Morgagni Lecture: light and shade of Evidence Based Medicine (EBM)

The demand for public health and healthcare practice and policy to be based on scientific evidence continues to grow, affecting programs, services, research and teaching.

Evidence-based medicine (EBM) has been championed as a 'new paradigm' for medical education and practice (The Evidence-Based Medicine Working Group 1992).

However, there is now an increasing recognition of limits inherent to the empirical evidence upon which EBM is founded.

Although the bulk of the literature of EBM focuses on the practical issues related to the development, acquisition, interpretation and incorporation of the results of clinical research into clinical practice, EBM rests on certain philosophical assumptions and arguments about the nature of medical knowledge that have not been as fully elucidated (Miles *et al*. 2004) from an epistemological point of view. As a matter of fact medical epistemology raised concerns about unresolved and fundamental questions on the nature of medical knowledge and in particular on the capacity of EBM to support knowledge-based clinical decision making.

One of EBM central goals is the development of explicit, universal rules for reading journal articles, evaluating research results, and applying these results to medical practice. These rules are meant to foster systematic, bias-free medical practice, but criticism of every proposed set of rules has shown them to be insufficient as reliable guides to medical practice.

Medical knowledge, indeed, is heterogeneous according to the complexity of genome functioning in single individuals and its interactions with environment.

Such a statement has gathered a further strength over the last 25 years in which biomedical research has witnessed a scientific revolution based on the application of molecular biology to mammalians, in particular to human beings.

The expanding awareness that patients' diseases relay on interaction among genome variability, environmental noxae, socio-economic and cultural factors paves the way for personalized therapy and has opened a debate among medical epistemologists on how to integrate such a new evidence into clinical practice.

This debate can't really leave aside the contribution and the cultural experience of the successors and heirs of G. B. Morgagni's labours and method.

G. B. Morgagni was the first one who directed autopsy toward the study of the correlation between organ lesions and disease symptoms in order to understand the origin of diseases.

From Morgagni to Virchow, until our biotechnology age, the anatomical pathologist plays a key role in applying basic research methodologies to clinical practice, in order to define diagnosis, predict the clinical behaviour of diseases and contribute to discover their causes.

The contribution of pathophysiology in building up the medical knowledge and its value as potential warrant for medical decision making into clinical practice is a matter of debate among medical epistemologists. The notion of a general priority of empirical evidence is increasingly challenged by clinicians many of whom pointed out the inherent limitations of attempting to apply knowledge gained from population studies to treat individual patients.

From the two traditions concerning the ultimate source of our knowledge, empiricism and rationalism, arise the two divergent theories of the medical epistemology, EBM and pathophysiological modeling respectively.

Considering the value of other kinds of medical knowledge, such as those derived from clinical experience or based on pathophysiological rationale, a core topic of the Morgagni Lecture will be how to integrate them into EBM and how to overcome limits of EBM principles, particularly when uncritically applied to clinical trials in developing new drugs.

The Morgagni lecture will be opened by a lecture given by Nobel Prize J. Robin Warren. This lecture is supposed to rise a debate on the consideration that Warren (together with his colleague Barry J.Marshall), "against prevailing dogmas, discovered that one of the most common and important diseases of mankind, peptic ulcer disease, is caused by a bacterial infection of the stomach. (..) Their discovery has meant that this frequently chronic and disabling condition can now be permanently cured by antibiotics to the benefit of millions of patients. (...Their...) pioneering work has also stimulated research all around the world to better understand the link between chronic infections and diseases such as cancer" (from the Presentation Speech by Professor Staffan Normark, Member of the Nobel Assembly at Karolinska Institutet, December 10, 2005).

Warren's discovery was not achieved applying the EBM method based on randomized clinical trials, meta-analysis, revision of scientific literature.

As a matter of fact Warren's research work was more physiopathology-based than statistics- epidemiology based.

This consideration will represent an occasion for a discussion on value and limits of EBM and its implications in medical education and training as well as in public health and on the role of knowledge deriving from pathophysiology in medical discoveries and their application to patients' care (translational research).

Finally, The Morgagni lecture represents an occasion for the scientific community and relevant society's stakeholders to focus both on the epistemological issues related to the nature of medical knowledge and on the practical issues related to the development, acquisition, interpretation and incorporation of the results of clinical research into clinical practice.

In this context the role of EBM in medical knowledge will be discussed especially with regard to a prospective personalized therapy.

The very first Morgagni lecture, which is supposed to pave the way for other regularly (annual) scheduled similar events, will take place in Rome, on October 20, 2008, under the auspices of Istituto Superiore di Sanità, Alleanza Contro il Cancro, Sigma Foundation.

