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## PAST, PRESENT, AND FUTURE

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## A Short History of Evidence-Based Medicine

*Issues for the Clinician*

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### INTRODUCTION

Evidence-based medicine (EBM) has made a clear contribution to medicine in a short 10 yr or so. Why then should we stop and consider where it came from and who the people were who generated this new direction? We do not expect any intervention in medicine, whether theoretical or therapeutic, to be perfect. The enthusiasm that greets a new approach gradually gives way to critique with the aim of improving it, of setting limits to its use, or of discarding it. There has sometimes been vehement criticism of EBM, countered with a, sometimes, evangelistic defense. The furor seems to have died down and now is a good time to take stock. What does EBM offer to the clinician in a field like endocrinology, and where might improvements be sought?

If we think of the progression of EBM, then there are traditions that fed into its genesis. There were certainly people who made decisions about the direction in which it should develop; but these decisions were constrained, if not determined, by circumstances: social, professional, and economic. Re-examining this history now gives access to some of the directions that could have been explored yet were not. Are there productive activities that can be introduced in the present time more easily than in the past?

My account draws on research that I conducted over the past 15 yr, interviewing the pioneers of EBM if they were still alive or using archival material to flesh out the

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activities of those who had died. The methods and more detailed discussion are to be found in my book, *Evidence-Based Medicine and the Search for a Science of Clinical Care (1)*. Here I provide a discussion of those aspects of the history that seem relevant to the clinician in the field of endocrinology.

My argument is that EBM was formed from the interweaving of two distinct strands, one arising in the United Kingdom and one in North America. Each of those strands drew on a different intellectual tradition in medicine and when they came together it created a powerful new approach. The examples I use are those of the Cochrane Collaboration and the McMaster University School of Clinical Epidemiology and Biostatistics. Before discussing these two approaches, I outline the intellectual heritage that existed in the 1960s, those researchers whose intellectual contribution underpins EBM.

## THE INTELLECTUAL PIONEERS

The two major figures whose work inspired EBM are Archie Cochrane in the United Kingdom and Alvan Feinstein in the United States. These two men both cast long shadows. Both of them were attracted to laboratory medicine, which was dominant in medical schools at the time, but instead they turned to the research that underpins much of EBM. Their careers initially took them in diametrically opposed directions.

### *Archie Cochrane*

Archie Cochrane believed that he could not be a laboratory scientist because of his social conscience. This is the view of Cochrane held by his contemporary, Sir Richard Doll:

*“Archie Cochrane was a man of the 1930s. His character and lifelong convictions were formed by the cataclysmic events that brought Hitler to power and plunged the greater part of the world into a devastating six-year war. In this he was not alone. What distinguished him from so many others of his generation was the depth of his emotional and intellectual reaction to these events and his fiery independence of mind, which prevented him from accepting any of the easy political solutions and kept him a rationalist to the day of his death.” (2)*

In the 1930s, Cochrane interrupted his clinical studies to volunteer in the Spanish Civil War for the republican Spanish Medical Aid Field Ambulance Unit, supporting the International Brigade. He was a prisoner of war for 4 yr during World War II, within which time he had to care for fellow prisoners suffering the effects of malnutrition and infectious diseases. All he had to treat them with was aspirin, antacid, and skin antiseptic. The German command was of the opinion that doctors were superfluous so Cochrane meticulously observed the prisoners' health needs and used a primitive trial of yeast supplementation (3) to argue for improved rations. In another camp he had to care for prisoners with tuberculosis. Later he concluded that he had enjoyed being a caring doctor, he found it intellectually satisfying, but he felt desperately worried that he was making decisions about interventions without knowing whether he was doing more harm than good. “I had never heard of ‘randomized controlled trials’ but I knew there was no real evidence that anything we had to offer had any effect on tuberculosis, and I was afraid that I shortened the lives of some of my friends by unnecessary intervention.” (4)

After leaving the army, Cochrane was awarded a Rockefeller fellowship in preventive medicine. He first studied at the London School of Hygiene and Tropical Medicine

where he was taught medical statistics by Austin Bradford Hill. In the 1930s, Bradford Hill had designed a randomized controlled trial for application to medical care (5) and this was put to use after the war in a trial of streptomycin in the treatment of tuberculosis (6). The drug was in short supply, there was only enough to treat 50 patients, and a randomized controlled trial was seen as the best way of allocating this scarce resource and of getting a definitive answer about effect.

