter studies questions such as 'does the health care system of this country allow equal access?' The former addresses questions concerning the appropriateness of individual patient management. Like all types of audit, such questions presuppose an implicit or explicit prior standard on the quality to be attained. In its application to the process of medical care, the question becomes whether the patient was managed according to the best of today's medical knowledge; a comparison between *actual* practice with the best *present* state of medical science.

Neither decision analysis nor quality control generates *new scientific knowledge* such as that aimed at by clinical epidemiology. The numerical facts brought to light by the application of epidemiology in the clinic often are the basis for decision analysis or medical audit; equally often, they are directly incorporated in our biological and medical knowledge of the disease process.

A history of numeracy in medicine

However sketchy, it is necessary to establish that the described aims of clinical epidemiology are already firmly embedded in the history of medicine. At all times, medical doctors have tried to advocate their opinion on causes of disease, or on the benefits of treatment by proposing numerical arguments. For eighteenth-century Britain, it has been shown that quantification in the description of patient series played an important part in the evaluation of therapies in both medicine and surgery (Tröhler, 1978). At the beginning of the nineteenth century, there was in Paris the towering figure of Charles Pierre Alexandre Louis, who advocated the 'numerical method' for the comparative study of the benefits of treatment, and who was made a lifelong president of the 'Société de Medicine d'Observation' (Ackerknecht, 1967). The numerical method did not gain firm ground in clinical medicine, however, for lack of sensitivity to some characteristics of clinical medicine, as masterfully described by Greenwood in 1936 (reprinted in 1986). Yet, Greenwood exclaimed: 'If only Louis had succeeded in really commanding the support of "les superbes" as a contemporary called them, the great clinical teachers of Paris, if Trousseau had had a "service statistique" and Dieulafoy! Why, we should have had something to do about it in England! I dare say that by now the Royal Colleges would be considering the desirability of establishing a

Diploma in Clinical Statistics and clinical units would have statisticians. But this is mere daydreaming'. By contrast the numerical method quickly gained adherence among the sanitary physicians, who wanted to make statistics their objective weapon for the betterment of the health of the public. These ideas were mainly carried on by Louis' overseas students from Britain and the United States (Lilienfeld, 1978, 1979). Within the public health movement, the numerical method grew into what is known today as general epidemiology.

While clinical medicine was thus temporarily left devoid, a first injection of numeracy came from the advent of medical statistics. Ideas from Galton, the two Pearsons, Fisher and Yule were brought into medicine either directly, or by Greenwood, Russel, Woods, and Sir Austin Bradford Hill (Susser, 1985). In practice, the main focus of biostatistics has been on probabilistic variability; hence the preoccupation with *P*-values in contemporary medical science. Today, we witness a new numerical booster in the form of clinical epidemiology. General epidemiology has matured from a purely infectious disease discipline into a chronic disease research tool (Susser, 1985). Its methods of investigation have been sharpened and refined, often to the point of becoming slightly esoteric. The application of these methods is now seen as a revitalization for clinical science: to help clinical reseachers to do better what they have always sought to do.

The daily practice of clinical epidemiology

The author of this overview, with a background in clinical medicine and epidemiology, has for nearly two years been building up a new department of clinical epidemiology, located in the new premises of the Leiden University Hospital. The outpatient clinics are to the left, wards, staff rooms and laboratories to the right. Close to two years of such activities in an ultramodern teaching hospital, coinciding with the fiftieth anniversary of Pickles' *Epidemiology in Country Practice* seems a good time to take stock.

The central activity in this department is teaching the logic of numerical research in medicine. This teaching is usually performed during discussions of new or even ongoing clinical research projects. As a good rule, such interviews, often with young clinical colleagues, are held in the reverse order of the usual sections of a scientific paper. One starts by inquiring in the most general way, what aspect of the human condition the young doctor really wants to improve: which gaps in our knowledge to explore, to the benefit of which type of patient. What in the state of medicine will be changed after his or her publication? What are the 'gut feelings' about the research proposed? In asking these questions directly, one kindly puts aside for a moment the way the research question was phrased in the rather unintelligible research proposal that was handed in hurriedly the evening before. Thus, one removes oneself from all particulars of time and place, all material constraints and all practical questions. These are dealt with in a later part of the interview. One tries to understand the grand idea behind the research proposal. When there is firm understanding and agreement on both sides what the real issues are, one tries out what parts of this grand idea might be transformed into manageable little pieces of research; i.e. measurable research questions. This is performed by phantasizing aloud all aspects of the general research question,

and by indicating which aspects might most readily be turned into bits and pieces of clinical research. It is important to discover at this point which aspects of the general research question appeal most and why. At this stage one also likes to get a feel for the real meaning of the research for the young researcher's own career ambitions. Once it is known which amenable research question appeals most, the many study designs, which might in theory be applicable, are discussed. One reviews all theoretical possibilities, again divorced from any particulars of time and place. Only after this does one try to settle for a particular design: knowing on the one hand the 'state of the scientific question', and on the other hand the personal ambitions, time and material constraints on the piece of research.