Alleanza contro il cancro

MORGAGNI LECTURE
Light and Shade of Evidence Based Medicine

October, 20, 2008

Aula Pocchiari
Istituto Superiore di Sanità
Viale Regina Elena 299
Rome, Italy

SCIENTIFIC PROGRAM

8.30 Registration

9.00 Opening ceremony
Welcome by the authorities
E. Garaci, President, Istituto Superiore di Sanità

Chairpersons: Luigi Giusto Spagnoli, Andrew Miles

9.30 Opening Lecture
"*Helicobacter* - the ease and difficulty of a new discovery"
J. Robin Warren, Nobel Laureate (Australia)

9.55 "Science: a limited source of knowledge and authority for the care of patients"
Andrew Miles (UK)

10.15 "The basis of medical knowledge: judgement, objectivity and the history of ideas"
Michael Loughlin (UK)

10.35 "Resisting the Violence of Stratification:
Capture, War Machines and the Evidence-Based Movement"
Dave Holmes (Canada)

10.55 "Potential and limitation of EBM: what kind of research do we need to produce relevant information?"
Alessandro Liberati (Italia)

11.15 Coffee break

Chairpersons: Gaetano Thiene, Filippo Belardelli

11.40 "EBM and translational research"
Dhavendra Kumar (UK)

12.00 "EBM and education"
Gian Franco Gensini (Italia)

12.20 "The Ramifications of EBM for Health Policy and Politics"
Sandra Tanenbaum (USA)

12.40 "The Hierarchy of Evidence - Fact or Fallacy?"
Joaquim Sá Couto (Portugal)

13.00 “Beyond evidence: other relevant topics for clinical decision making”
Mark Tonelli (USA)

13.20 “The sources of knowledge inspiring current medical practice in oncology: results of a survey in Italian Comprehensive Cancer Centres”
Silverio Tomao (Italia)

13.30 “The Morgagni clinico-pathologic method in the era of clinical imaging and molecular medicine”
Gaetano Thiene (Italia)

13.40 “Lunch”

14.40 “Round table”
Chairperson: Adriana Bazzi
Sottosegretario/Direttore Generale, Ministero del Lavoro, Salute e Welfare
Claudio Cavazza
Enrico Garaci
Gian Franco Gensini
Renato Lauro
Andrew Miles
Guido Rasi
Presidente Conferenza Stato-Regioni
Presidente Federazione Nazionale Ordini Medici Chirurghi e Odontoiatri

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Prof. J. Robin Warren, Nobel Laureate in Physiology or Medicine 2005, Emeritus Professor, University of Western Australia, Emeritus Consultant Pathologist, Royal Perth Hospital

Fondazione sigma tau

Helicobacter
The ease and difficulty of a new discovery

J. Robin Warren

Before the 1970's, well fixed specimens of gastric mucosa were rare. Then the flexible endoscope was introduced. This enabled gastroenterologists to take numerous well-fixed small biopsies from the stomach. Gastric histology and pathology were clearly demonstrated. Whitehead accurately described it in 1972, including a feature he termed 'active' gastritis. This involved only the superficial gastric epithelium, with polymorph infiltration and epithelial cell distortion.

In June 1979 I was examining a gastric biopsy showing chronic inflammation and the active change. A thin blue line on the surface showed numerous small curved bacilli. These were clearly visible with a Warthin Starry silver stain. They appeared to grow on the surface of the foveolar epithelial cells.

Over the next two years I collected numerous similar cases. The changes were often much milder or more focal than the original biopsy, but the main features were usually similar, with chronic gastritis and usually some of the active change. These features could show considerable variation, from near normal to severe.

In 1981 I met Barry Marshal and we completed a clinico-pathological study of 100 outpatients referred for gastroscopy. There was little relation between the infection and the patients' symptoms. Peptic ulcers, particularly duodenal ulcers, were very closely related to the infection. We cultured *Helicobacter pylori*.

In 1986, with Marshall et al, I studied the effect of eradication of *H pylori* on the recurrence of duodenal ulcer. I graded the gastritis (0 - 36) using the features seen with active gastritis. The range was 15 - 35 before treatment. After eradication of *H pylori*, this changed to 5 - 20 within 2 weeks. This provides powerful evidence that *H pylori* causes the active change.

Duodenal ulcer usually occurs in the duodenal cap. Gastric mucosa normally extends through the pylorus. In this study, the proximal border of all ulcers was either definite gastric mucosa, or scarred and consistent with a gastric origin. This suggests duodenal ulcer is either actually a distal pyloric ulcer or gastro-duodenal. It may well arise in the damaged, inflamed and infected mucosa in the position of maximum stress - the lip of the pyloric sphincter.

Lecture notes

This is the story of my discovery of *Helicobacter*. I have been asked if I stole my discovery, found it by accident, did brilliant research or was it serendipity. I think it was serendipity. I was in the right place at the right time and I had the right interests to do more than just pass it by.

Most previous reports of gastric bacteria involved veterinary biopsies or research animals. The bacteria were thought to be spirochaetes. Some reports on human tissue do exist. They were largely ignored and not considered to be of any importance.