The second stage of Cochrane's fellowship was spent in the United States where Birkelo et al. (7) had published a study of differences between radiologists in the interpretation of the same chest films. At the Henry Phipps Clinic, Cochrane studied tuberculosis, including the problem of medical error in the interpretation of X-rays, related to prognosis (8). He returned to the United Kingdom with a fierce interest in medical error and accepted a position in the Pneumoconiosis Research Unit of the Medical Research Council, in Cardiff, South Wales, one of the poorest areas in the country. Cochrane's role was to improve classification of the chest X-rays of coal miners and to conduct surveys of mining populations.

Near Cardiff, there were two mining valleys with a population of about 30,000 people and here Cochrane started his Rhondda Fach studies of factors affecting the progression of lung disease (9,10). Cochrane immersed himself and his researchers in the area. They lived there, based themselves in the small hospital in Llandough (where the Cochrane archives are now located) and set about X-raying the entire adult population and testing all schoolchildren for exposure. Their field workers were from the area and there were regular meetings reporting back to the community. Cochrane's strategies for maintaining response rates of never less than 90% became legendary—including fetching recalcitrant research participants from their homes in his Daimler.

The 20 yr of effort required to maintain the studies deepened Cochrane's commitment to the eradication of error and bias in research. Cochrane had become an epidemiologist. He showed that a team such as his could achieve measurements with a precision matching that of laboratory studies and his main concern became that population studies representative of a community should be rigorous and fully exploited. The Rhondda Fach studies failed to achieve their main aim because the introduction of streptomycin changed the pattern of lung disease, but by then a number of other studies had been nested around this original purpose.

He also became impatient. Lord Cohen of Birkenhead was later to recall, "Bias, indeed, in all its forms, scientific or otherwise, became almost a personal enemy, and once it was detected, he was ruthless in exposing it." Cohen added, "He cannot always have been the easiest of colleagues." (11)

Cochrane had been deeply influenced by his participation in the Spanish Civil War. He had concluded that pacifism was impossible in the face of fascism, but he also developed an aversion to communists who, he believed, did not know how to run either a country or a revolution (12). On the other hand, he was committed to social medicine and a passionate supporter of the National Health Service introduced in the United Kingdom after World War II. He was moved by the "gloomy picture" of inconsistent and inadequate health care in South Wales and realized the importance of the randomized controlled trial in measuring the effectiveness of therapies. It "offered clinical medicine an experimental approach to the validation of its practices and treatments. It was high time that medicine and the National Health Service monitored and accounted

for how they were serving the public. Too much that was being done in the name of health care lacked scientific validation.” (12)

While Cochrane extolled the randomized controlled trial as a “very beautiful technique” (4) for resolving issues of bias, he proceeded to target his colleagues for sub-standard care, on local and national committees. In the process, he became notorious as a gadfly but caught the attention of the health bureaucracies. In 1972, he was invited to deliver the Rock Carling lecture, simultaneously published as *Effectiveness and Efficiency: Random Reflections on Health Services* (4). The book enjoyed immediate popular acclaim for what seemed to many to be a sensible message: that medical care is expensive, that any procedures that could not be shown to be effective should be eradicated and the savings should be committed to proper care for underserved communities. Ten years later, *The Times Health Supplement* (January 22, 1982) reported that Cochrane’s medical colleagues were still reeling under the onslaught.