Quite often this author emphasizes the value of starting with the simplest design, if possible with the use of more or less available data. Equally often, this leads to some opposition because the research question looks almost childish and, even worse, the design has a 'retrospective' appearance. To overcome such opposition, one can use several remedies. Firstly, one describes the procedural details necessary for a rigorous study of a *very* simple question, such as counting single events in the course of a patient follow-up; identifying the complete cohort, performing a 100% follow-up, standardizing measurements, filling in computer-readable forms, learning to use database and statistical computer packages, and finally, setting enough time aside for the writing and rewriting of the paper. Such activities may be undreamed of by the young research worker. Secondly, to those who still nurture elaborate and long-winded research questions and protocols, one tells the story of Dr Pickles. The true greatness of a man like Pickles is that he pruned his research to questions so very simple, yet so basic, that they necessitated only the entry of a single, tiny pencil cross for each patient. Dr Pickles knew the application of the 'art of the soluble', long before Medawar coined the phrase (1979). In doing so, and in examining his charts with a mind prepared by clinical experience, Dr Pickles came to great conclusions. The author always urges clinical researchers to think so hard about their research questions, that they might come up with something as lucid as that. They rarely succeed; neither does the author. In similar frustration, a long time ago, one of Dr Pickles' friends, Professor Greenwood, wrote to Pickles 'no scientific note I have done will live, but I have stimulated others who will do something' (Pemberton, 1972).

The final test of mutual understanding and agreement is to ask the young clinician to draw on the blackboard the ultimate two by two table, which will carry the basic message of the research. After he or she has done so, one asks how clinical colleagues will interpret that table when they see it. That brings us back to the original grand idea.

Once a research question and the design, appropriate to deliver a single piece of numerical information, are agreed upon, there should be a protocol and a pilot study. Some parts of the protocol handed in earlier might now become useful. Always, the protocol should be tried out in a small pilot study, lasting only a few weeks, after which there should be a few weeks pause to see how things really worked out.

In the process of accompanying the young doctor further upon the thorny path to scientific fame, several other skills and interests are necessary. The young researchers have to learn to design forms, to write letters directly to patients

inviting their co-operation, to use computers, to do part of the data entry and analysis themselves, and to use word-processors. In doing so, they extract much more information from their own data than if data entry and analysis were to be performed solely by administrative or statistical aides. Only after they themselves know all the tricks of collecting the data, can the task be passed on to another person; and only when they have grasped the essentials of statistical analysis, can they meaningfully interact with a department of biostatistics.

The young medical researcher has to learn to write papers. Usually, this author emphasizes the importance of starting to write the paper as early as possible, preferably before any data collection takes place, or right after the pilot study – at the very latest in the midst of the data collection. To the incredulous reaction of the researchers, it is made clear that by discussing the research, they:

(1) already know why they started the research, which is the Introduction,

(2) already know how they will collect data, which is the Materials and Methods,

(3) already have drawn the final two by two table on the blackboard, which is the body of the Results section, and

(4) already know what the contents of the table might look like (there are usually no more than three possibilities: positive, negative or ambiguous), and that they have already explained what the interpretations of their colleagues might be, which is the essence of the Discussion.

So, one proposes to write a provisional paper with three different Discussions. Of course, one reassures the anxious researchers that revisions will be possible when the data come in. For practical advice about writing, the researchers should be guided into the vast literature on 'How to write and publish...'.

Lastly, one often has to teach young researchers to manage their scientific relations. Teach them how to discuss their affairs, scientific and otherwise, with other clinicians and administrative persons involved in the research. Make them understand the point of view of others, and teach them how to collaborate to arrive at the final aim of their research.