Standard medical teaching for a century was that the stomach was sterile. Bacteria rarely grow there. This was a generally known "fact" rather than actively taught. "Everyone knows the earth is flat". It is hard to change such a paradigm. The medical establishment is conservative and does not like sudden change.

Well fixed biopsies had to be taken with a rigid gastroscope or by the suction method and were rarely seen. Gastrectomy specimens are clamped at each end, with the contents inside. They fix slowly from the outside. Meanwhile the mucosa autolyzes and any organisms disappear.

Chronic gastritis was described as 'superficial' or 'atrophic' and showed no real relationship to anything. Specific types, which are easily recognisable, such as acute gastritis or gastric aplasia are rare.

The flexible endoscope enabled gastroenterologists to biopsy many of their patients. Small biopsies, placed immediately into formalin, fixed well. These became some of our most frequent biopsies. Whitehead accurately described them in 1972.

He described 'active' changes. These changes were common and they provided a specific feature to diagnose. His pictures show polymorph infiltration in the necks of the glands and gross distortion of the foveolar epithelium, with marked cell irregularity.

Whitehead's classification was based on the features actually seen. Most of these features are mentioned in the diagnosis. This allows any associations between histology and other features to be noted. After reading his descriptions, I found reporting of gastric biopsies much more interesting and satisfying and I developed a particular interest in them.

I used the classification as in the top line, the heading, saying where the biopsy is from, what changes are present and any other features.

I simplified Whitehead's classification so that the main features could be placed in one short line to diagnose each biopsy.

At this time I was experimenting with alternative stains for bacteria in tissue sections. Microbiological stains are excellent for staining bacteria in smears, especially from a clean culture. However, histology shows a complex mass of tissue structures, cells and organelles that also stain. It is necessary to contrast the bacteria with the tissue. Gram positive organisms and, with care, acid fast organisms can be seen in tissue sections. Silver stain (Warthin-Starry) shows spirochaetes in chancres and bipolar Donovan bodies, the Gram negative bacilli in granuloma inguinale. I was experimenting with this stain on other Gram negative organisms in 1979.

I was a young consultant pathologist when the fibre-optic gastroscope became widely used. Well-fixed gastric biopsies became some of our commonest specimens. Whitehead's description, particularly active gastritis, caught my interest. I was experimenting with special stains for bacteria. In addition, I was also interested in electron microscopy, which was starting in our department. A lifelong interest in drawing and photography helped me to see detail.

My adventure with *Helicobacter* began in June 1979. A routine biopsy showed severe active chronic gastritis. I saw a blue line on the surface, which, with high power, appeared to be a mass of bacteria.

This is my first case, photographed in June 1979. It shows quite severe active gastritis, as described by Whitehead. The epithelium shows gross cobblestone change. Nuclei are out of alignment. Mucus secretion shows a marked patchy reduction. There are numerous lymphocytes and plasma cells in the stroma. A thin blue line of bacteria is visible on the surface.

With the Warthin-Starry silver stain, numerous bacteria are visible at low power, for all to see. This was my first case, photographed 25 years ago.

At high magnification the Warthin Starry silver stain shows the bacteria well. The bacteria stain black, against brown tissue structures and between the bulging distorted epithelial cells.

This diagram of the stomach puts the size and position of an endoscopic biopsy (bottom) in perspective.

This high power diagram continues on from the previous one. It shows a high power view of the antral epithelium. Normal at the top compares with infected epithelium below, with bacteria on the surface, cobblestone change, polymorph infiltration and a microcrypt.

I took tissue from the wax block used for standard histology and obtained the electron microscopy. The images were of good quality and showed the bacteria well.

Electron microscopy of normal foveolar epithelium shows numerous small microvilli on the surface. These contain filaments that attach to the top of the villus and extend to the base of the cell, giving it a rigid structure. Note the flat surface, plentiful mucus and basal nuclei. This is actually a case recently treated for *H pylori* infection. The specific changes have rapidly returned almost to normal.

My first case shows numerous small curved bacilli closely applied to the surface. Some are attached to microvilli. The cells bulge out. Mucus secretion is reduced. Bacteria are between the bulging tops of the cells, in the centre of the picture.

Helicobacter pylori attaches to epithelial microvilli with a junction that shows some features resembling a cell junction. When this happens, the filaments attached to the top of the microvillus become detached. They are still visible here. When the fibrils detach, the cell becomes amoeboid, giving the cobblestone appearance seen with 'active' change.

Those who want to know what I thought at the time may examine the conclusion to my original report on these bacteria.

My colleagues still did not think the bacteria were of any significance and they challenged me to find any more. I tried and, to my surprise, I found them in quite a significant number of biopsies. The number increased with experience. Many cases showed only mild pathology, but they were otherwise similar.