In the United States, Kerr White, who considered Cochrane to be “an icon and an iconoclast,” introduced the Cochrane book to the newly established Institute of Medicine (13). There was the perception that Cochrane’s book was seen as useful “to halt a lot of costly pie-in-the-sky nonsense from the hi-tech aristocrats aching to get into the health scene, who were very much in the ascendancy in the United States, after the moon landing.” (14)

The randomized controlled trial was at the heart of Cochrane’s radical proposals. Cochrane then went further, calling on each medical specialty to maintain a list of all trials that related to its own practice and to ensure that this list was regularly updated. At this stage, in the 1970s, Cochrane met Iain Chalmers who was to carry this program through to form the international Cochrane Collaboration in the 1990s.

### ***Alvan Feinstein***

Like Cochrane, Alvan Feinstein was respected but feared. The targets of his criticisms had to suffer his capacity to coin eloquent new terms to denigrate opponents. An over-commitment to the randomized controlled trial was described as “randophilia;” his critique of clinical biostatistics decried “the haze of Bayes, the aerial palaces of decision analysis, and the computerized Ouija board;” (15) meta-analysis was described as “statistical alchemy for the 21st century.” (16)

Unlike Cochrane, Feinstein was not interested in the health system and he did not want to destabilize the medical establishment: “I am willing to utter heretical remarks, in the inner councils but I don’t break up the service in the church.” On the other hand, he was in favour of dissidents: “Harold McMillan when he was prime minister of England, made a remark that is one of my guiding lights, he said that whenever the establishment is unanimous in a particular position, he noted that carefully because they were almost invariably wrong. So you always want to have some dissidents.” Feinstein certainly was a dissident.

Feinstein first trained in mathematics. When he found that he was unable to make the leaps in understanding of a great mathematician, he switched to medicine. To his surprise, he found that he enjoyed being a doctor and he was good at it. Medicine also gave access to “some wonderful goldmines” both financial and intellectual. In search of this gold, he said, he moved to New York, to the Rockefeller Institute where all good academicians trained. Feinstein was something of a raconteur and could sing self-composed ditties about having to run endless tests on urine and feces while being

treated as “somebody’s lab boy.” Instead he decided to aim for private practice in New York and so he became Clinical Director at Irvington House, a rheumatic fever hospital and convalescent home. Here researchers were conducting a trial of prophylactic treatment for prevention of a recurrence of rheumatic fever. Feinstein’s task was to collect the clinical data for the study. He was hooked.

Like Cochrane, Feinstein was immediately concerned about the disagreement in the interpretation of heart sounds and uncertainty in the diagnosis of rheumatic fever. Laboratory tests could establish the presence of a streptococcal infection but the diagnosis of rheumatic fever rested on clinical interpretation of the difference in heart sound between a normal heart (sometimes with a normal murmur) and the heart sound of an affected child. The textbooks were little help and when he tried to get clinicians to state the criteria for a diagnosis, he was told, “Just stay with me and you will learn it.” After much “sticking around” he concluded that diagnosis was all too often based on the idiosyncratic views of authoritative clinical teachers. His first aim was reduce inter-observer error.

*“The first step was to recognize what we heard. I’d say, ‘Look, do you agree that what you hear sounds like lubssshh, lubssshh, lubssshh, lubssshh?’ ‘Yeah, that’s what it sounds like.’ ‘Okay, then what do you think is the lub and what do you think is the sshh? Or do you agree that it sounds like lp dp, lp dp, lp dp?’ ‘Yeah, yeah.’ ‘Okay what do you think is the lur, up, the dd and the pp.’ This type of cardiophonetics led my colleagues and me to agree on what we heard. We could then go on from there.” (1, p 28)*

In time, the researchers on the team developed explicit criteria for classification for each of the manifestations of rheumatic fever. Feinstein then classified patients into subgroups, based on various combinations of symptoms, signs, and test results. He found that overlapping circles were a convenient way of illustrating these subgroups. “I used a circle to represent patients who all had a single common property (such as arthritis) and another, overlapping circle to represent patients with another property (such as carditis). The overlap of the circle would denote patients with both properties; the non-overlapping sectors would denote patients who had one property or the other but not both (17).”

