Basic Science and Clinical Medicine: A relationship on the rocks?

Warren Lee MD PhD
Keenan Centre for Biomedical Research
St. Michael’s Hospital and the University of Toronto
Medicine: Science or Art?

S.C. Panda

Abstract

Debate over the status of medicine as an Art or Science continues. The aim of this paper is to discuss the meaning of Art and Science in terms of medicine, and to find out to what extent they have their roots in the field of medical practice. What is analysed is whether medicine is an “art based on science”; or, the “art of
A New Initiative on Precision Medicine
Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

“Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes — and to give all of us access to the personalized information we need to keep ourselves and our families healthier.”

— President Barack Obama, State of the Union Address, January 20, 2015
**WHAT IS IT?**

**Precision medicine** is a groundbreaking approach to disease prevention and treatment based on people’s individual differences in environment, genes and lifestyle.

“The PMI aims to leverage advances in genomics, emerging methods for managing and analyzing large data sets while protecting privacy, and health information technology to accelerate biomedical discoveries.”

http://www.pbs.org/newshour/updates/dec-14-1799-excruciating-final-hours-president-george-washington/
COCAINETOOTHACHE DROPS
Instantaneous Cure!
PRICE 15 CENTS.
Prepared by the
LLOYD MANUFACTURING CO.
219 HUDSON AVE., ALBANY, N. Y.
For sale by all Druggists.
(Registered March 1885.)
MEDICAL EDUCATION
IN THE
UNITED STATES AND CANADA
A REPORT TO
THE CARNEGIE FOUNDATION
FOR THE ADVANCEMENT OF TEACHING
BY
ABRAHAM FLEXNER
WITH AN INTRODUCTION BY
HENRY S. PRITCHETT
PRESIDENT OF THE FOUNDATION
BULLETIN NUMBER FOUR (1910)
Three characteristic stages are to be discerned in the evolution of medical teaching.\(^1\) The first and longest was the era of dogma. Its landmarks are Hippocrates (B.C. 460–377) and Galen (A.D. 130–200), whose writings were for centuries transmitted as an authoritative canon. Observation and experience had indeed figured considerably in their composition,\(^2\) but increasingly remote disciples in accepting the tradition lost all interest in its source. The Galenic system took its place in the medieval university with Euclid and Aristotle,—a thing to be pondered, expounded and learned; facts had no chance if pitted against the word of the master. So completely was medicine dominated by scholasticism that surgery, employing such base tools as sight and touch, was held to be something less than a trade and accordingly excluded from intellectual company.
The second era is that of the empiric. It began with the introduction of anatomy in the sixteenth century, but did not reach its zenith until some two hundred years later. At its best it leaned upon experience, but its means of analyzing, classifying, and interpreting phenomena were painfully limited. Medical art was still under the sway of preconceived and preternatural principles of explanation; and rigorous therapeutic measures were not uncommonly deduced from purely metaphysical assumptions. The debility of yellow fever, for example, Rush explained by “the oppressed state of the system;” and on the basis of a gratuitous abstraction, resorted freely to purging and bleeding. His first four patients recovered; there is no telling how many lives were subsequently sacrificed to this conclusive demonstration. The fact is that the empiric lacked a technique with which to distinguish between apparently similar phenomena, to organize facts, and to check up observation; the art of differentiation through controlled experimentation was as yet in its infancy. Under vague labels

- non-mechanistic thinking
- grouping by patterns
through controlled experimentation was as yet in its infancy. Under vague labels like rheumatism, biliousness, malaria, or congestion, a hodgepodge of dissimilar and unrelated conditions were uncritically classed; the names meant nothing, but they answered as explanation, and even sanctioned severe and nauseous medication. Ignorant of causes, the shrewdest empiric thus continued to confound totally unlike conditions on the basis of superficial symptomatic resemblance; and with amazing assurance undertook to employ in all a therapeutic procedure of doubtful value in any. He combined the vehemence of the partisan with something of the credulity of
We don’t know what causes sepsis

SCIENCE IN MEDICINE

The enigma of sepsis

Niels C. Riedemann, Ren-Feng Guo, and Peter A. Ward

Department of Pathology, University of Michigan Medical School, Ann Arbor, Michigan, USA

Sepsis remains a serious cause of morbidity and mortality, and the pathophysiology of the disease is not clear. The definition of the clinical manifestations of sepsis is ever evolving. This review discusses the search

• “the graveyard for pharmaceutical companies”
The third era is dominated by the knowledge that medicine is part and parcel of modern science. The human body belongs to the animal world. It is put together of tissues and organs, in their structure, origin, and development not essentially unlike what the biologist is otherwise familiar with; it grows, reproduces itself, decays, according to general laws. It is liable to attack by hostile physical and biological agencies; now struck with a weapon, again ravaged by parasites. The normal course of bodily activity is a matter of observation and experience; the best methods of combating interference must be learned in much the same way. Gratuitous speculation is at every stage foreign to the scientific attitude of mind.
Flexner report

• Increased pre-requisites for medical school
• Training physicians in the scientific method
  – Engage medical faculty in research
Flexner report