I was unable to convince the clinicians of the importance of the organisms. Generally, they did not believe they were there at all. Gastritis was not considered to be of much significance. Most thought that if the bacteria were there, they were just secondary to the gastritis. While the histology suggested the opposite, it was hard to prove. I worked in a laboratory, without patient contact. I could not obtain the biopsies I wanted. The idea of taking gastric biopsies for culture was not considered in the patients' interest.

Barry came into my office and asked to see my work. He was the first person to show any real interest, so I it showed him.

He did not seem impressed at first, but he agreed to send me a series of biopsies from apparently normal gastric antral mucosa, to see if the same findings were present. The changes were there and were more obvious. Barry soon became enthusiastic, and I finally had a clinical collaborator.

We obtained biopsies for culture and histology from 100 consecutive outpatients sent for gastroscopy. Most complained of peptic symptoms or pain. They all completed a detailed clinical protocol.

The results were totally unexpected. First, the histology was not related to any significant symptoms. When the gastroscopy reports were examined it became apparent that all duodenal ulcer patients, as well as most gastric ulcer patients, had the infection.

At first, no bacteria were cultured. Finally, plates incubated over the Easter holiday showed a culture of a new type of bacteria, not described previously.

I sent a letter to the Lancet in 1983, a summary of the paper I was preparing when I first met Barry. Barry sent an accompanying letter describing our joint work. He also presented our findings at the Brussels Campylobacter conference. Martin Skirrow, who chaired the conference, was very impressed with our work. This became very advantageous to us when we attempted to publish our definitive paper.

We sent our definitive paper to the Lancet in 1984. Although the editors wanted to publish, they were unable to find any reviewers who believed our findings. Our contact with Skirrow became crucial here. We told him of our trouble, and he had our work repeated in his laboratory, with the same results. When he informed the Lancet, they published our paper immediately, unaltered.

I continued doing pathology, with an interest in *Helicobacter*. The subject rapidly expanded throughout medicine over the next decade. Original methods for diagnosis and treatment were all suggested by Barry. I was involved with the pathology from two attempts to fulfil Koch's postulates, as well as studies of the culture of *Helicobacter pylori*, the diagnosis of the infection and the treatment of duodenal ulcer.

Helicobacter patients show considerable variation. I was involved with these early examples.

- Barry gave himself acute gastritis, to the disgust of his wife, in an attempt to fulfil Koch's postulates.
- Morris, in New Zealand, gave himself chronic gastritis and took years to cure it.
- My wife developed arthritis and as soon as she took NSAIDs she developed severe epigastric pain. Stopping the NSAIDs reversed this. And again. I sent her to Barry, who found *Helicobacter*, treated it and she was able to take the NAISD. Don't take it for granted that NSAIDs are the only guilty party.
- Most patients are symptomless. I was an example of this. After she was treated, my wife complained I had bad breath. I was positive for *H pylori* and after treatment marital bliss returned.

In 1986, we undertook a double blind trial to find the effect of treatment of *Helicobacter pylori* infection on ulcer relapse. All patients received treatment for their ulcers. They received antibacterial therapy or placebo for *Helicobacter* infection. All were examined by multiple gastroscopies and biopsies for 12 months and again after 7 years.

This provided me with excellent material for the study of the pathology related to *Helicobacter* and, also, the pathology of duodenal ulcers. I quantified the level of gastritis on a 0 - 36 scale by giving a value 0 - 9 for each of the main four features.

From this I made a histogram to show the levels of inflammation before and after eradication of *H pylori*.

The grade of gastritis when *Helicobacter pylori* was present was high, above 15. This includes all patients in the study, including pre-treatment biopsies of those in whom the bacteria were later eradicated.

After successful treatment, the gastritis grade without *Helicobacter* is much lower. A true normal extends to about 14. These are the successfully treated cases of active chronic gastritis, some biopsies taken only two weeks after treatment, with gastritis grade up to 20.

Finally, we see the absolute difference between the two groups. There is some overlap, but the difference in the gastric pathology with and without *Helicobacter pylori* is incontrovertible. One interesting feature was the consistency of the results over time. The histology patterns in each patient remained constant throughout the study, for 7 years or more, as long as the bacteria remained. The active changes vanished as soon as the bacteria were eradicated, within weeks. This strongly suggests the bacteria caused these changes. Other changes remained longer, particularly structural damage such as scarring, and epithelial changes like atrophy, metaplasia and dysplasia.

We were surprised to find duodenal ulcer so closely related to *Helicobacter*. However, further investigation shows that most duodenal ulcers can be viewed as distal pyloric ulcers. They are in the duodenal cap and the pyloric mucosa normally extends there, forming the proximal border of duodenal ulcers,

as shown here.

Pyloric mucosa normally extends through the pylorus.

The pyloric mucosa extends to the proximal border of a duodenal ulcer. This mucosa is very mobile and easily moves some distance through the pylorus. When the stomach contracts, a mixture of food fragments and corrosive gastric juice squirts through the pylorus. Perhaps it is not surprising that ulcers are so common here, especially when the epithelium is damaged by infection and active inflammation.