When a prognosis was obtained for each of these classificatory groups, it was clear that there was a spectrum of the disease. Antibiotics were found to be effective in preventing recurrence of rheumatic fever in children with abnormal heart sounds but children with the first attack of rheumatic fever who did not have abnormal heart sounds were not at increased risk (18). These were important findings. Prolonged bed-rest was prescribed for any child with rheumatic fever, seriously disrupting their lives. Feinstein celebrated his victory over the “cardiopathic doctors.” “Quit keeping them in bed, quit keeping them from athletics, quit keeping them from having children!” As a result of this research, he claims, Irvington House was closed. “They couldn’t keep the beds full!”

In the process of conducting this study, Feinstein realized that there was a fundamental problem in clinical research. The study, a trial, was funded to test effectiveness of antibiotic prophylaxis. Feinstein’s clinical research addressed practical clinical problems but was regarded as intellectually inferior. Whereas the statisticians on the team categorized data according to demographic variables, they rejected clinical data as unreliable and only considered these data when Feinstein devised ways of making them reliable. But he also realized that the familiar demographic variables were mutually exclusive whereas clinical variables were overlapping. Then Feinstein, the math-

ematician, saw the solution. “I did not have to remove the overlap; I could preserve and classify it. Boolean algebra and Venn diagrams were a perfect intellectual mechanism for classifying overlap; they were an ideal way to distinguish multiple properties that could be present or absent, alone or in combination.” (17)

From 1964 onwards, Feinstein was publishing articles on the scientific methods to be used in conducting research specific to clinical care (19–22). Clinicians, Feinstein argued, understand the heterogeneity of clinical practice. It was this heterogeneity that should be accurately observed, classified, and used to determine prognosis and treatment. Clinicians think in terms of overlapping categories and in terms of a systematic taxonomic classification of disease; his 1967 book describing this approach was called *Clinical Judgment* (17). He described the book as a labor of love, providing a way for clinicians to analyze their own practice. This was the real goldmine. The benefits to clinical practice were clear: there would there be research directly relevant to clinicians’ concerns and, in the process, they would gain an additional basic science specific to clinical care (23), additional to the medicine of the laboratory.

By now located at Yale University, Feinstein had defined his life’s work. It was not a minor undertaking. He was passionately opposed to the idea that clinician-researchers would borrow research methods from other disciplines. “Clinicians should make use of all the effective, consultative help they can get, but should not abandon fundamental challenges that require direct clinical solutions from wise intellects.” (24)

He saw the benefits of the randomized controlled trial but he did not define himself as an epidemiologist; since he had entered epidemiology by the “clinical backdoor,” he described what he was doing as “clinical epidemiology.” (25–27)

Feinstein set out a challenging program but, as he himself recognized, his initiative was overtaken by developments at McMaster University. With characteristic vigor he opposed what he saw as their preoccupation with the randomized controlled trial, which, he argued, answered regulatory rather than clinical questions. Although he “dearly loved the gang at McMaster,” he felt that the fascination with trials had displaced the program he outlined in *Clinical Judgment*:

*“Clinical Judgment is dead. This generation has never heard of it. Everything that I recommended in Clinical Judgment has been utterly ignored in most of the clinical epidemiology today. What I talked about in that book was a need for clinicians to develop a scientific taxonomy for what they do, and that taxonomy has been utterly ignored during the infatuation with mathematical models, which is why the randomised trial is so powerful because if you don’t want to think the randomised trial is a perfect way to avoid thinking. I am not attacking randomised trials, mind you, they have made some wonderful contributions and I am all for them, but it is just absolute folly to think that you are going to answer the questions in clinical practice with randomised trials.”*

Despite these views, he had a close relationship with academics at the Department of Clinical Epidemiology and Biostatistics at McMaster University and spent 2 yr there, urging them on to greater scientific rigor.