The qualities of a clinical epidemiologist

The central quality of a clinical epidemiologist, in the judgement of the author, is the need to be trusted as a medical colleague who has lots of time. This means that a clinical epidemiologist should have broad medical knowledge and experience and be aware of the current medical literature; some idea of the essentials of DNA technology and immunogenetics has lately become necessary. This means that he also understands what it means to have a heavy rota of night and weekend duties, a young family, another outpatient clinic to take over from a lazy colleague, and still the desire to do one's own piece of research. A clinical epidemiologist should be a good-humoured observer of human nature in large medical institutions. He or she should have first hand knowledge of all types of epidemiological research, their design, practicalities, and analysis. He should be equally versed in case-control methodology, retrospective design, person-years calculation, life-table techniques, logistic models and the complexities of randomized controlled trials. Among lesser qualifications, the clinical epidemiologist has to be conversant with computers, and a more or less talented teacher of medical journalism with a good

command of the English language. Finally, it helps to have a perspective of the history of medicine, especially of modern therapeutics. Medical persons in general and young doctors in particular have little historical knowledge of their own field. It is usually appreciated if one can outline the humble place of a piece of research in the general progress of medicine.

To have lots of time for discussions about research protocols, i.e. more than the average clinical supervisor, it is necessary to delegate tasks as quickly as possible. A clinical epidemiologist should have a small dedicated staff who can take over the daily supervision of clinical research. A clinical epidemiologist should only help to draw outlines, and explain to clinical researchers where and how to find the resources to perform the task *themselves*: for example from books, computer tutorials and from the staff of the department of clinical epidemiology.

A perspective on clinical epidemiology

The case for clinical epidemiology is suffering from an acute overdose of academic popularity. Clinicians have always studied aetiology, diagnosis, prognosis and therapy; these words are 2000 years old, or older. The present over-enthusiasm is also reflected in the description of the historical roots of the discipline. All too often one hears the tale that 'the medical profession' has leeched for centuries, and that only the application of the numerical method by Louis has put an end to this crazy practice. One should realize two things. Firstly, Louis' observations fell into receptive soil, since the indications and contra-indications of bleeding had already been extensively discussed, even before his time. Secondly, Louis only demonstrated that failure of leeching in acute pneumonia. Bleeding was used up to the 1940s, as an excellent palliative measure in all cases of chronic generalized oedema, such as those due to heart failure, pulmonary, hepatic or renal failure. In those times, there were no efficient diuretics, except for the extremely toxic mercury.

The numerical aspect of medical research is only one side of this research. In a recent overview of the use of statistical methods in the *New England Journal of Medicine*, it was found that roughly one half of the published papers used little or no statistics (Emerson & Colditz, 1983). The majority of the other papers used only elementary statistics, and a tiny percentage needed the full armamentarium of modern epidemiology. Those papers that did not use numerical methods might by some be claimed to be the most 'significant', since these are the papers that describe advances in knowledge about biological mechanisms of aetiology, pathogenesis and therapeutics. Epidemiology is complementary to basic medical science, and should not lead it. Likewise, clinical epidemiology should be a servant to the broad issues of clinical science. A clinical epidemiologist should be a collaborator who tries to help clinical researchers to solve their questions. To paraphrase Sir Thomas Lewis (1934), the research questions will emanate from the bedside and the potential solutions should be tried out at the same place.

The rather dogmatic application of some hierarchy of methodologies is to be avoided. Such hierarchies place the randomized controlled trial on top and the case-history or patient series at a suspect bottom (Sackett *et al.* 1985). That this attitude is counterproductive becomes apparent if one studies the path of the real progress of medicine. Recently the cardiologist Rahimtoola (1987) described the

role of different study designs in clinical research. He proposed that the creative heart of progress in medicine is with large numbers of young innovative investigators, pregnant with new hypotheses, who perform their observations on small numbers of patients: description of patients and patient series, physiological and biochemical investigations and small clinical trials. The large multicentre randomized controlled trial to guide the greater decisions in health care, will only come later – according to Rahimtoola as the domain of the burned out middle-aged researcher who is still only fit enough for administration and organization. Moreover, new medical problems will challenge existing research methodologies. The clinical epidemiologist should first and foremost be adaptable to the clinical problem and never be a slave of theoretical paradigms. Dr Pickles' patient series are a case in point.

Finally, in the application of the results of numerical research to the management of the individual patient, we have to realize that clinical epidemiological research necessitates much abstraction. Patients are categorized into broad and mutually exclusive groups. The rich variety of the clinic is lost. The results of a clinical epidemiological investigation will never be more than global background knowledge. In practice, the individual patient does not precisely fit into one category from one investigation. The individual and his disease have several characteristics upon which different research data might be available, yet never before in that unique combination. The individual doctor will thus not escape the obligation to decide to the best of his wits, by physiopathological reasoning with some numerical data as a general guide on the background. Greenwood previously described the fallacy of relying too much on numerical arguments in clinical medicine, as in his opinion the doctor 'is not an actuary advising a company to accept (or decline) "risks" but a physician called to help a sick man'.

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