Now, the importance of *Helicobacter* is generally recognised, particularly with regard to duodenal ulcer. As a pathologist, I am disappointed that active gastritis is not considered worthy of treatment. I see it in all infected stomachs, although often mild. Unfortunately, it does not cause many symptoms and nobody is interested.

In conclusion, we now know that *Helicobacter* had been seen and largely ignored for over 100 years. I saw them 25 years ago and linked them with active gastritis. Barry Marshall and I cultured the bacteria and linked them to duodenal ulcer. In various different ways over the next few years we proved these relationships.

Science: a limited source of knowledge and authority in the care of patiens

Andrew Miles

Not all questions are scientific in their nature. The first chord of Wagner's *Tristan* resolves onto the dominant seventh of A Minor and why this should be is, to Wagnerians and musicologists alike, an extremely important question. But it is not a scientific question and cannot therefore be answered by science. Likewise, not all questions of relevance to clinical decision making and the care of individual patients are scientific in their nature and, similarly, cannot be answered by science. Therefore, science can never provide the basis for good clinical medicine in any fundamental sense. Medicine is not a science, rather it is a rational practice based on a scientific education and sound clinical experience and expertise. Clinical decisions are typically made through a plurality of means and are formulated on what might be termed the 'evidence of the clinic', constituted not solely by scientific data derived from methodologically limited studies such as randomised controlled trials, megatrials and meta-analyses, but from a variety of other sources including raw clinical experience, complex patient biography, a 'telling phrase', even an inadvertent gesture. The idea that the technique of evidence-based medicine (EBM) could be used to determine the extent to which a physician's practice was based on 'cold' scientific data and then to judge one physician's practice as 'evidence-based' and another's as 'non evidence-based', in an attempt to define a 'good' and 'bad' physician, was always an intellectual and clinical absurdity destined to obscure excellence in clinical practice, rather than to illuminate it. Thus, while certainly referring closely to an ever-expanding scientific knowledge base, clinical medicine remains fundamentally a human experience, drawing on a dynamic hermaneutic interaction between physician and patient, so that the information required to choose optimal therapy may be gathered and integrated. This complex nature of medicine as a practice employing both both science and 'art' indicates the necessity for attempts to define good practice to integrate both of these sources of knowledge and expertise, avoiding a preferential concentration on scientific data alone with a consequent neglect of all those vital aspects of good medicine - listening, empathy, intuition, insight, compassion, reassurance, consolation - that are non-scientific in nature and not amenable to quantitative measurement. This is not to say that science is unimportant in medicine. On the contrary, science occupies a *central* place in the care of patients, but science and clinical practice move in different directions. Science moves from individual observation to generalisable theories and laws. But it is clinical practice that brings this generalised body of knowledge to bear - in the context of the intimacy of the physician-patient consultation - to the benefit of the individual. The rise of EBM has threatened to disturb the character of medicine as a practice employing both science and 'art', by demanding a primacy of the biomedical paradigm and the fallacy of the 'hierarchy of evidence' as fundamental to 'modern' medical thought. In doing so, EBM had demonstrated a form of 'scientific fetishism' that exalted probability values and denigrated clinical expertise and which reached its orgasm in the cumulative meta-analysis of quantitative studies. In this way, EBM has threatened to promote bad rather than good medicine by claiming that it alone represented the true epistemic voice of medicine, while at the same time utterly failing to represent medical knowledge adequately and excluding the human interpretation that constitutes the fundamental basis of the historic mission of medicine. Physicians have comprehensively rejected the absurd reductionism of this narrow scientism in favour of the development of patiented centred approaches and shared decision making in clinical care where the 'art' of medicine can more easily be applied in conjunction with scientific knowledge. The rise of genomics and translational science has marginalised EBM further. Thus, we are now moving from evidence-based medicine to personalised knowledge-based medicine, from a false concept of clinical practice to a modern and important one.

The basis of medical knowledge: judgement, objectivity and the history of ideas

Michael Loughlin

What is EBM? Many accounts render the doctrine platitudinous, raising the question: 'why such a vast literature in defence of a platitude?' Belief in a 'gold standard' of evidence renders EBM a substantive doctrine with implications for medical epistemology, requiring (but lacking) argumentative support. Its defenders' uses of key terminology reveal commitment to a set of semantic oppositions between 'objectivity', 'science' and 'evidence' on the one hand and 'personal judgement' on the other. These oppositions are only philosophically sustainable if logical positivism is true. But the history of ideas reveals that this underlying philosophy was refuted before EBM was even invented. So EBM is either a platitude or a substantive, but unsustainable, doctrine.