## DAVID SACKETT AND THE DEPARTMENT OF CLINICAL EPIDEMIOLOGY AND BIOSTATISTICS

It is with the founding of the new medical school at McMaster University that clinical epidemiology became a separate medical discipline and it is here that EBM emerged.



When the new medical school was established in the 1970s, there was concern about the rising cost of health care and, in the next 20 yr, this grew into a sense of crisis especially in the United States (28). There was evidence of regional variations in practice that cast doubt on clinical decision making (29). Medical students joined into the student revolt by questioning the medical curriculum, and began to consider careers outside the traditional academic pathways. Feinstein foresaw that the effectiveness of clinical care was going to be evaluated and he wanted clinicians to do this work. Cochrane saw the randomized controlled trial as well suited for the task of administering a health system. McMaster University combined the two approaches.

In North America there was a tension between clinical care and public health, sometimes so intense as to be described as a schism (30). Although public health addressed issues in the population at large, clinicians saw their own role differently. David Sackett, who was appointed as the first chair of the new department, had the experience of working in a “terrible outfit,” the Heart Disease Control Program, when he was drafted into the US Public Health Service during the Cuban missile crisis in 1962. He had to be trained in epidemiology and biostatistics in order to conduct surveys of disease outbreaks and found the work soul-destroying. Then, in 1963, he read Feinstein’s paper *Boolean Algebra and Clinical Taxonomy* (31) and was converted to try to work at the interface between clinical medicine and epidemiology and biostatistics.

In 1967 Sackett was at the State University of New York, Buffalo, establishing himself in the Department of Medicine, when he was invited to come for an interview to McMaster University. He was asked what sort of Department of Social, Community, and Preventive Medicine he thought they should have, and he proposed instead that they should have a department that would do research but serve as a resource for people doing research of all kinds in the medical school and to induct family physicians into critical clinical reasoning about measurement issues and prediction. He was appointed to the new Department of Clinical Epidemiology and Biostatistics.

In the present time, what Sackett proposed may not seem very revolutionary but, at the time, these ideas encountered stiff opposition. Biomedical colleagues thought that what the new department proposed was “not really science”; they saw science as firmly located in the laboratory. What the department needed was somebody to persuasively sell their message. David Sackett filled the role to perfection.

The first people whom Sackett appointed to the department were two statisticians. They joined this risky new venture, persuaded by Sackett. Repeatedly in interview the early recruits to the department recount how they were converted and joined the new Department because of Sackett’s vision. Repeatedly these early recruits talk about meeting a charismatic man who was proposing a challenging new program. Here is the account of Mike Gent, statistician and later second chair of the department: “The single thing that moved me here was Sackett. I couldn’t believe Sackett! He actually interviewed me, lying on one elbow on the floor. He had outrageous ideas, half of which would never work, but if only 10% worked it would be fantastic. All the concepts about clinical epidemiology were there including getting together a group that was really going to shape the thinking of medical colleagues.” (1, p 58)

The material generated is now familiar to us under the term “clinical epidemiology.” They promoted their approach in journals, in textbooks and in a seemingly endless series of international presentations. They persuaded the Rockefeller Foundation to fund the International Clinical Epidemiology Network (INCLEN) to train international

fellows in the new approach. Their approach is set out in the textbook that they published (32) and later updated (33). The books give a common sense approach to the scientific principles underlying diagnosis and management in clinical care. They taught clinicians to be critical in their decision making, for example, factoring into diagnosis the effects of the sensitivity and specificity of a diagnostic test and the prevalence of disease in the community. The methods they described could be used to conduct critical appraisal of the medical literature, and this evidence could then be applied to their own clinical practices. What they proposed was a scientific approach to replace clinical intuition promulgated by clinical authorities:

*“Our underlying assumption, once again, is that medicine is rational and so are you. That is, your clinical acts of diagnosis and management reflect your assessment of the evidence that this or that diagnostic test is valid and will do more good than harm. If this view of clinical practice is correct, then you should constantly be seeking evidence, not just conclusions or, worse still, authoritarian opinions. Just as your ability to achieve accurate diagnosis and efficacious therapy determines your clinical effectiveness today, it is your skills in self-assessment and in tracking down and assessing biomedical knowledge (most of which resides in the journals) that will more and more determine your clinical effectiveness tomorrow.” (32, p 246)*

Sackett gives a humorous summary of why they succeeded. “A group of us came here in the late sixties, rebels with a cause. We set this thing up. We said, ‘We know a lot of stuff about medical education (we think it’s crap) and we ain’t going to do any of that.’ We had an idea about how it might work. We got it all done” (1, p 57). But he also points out that clinical epidemiology provided a scientific discipline for general internal medicine, that it was a source of interesting new research and, finally, that it allowed Departments of Medicine “to justify themselves to the public, to their universities and to funding agencies as doing things with direct payoff to patients.”

## THE EMERGENCE OF EVIDENCE-BASED MEDICINE

It was in this department that the idea of EBM arose. In common with Cochrane and Feinstein, there was distrust of traditional clinical authority and the search for a more scientific and systematic approach to clinical decision making. From the Cochrane agenda came the emphasis on the randomized controlled trial and its capacity to demonstrate what works. From the Feinstein agenda came the focus not on the health service or public health epidemiology but on the decision making of clinicians, studied by clinicians.

The randomized controlled trial gave a solid foundation for the new discipline. To Feinstein it was an unfortunate choice because it was an epidemiological tool and delivered an outcome based on a population average. In the process the heterogeneity of patient care was obliterated. This problem was to dog the new discipline; clinicians found it difficult to decide how the results of a trial were to be applied to one particular patient. The *N* of one trial was a response to this problem (34). But the randomized controlled trial design had other advantages. It was difficult to establish the scientific credibility of the new initiative and only in a new medical school would the substantial challenge to traditional medicine even be possible. The trial used an experimental design, allied to the experimental approach of the dominant paradigm of laboratory medicine. It provided a common sense basis for the educational efforts of the department, here described by Gordon Guyatt:

*“What we talk about is applying certain rules and concepts of science to clinical experience and systematizing it. ‘How do you know that treatment x works?’ ‘Well I gave it out and the person did well.’ OK. And then you say, ‘But to what extent can you be confident?’ You find out very quickly that you can’t be confident at all. And then you say, ‘OK, well how can I be more systematic in my accumulation of clinical information to strengthen my inference?’ And if you push it, you end up with a double blind randomized trial as a systematic way of accumulating clinical experience. The problem isn’t clinical experience, the problem is that we were so unsystematic, intuitive and with no notion of scientific principles in our accumulation of clinical experience. And now is clinical experience worthless? No, but with the appropriate level of skepticism and knowing how things go wrong.” (1, p 88).*

In 1990, Guyatt was Director of the Internal Medicine Residency program. He saw their approach as a “new brand of medicine,” “scientific medicine,” an approach so important that it could be seen as a paradigm shift in clinical thinking:

*“What were the assumptions of the old paradigm? First, that clinical experience was a valid way of obtaining knowledge about prognosis, the value of diagnostic tests and therapy. Second, that one could work out the appropriate way of treating people just on the basis of physiology and physiological principles. If you knew the physiology and you knew how the drug affected the physiology, you could predict its clinical effects. The third assumption is the high value on authority, and the fourth is that good medical training and commonsense allows you to be appropriately critical about the medical literature. Those are the four assumptions of the old paradigm.*

*The assumptions within the new paradigm are different in all four. The new paradigm suggests that clinical experience has severe limitations as a guide to understanding the properties of diagnostic tests, whether treatment works, or prognosis. Second, medical training and commonsense are very inadequate guides to deciding whether something is scientifically valid. One needs rules of evidence that are, essentially, clinical epidemiology. Third, reasoning on the basis of physiology often proves misleading without empirical testing and, fourth, following from all this, a much lower value in authority and, in fact, a sort of iconoclasm.*