Resisting the Violence of Stratification: Capture, War Machines and the Evidence-Based Movement

Dave Holmes

Drawing on the compelling and radical philosophy of Gilles Deleuze and Félix Guattari, this paper constitutes a definite call for resistance against the ways knowledge is stratified through the evidence-based movement (EBM) in health sciences. While the "evidence-based" paradigm allegedly promotes the noble ideal of "best knowledge" (to produce best practices), supposedly free from political bias, in reality this apparent neutrality masks the ways power silently operates to impose specific research designs while excluding others. It is argued here that the Cochrane taxonomy is no more than a political device that the majority of its disciples disguises as a needed scientific tool. In this paper, the nature/structure of the EBM is theorised as an imperialistic apparatus of capture which excludes many marginal forms of knowledge (savoirs délinquants) and as a consequence, requires that we stand ready to resist the violence of this stratification.

Potential and limitation of EBM: what kind of research do we need to produce relevant information?

Alessandro Liberati

Evidence-based Medicine and Translational Research

Dhavendra Kumar

The concept of ***'evidence-based medicine'*** dates back to mid-19th century. It rapidly gained momentum and recognition by several institutions and is now pivotal in planning, funding and in delivering the quality health care. Clinicians, public health practitioners, health commissioners/providers and planners, politicians and public seek formal ***'evidence'*** in approving and funding any form of health care provision. Essentially ***'evidence-based medicine'*** [EBM] aims at the conscientious, explicit and judicious use of the current best evidence in making decisions about the individualised patient care. It is *de facto* '***personalized medicine'*** in practise.

During the last three decades, EBM has established as a model of good medical practice that became possible with the emergence and acknowledgement of translational medical research, in particular incorporation of biomedical research. Human and medical genetics research has contributed enormously in the clinical care of patients and families. Clinical genetics offers truly evidence-based health care in dealing with a number of inherited disorders that requires the accurate diagnosis and factual information on the molecular pathology and phenotypic correlations. Since the completion of the human genome project and the rapid accumulation of huge amount of data on genomics, scientists and physicians alike are excited on the prospect of ***'personalized health care'*** based on individual's genotype and phenotype.

Translational research in human genetics and genomics has led to developing powerful tools for clinical diagnosis, assessing individual's genomic profile for disease prediction and prevention, high-throughput genome-wide screening for predisposition and/or protection to complex medical conditions, and discovery and development of new drugs and vaccines. Key illustrative examples may include cascade genetic testing in cystic fibrosis, familial hypercholesterolemia, inherited cardiomyopathies and channelopathies and familial breast/ovarian cancers. Unravelling of the basic biological mechanisms has led to new pharmacotherapeutic approaches in managing neoplastic lesions in certain Mendelian cancer family syndromes such as dominantly inherited tuberous sclerosis.

The first decade of the new millennium now witnesses the transition to the ***'genomic medicine'***. The practice of medicine, including health promotion and prevention of disease, stands now at a wide open road as the scientific and medical community embraces itself with the rapidly expanding and revolutionising field of translational genomic research.

Key words: genetics; genomics; evidence-based medicine; genomic medicine; translational research; personalized medicine; micro arrays; high-throughput screening; pharmacogenomics.

Evidence based medicine and education

Gian Franco Gensini, Andrea A. Conti

According to the definition of David Sackett and co-workers, "Evidence Based Medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" (1).

In the last few years the potential and the limits of Evidence Based Medicine (EBM) have clearly emerged in the educational settings, and nowadays many formative tools aimed at disseminating the teaching of evidence based health care are available. The personal clinical competence and the best scientific evidence were considered ten years ago the basic elements for practicing effective EBM (2).

However, at present time, it has also to be clearly understood and considered the fact that much "evidence" produced in the past was related to settings presently deeply changed, which implies the need for re-evaluating its strength and applicability. Evidence obtained in population samples different according to ethnicity, life style habits and environmental risk factors has to be precisely re-assessed in a dynamic process.

Through time, patients' values have integrated these initial components of EBM implementation and didactics. In effect, in the academic environment, the one in which the authors of this contribution daily work, the teaching of EBM should aim more and more at the integrated inclusion of individual preferences and attitudes, both on the part of health operators and persons/patients, in the methodological framework represented by external clinical evidence.

In our daily formative and professional activity the challenge for the present and the future of EBM education is that of incorporating the "historical" EBM elements with the "classical" components of what at present is called Narrative Medicine. Narrative medicine is medicine practiced with the narrative competence to perceive and be active on the basis of the quandaries of others, and it is characterized by the systematic objective to shorten the distance between health professionals and patients, health operators and their different colleagues and, more in general, the whole society (3). Far from being an alternative to EBM, Narrative Medicine recuperates and magnifies the communicative aspects between health workers and individual patients in a time-allowing context.

The particular "scientific" attention to patients' values, linking EBM and Narrative Medicine, now appears the methodological and operational setting in which Evidence Based Medicine and Narrative Based Medicine integrate themselves to improve modern medical education at the University level.

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The Ramifications of EBM for Health Policy and Politics

Sandra Tanenbaum

In the U.S., as elsewhere, evidence-based medicine (EBM) and its progeny - evidence-based practice, programming and policy - are ubiquitous. EBM has become a concern not only of scientists and physicians, but also of legislators, bureaucrats and advocates for health policies and programs. This paper will offer a brief discussion of the rise of the EBM movement in the U.S. and describe two ramifications of EBM for health policy and politics. First, randomized controlled trials (RCTs) and other statistical analyses have supplanted traditional sources of legitimacy for "claims-making" on health care resources. This includes claims on payers for medical care, on malpractice courts to redress poor patient outcomes, and on public resources for health and social services. Second, EBM creates a false sense of certainty on which policy-makers and the public are invited to rely. Not only does RCT methodology limit the usefulness of study findings to the larger health care system, but despite EBM's arrogation of objectivity, controlled trials entail subjective - even normative - judgments by investigators and funders.

The Hierarchy of Evidence - Fact or Fallacy?

Joaquim Sa' Couto

Evidence Based Medicine (EBM) has been described as the "conscious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" (Sackett 1996). This definition is so vague that most physicians can claim to be EBM practitioners, if not EBM apostles.

Upon closer scrutiny, however, this initial appeal of EBM quickly fades when we realize that the assumptions of EBM's touted new paradigm are simply irrational and cannot be applied to the medical praxis.

The most irrational of EBM's assumptions is the preponderance of empirical evidence, defined as evidence derived from systematic clinical research, over pathophysiological rationale and clinical experience. Over the last decade, EBM protagonists were heavily criticized for their approach to medical knowledge integration (Miles et al. 1997, 1998) and have revised their position, admitting that some non-evidentiary kinds of medical knowledge needs to be integrated as evidence (Ellrodt et al. 1997), (Guyatt & Rennie 2002).

A hierarchy of evidence was then construed, attributing the highest ranking to empirical evidence, immediately followed by the results of physiological studies and lastly, the results of unsystematic clinical observation, or clinical experience. Expert opinion was never rehabilitated as valid evidence (Tonnelli 1999).

As I have pointed out before (Couto 1998, 2006), this hierarchy is fallacious because pathophysiological data, which is derived from the biological sciences, concerns "general laws that are common to all causal sequences and that are absent in all coincidental sequences" (Hume 1748), therefore, once established, these laws allow us to predict the effects that arise in the presence of certain causes, not only for the "average patient" (as do RCT's), but for all human beings (Couto 2006).

Whenever a physician is confronted with conflicting warrants for action, derived from empirical data and pathophysiological principles, there should be no doubt about how to proceed: the dominant medical paradigm imposes reliance on pathophysiology, because of its predictive value and rejects the empirical evidence because this may or may not apply to the individual case.

When reviewing the literature for this conference, I saw the scope of EBM's impact on medical practice in recent times. It reformed the way medicine is practiced, by forcing physicians to support their decisions with the best available evidence. EBM challenged the established authority and democratized access to knowledge. Finally EBM, in my opinion, also led physicians to study philosophy and epistemology of sciences.

The end result was positive but it did not change medicine in a fundamental way. We continue to value expert opinion and our own experience, pathophysiologic knowledge, and of course, we all try to integrate the best empirical evidence available as we always done.

Beyond Evidence:
Other relevant topics for clinical decision making

Mark R. Tonelli

Focused almost exclusively on the published results of clinical research, evidence-based medicine (EBM) has thus far failed to adequately account for the appropriate incorporation of a wider variety of facts and warrants for medical decision making into clinical practice. In particular, EBM has struggled with the value and integration of more traditional kinds of medical knowledge, those derived from clinical experience or based upon pathophysiologic rationale.

Despite being the central concept of evidence-based medicine, "evidence" remains an elusive and controversial term and notion. Ongoing debates regarding what does or does not constitute evidence and how evidence should be prioritized primarily serve to confuse and obfuscate. By examining the nature of medical decision making without any appeal to "evidence," a more complete understanding of the optimal practice of clinical medicine is possible.

Such an examination yields five distinct topics that are relevant to clinical decisions: 1) results of clinical research, 2) primary clinical experience, 3) pathophysiologic rationale, 4) patient goals and values, and 5) system features. The value of the knowledge contained within each of these topics differs in kind, not degree. The general preference given to the results of clinical research by the EBM movement is not defensible on epistemic grounds; the results of clinical research are not necessarily more valuable than clinical experience or pathophysiologic understanding to the care of an individual patient. No single topic has a general priority over any other and the relative importance of a topic will depend upon the circumstances of the particular case. The skilled clinician must weigh the potentially conflicting facts and warrants for action, employing both practical and theoretical reasoning, in order to arrive at the best choice for an individual patient. The relative weighting of potentially conflicting warrants for a medical decision comprises the critical process of clinical judgment. This casuistic approach allows clinical medicine to remain a personal and prudential undertaking, arising from and focused on the individual patient.