*At the point where you say I’m going to be tremendously rigorous and systematic in my accumulation of clinical evidence, you’re into the new paradigm and you’re into doing science.” (1, pp 88–89)*

Guyatt was criticized when he called the new approach “scientific medicine.” He then called it “evidence-based medicine,” evidence being, after all, what they had doing been emphasizing in their approach all along. “Evidence” is what clinical epidemiology produced, and EBM is the practical application of clinical epidemiology to patient care. Guyatt first used the term in 1990 in an information document for residents. In 1991, he defined it as “the application of scientific method in determining the optimal management of the individual patient (35).”

In the 20 yr after the department was established, the number of published randomized controlled trials rapidly increased. Brian Haynes, also in the department, was alert to the problem that this burgeoning literature was posing a substantial challenge to clinicians in terms of keeping up to date with the latest developments in a field. He initiated the *American College of Physicians (ACP) Journal Club*. This publication gave

clinicians access to the abstracts of selected studies from medical journals, articles that were relevant to internal medicine and that met explicit criteria for validity. A team of researchers worked to extract the articles and a clinical commentator placed the article in the context of other relevant work. Clinicians could breathe a sigh of relief, he believed, especially when this resource and a growing number of others, were produced in readily accessible electronic format.

In the 1970s, Archie Cochrane had called for every medical specialty to collect, and prepare critical summaries of all trials relevant to their field of practice. A parallel initiative in which this was also being done was the Cochrane Collaboration.

## THE COCHRANE COLLABORATION

Central to the activities of the Cochrane Collaboration was the work of another North American, Tom Chalmers who had developed meta-analysis as a way of statistically combining the results of multiple different trials of the same intervention. Many published trials were too small to show a statistically significant result. Combining these trials, argued Chalmers, was better than trying to conduct a bigger trial. If meta-analyses were done as soon as trials were completed, the cumulative effect could be assessed so that there was no delay in implementing the evidence (36). A famous example shows that intravenous streptokinase as thrombolytic therapy for acute myocardial infarction could have been demonstrated to be effective in 1973, before a single trial demonstrated this effect and long before clinical opinion changed (37).

The work done by Tom Chalmers provided one of the methodological skills needed to fulfill Archie Cochrane's plea that each clinical specialty should keep an up-to-date summary of work in their field. Iain Chalmers was an obstetrician who had encountered the problem of bias in his own practice, and his research. Three carefully designed consecutive studies had failed to find any effect but he was not sure that he had managed to exclude bias and this bothered him (38–40). Then he read Archie Cochrane's book, met him, and committed himself to the Cochrane agenda in the field of obstetrics.

Iain Chalmers was persuaded that randomized controlled trials would have an important role in changing practice but the cumulative effect would be even more powerful. "Once you start to get trials which show, for example, that 50 yr of radical mastectomies have not been justified, then you can start to see what a powerful weapon such evidence is for those who wish to challenge authority" (1, p 161). From 1978, a team comprising Chalmers, Murray Enkin (an obstetrician from Hamilton and McMaster University), and Eleanor Enkin (a librarian) collected and classified over 3000 reports of trials from 250 journals. They surveyed 42,000 obstetricians and pediatricians in 18 countries, obtaining data on 395 unpublished trials. To deal with the problem of publication bias they set up registers for published, unpublished trials and planned trials. They collected overviews or meta-analyses, conducted according to explicit procedures and regularly updated.

They published their work in an edited collection, *Effective Care in Pregnancy and Childbirth* (41) with the database itself published as the *Oxford Database of Perinatal Trials* (42). Contributors to the book had access to the Database, which was expanded to include any further trials that authors wanted to use. The emphasis was on combining the results of trials, where possible. A standard format for displaying results included the graph that represents point estimates and confidence intervals for each of the trials of an intervention; it became the logo for the Cochrane Collaboration. The

book includes a telling chapter by Peter Goldstein, Henry Sacks and Thomas Chalmers that demonstrates that the prescription of diethylstilbestrol for the maintenance of pregnancy would have been stopped by 1955 by a large well-designed randomized controlled trial or by a systematic review of properly controlled trials.