The sources of knowledge inspiring current medical practice in oncology: results of a survey in Italian Comprehensive Cancer Centres

Silverio Tomao

The Morgagni clinico-pathologic method in the era of clinical imaging and molecular medicine

Gaetano Thiene

With the publication of *De Sedibus et Causis Morborum per Anatomen Indagatis*, 1761, Giovanni Battista Morgagni established Pathological Anatomy as Science, by introducing the method of clinico-pathologic correlations and thus changing the course of medical diagnosis. This method was possible because he had held the chair of Theoretical Medicine and, when moved to Anatomy, he continued to practice clinical consultations.

While performing autopsy in patients he visited in life, he was able to compare signs and symptoms with gross postmortem findings, thus giving an explanation of clinical manifestations based upon structural abnormalities.

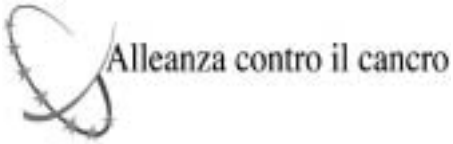
The meaning of the title was intended to be the reason ("*Causis*") of the disease in terms of signs and symptoms ("*Morborum*") rather than the etiology. The epicrisis gave the final *pathophysiological* interpretation of the clinical course. The ancient humoral theory of diseases was replaced by anatomical observations at organ level (*Organ Pathology*).

With this novel epistemologic approach, Pathological Anatomy was legitimated as the Medical Science which translates the morphological information from bench to bedside. The advent of microscopy and histology made possible a further insight into the basis of diseases (*Cellular Pathology*) and, with the use of biopsy, the application of clinico-pathologic method was accomplished also in vivo.

The clinico-pathologic conference we weekly hold is still based on this method of correlations and play a key role in the patient management. The technological revolution of non-invasive *clinical imaging* (echo, CT, PET, MRI) allowed a delineation of the human body equal or even superior to anatomical dissection, with gross and histologic investigations still employed as an essential way of validation.

Molecular biology techniques are nowadays an fundamental part of the pathologist armamentarium with terrific diagnostic potential (*Molecular Pathology*), well beyond the microscopic resolution power. The use of PCR and gene sequencing allows identification of viruses or gene mutations even in so called "*Mors Sine Materia*" (*Molecular Autopsy*).

The latter is particularly important in inherited mendelian diseases, where the deceased patient may be the index case of *genetically transmitted disorder*. The precise molecular diagnosis at postmortem entails fundamental implications for prevention, through familiar genetic screening. With such scientific advances, from gross to molecular pathology, the anatomical theatre is still the "*the locus ubi mors gaudet succurrere vitae*".



Alliance Against Cancer (ACC) is the Italian Association of Comprehensive Cancer Centres. It was created in 2002 with the task of promoting an active collaboration among Italian Cancer Institutes through the exchange of information, knowledge, data, scientific results and human resources and in order to respond, in an appropriate and harmonised way, to the building of the European Research Area for Cancer.

The final aim of ACC is to better support and harmonise cancer research promoting the transfer of results into clinical practice and to assure equal care to cancer patients across Italy, thus reducing health migrations. The studies on the Aetiology of cancer play an important role in the association's planning of research activities.

The President of ACC is the President of the Istituto Superiore di Sanità (Italian National Institute of Health). ACC is financed mostly by public funds. All the funds provided by the Italian Ministry of Health have been allocated considering the 3 different goals to achieve as set out by the statute of the Association: strengthening translational research, building up networks of facilities, improving communication to reduce disparities.

In 2006, ACC received 30 million euro financial support from the Italian Ministry of Health under the programme called "Rete nazionale solidale e collaborazioni internazionali" (Joint national network and international cooperation initiatives). This amount has been allocated through specific calls for proposals to support cancer research including activities related to new approaches in cancer diagnosis, treatment and classification as well as to promote the international dimension of Italian cancer research and its relationship with the European 7th Research Framework Programme.

A specific Focal Point for International Affairs was launched in 2007 in order to facilitate and improve the participation of ACC members in European and large international projects.

The ACC network has the fundamental critical mass able to: help to strengthen qualified national cancer research; cope with the challenges emerging from research fragmentation and increasing globalisation of science and technology; implement a real sharing of knowledge, an adequate flow of young and skilled scientists and integrate research infrastructures into a network; coordinate research programmes in line with the European strategy foreseen by the Green Paper of the European Commission "The European Research Area: New perspectives", 4 April 2007.

The long experience gained by Alliance Against Cancer and its members on large international cancer research programmes in the field of experimental and applied cancer research and related disciplines makes it the natural contact point for the Italian participation in the building of the European coordination actions aiming to reduce the existing fragmentation.

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