In 1992, the National Health Service Research and Development Programme decided to support this effort by funding the Cochrane Centre, a small group based in Oxford, independent of the university and part of the National Health Service, to conduct similar work in other areas of clinical care. Chalmers knew that the task could not be done by one center. It needed an international collaboration of researchers and reviewers to voluntarily commit their time to generating reviews according to specific criteria (43), regularly updated. There are now about 50 international review groups, each with a coordinating editor supported by an editorial team, focusing their research on an issue of interest to the group. There are 14 Cochrane Centers with national or regional responsibilities for supporting and coordinating Cochrane initiatives. Brian Haynes established the Canadian Cochrane Centre at McMaster University.

### WHERE TO FROM HERE?

EBM is iconoclastic. In both the North American and British contexts it set out to generate an alternative to an unthinking acceptance of traditional clinical authority. Clinicians should assess traditional clinical claims critically, using an additional science, additional to biomedicine, a science that addresses the application of biomedical knowledge to the care of live patients. Over decades a powerful new approach was developed and justified.

The question now is what the status is of EBM as a science of clinical care. Especially at McMaster University, it is argued to represent a new paradigm. This claim is not controversial if by “new paradigm” we mean a new way of doing things, additional to the old, requiring some fine new skills with new benefits to reap from improved patient care. But a “new paradigm” can also mean that there has been a fundamental shift in the way in which we understand clinical decision making so that the old way of doing things is no longer acceptable. It may even mean that the way in which we speak about clinical care has changed so that the things that were said in the past are no longer intelligible to those practicing in the new paradigm. It is the latter meaning that raises concern.

If there has been a shift to a fundamentally new understanding of clinical care, then there are serious disadvantages for clinicians practicing in those areas of clinical care where the evidence from randomized controlled trial and systematic reviews is thin on the ground. Clearly there should be a concerted attempt to generate the evidence, but this takes time. Some areas of clinical care are beset with complexity that does not readily yield a single issue for testing by randomized controlled trial and here EBM may be particularly difficult to practice. One of the problems encountered in clinical care is the need to take account of the social contexts of patients. In a comprehensive textbook from the Evidence-based Medicine Working Group (44), these additional issues are captured under a description of the way in which clinicians and patients negotiate about patient values and preferences. Clearly evidence about the ways in which knowledge of social context enters into clinical decision making is difficult to address in a randomized controlled trial. The risk is that such knowledge will be seen as dispensable to the research agenda.



In contrast, if we mean that EBM represents a new, additional way of proceeding, one that allows for other evidences additional to the evidence produced by randomized controlled trial, then a more complex resolution is possible.

David Armstrong (45) presents a sociological analysis of the way in which general practitioners incorporate new drugs into clinical practice. He shows that it is a gradual process over time, not one that is set in place by a single decision based on new evidence of the effectiveness of a drug. Clinicians took account of their own small personal experiments with the drug to see on which patients it seemed to have the best effect, adjusting their prescribing to take account of what they knew about the psychosocial needs of specific patients.

Armstrong's conclusion is that this way of gradually testing and incorporating a new treatment is complex and changeable and "seems inimical to the logic of evidence-based medicine." (45) In other words, clinicians take account of other evidences than the evidence of effectiveness. This raises the question of the scientific status of these other evidences and also raises the issue that we may need a broader repertoire of methods if we are to judge these other evidences generated by methods other than the randomized controlled trial. We might even revisit the Feinstein project of basing analysis on the carefully defined spectrum of disease instead of a population average. We might return to Archie Cochrane's aim of diverting funds from those interventions that do not work to those geographic areas that are underserved.

If Feinstein was right and clinical practice is a goldmine for researchers, much ore has now been mined. But we can take heart, there is still a rich vein or two left to mine.

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