• Closing of many medical schools
• Association with universities
• Emphasis on instruction in the sciences and the scientific method

• “At the time, “modern medicine” faced competition from osteopathic medicine, chiropractic medicine, electrotherapy, eclectic medicine, naturopathy and homeopathy.”
The first antibiotic

Penicillium Notatum. Fleming’s own photograph of the original mould which produced penicillin
(courtesy of St. Mary’s Hospital)

http://www.biography.com/people/alexander-fleming-9296894

Circa 1928


Epidemiologic Notes and Reports

Pneumocystis Pneumonia --- Los Angeles

In the period October 1980-May 1981, 5 young men, all active homosexuals, were treated for biopsy-confirmed Pneumocystis carinii pneumonia at 3 different hospitals in Los Angeles, California. Two of the patients died. All 5 patients had laboratory-confirmed previous or current cytomegalovirus (CMV) infection and candidal mucosal infection. Case reports of these patients follow.
A triumph of basic science

LETTERS TO NATURE

Suppression of mouse viraemia and retroviral disease by 3'-azido-3'-deoxythymidine


* Dana-Farber Cancer Institute, 44 Binney Street, Boston, Massachusetts 02115, USA
† Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709, USA

The retroviruses human T-cell lymphotrophic virus-I (HTLV-I)\(^1,2\) and HTLV-III/LAV (lymphadenopathy-associated virus)\(^3,4\) are clearly linked to human diseases. Patients with HTLV-I-positive neoplasms may respond transiently to traditional chemotherapy, but are not cured\(^5\). For patients with acquired immune deficiency syndrome (AIDS) there is no curative therapy\(^6\). In retroviruses of
Manulife to offer HIV life coverage

Extension of coverage represents a shift in the way the company is underwriting new policies

JACQUELINE NELSON

Financial Services

Manulife Financial Corp. will offer life insurance to people living with HIV as part of a company-wide push to make applying for coverage easier.

The Toronto-based insurer will be the first in Canada to offer individual life insurance policies of up to $2-million to those who have tested positive for the human immunodeficiency virus. Manulife has carefully studied scientific data on health and HIV for years and now considers it a chronic condition.

The extension of coverage represents a shift in the way the company is underwriting new insurance policies, using more analytics and data to assess survival rates and other factors. It's also part of the insurer's efforts to make obtaining life insurance easier.

“We're going to be changing underwriting requirements to make it simpler for people to apply for an insurance product,” said Karen Cutler, Manulife's chief underwriter. That means changing the parameters for some of the underwriting tests that are done on new insurance applications. Manulife will be rolling out more measures to improve the application process in the coming months.

HIV-positive Canadians seeking life insurance must be between 30 and 65 years of age and on a stable course of antiretroviral therapy, among other conditions. About 75,000 Canadians have tested HIV-positive, according to government assessments; not all of them would qualify for coverage. “It's not a massive market for us – that's not what this is about. It's about how we are progressing forward on something that has been prohibiting people with HIV to apply for insurance,” Ms. Cutler said. “It's one step forward toward modernizing insurance and thinking about insurance differently.”

Still, the change affects Manulife's businesses across North America, including its Boston-based insurance group, John Hancock Financial. In the United States there are 1.2 million people living with HIV, according to the U.S. Centers for Disease Control and Prevention.

The insurer constantly reviews new medical data but needed time to reflect on the effectiveness of various new HIV treatments. “We're at the point now where we've got enough information and there's enough long-term studies in the medical field that show that HIV-infected individuals are doing quite well and the mortality has improved significantly over the years,” Ms. Cutler said.

Manulife Financial (MFC)
Close: $18.78, down 18¢
Familial Hypercholesterolemia: Identification of a Defect in the Regulation of 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Activity Associated with Overproduction of Cholesterol

(cholesterol synthesis/hyperlipidemia/low-density lipoproteins/enzyme regulation/coronary heart disease)

JOSEPH L. GOLDSTEIN AND MICHAEL S. BROWN

Divisions of Medical Genetics and Gastroenterology-Liver, Department of Internal Medicine, University of Texas Southwestern Medical School, Dallas, Tex. 75235

Communicated by E. R. Stadtman, June 20, 1973
Purification of the Low Density Lipoprotein Receptor, an Acidic Glycoprotein of 164,000 Molecular Weight*

(Received for publication, August 20, 1981)

Wolfgang J. Schneider, Ulrike Beisiegel‡, Joseph L. Goldstein, and Michael S. Brown

From the Departments of Molecular Genetics and Internal Medicine, University of Texas Health Science Center at Dallas, Dallas, Texas 75235

This paper describes a rapid two-step procedure for the purification of the low density lipoprotein receptor from bovine adrenal cortex membranes. After solubil-

The purification procedure involves solubilization of the receptor with the nonionic detergent octyl-β-D-glucoside, followed by chromatography on DEAE-cellulose and agarose.
A Century of Cholesterol and Coronaries: From Plaques to Genes to Statins

Joseph L. Goldstein1,∗ and Michael S. Brown1,∗

1Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

Cell 161, March 26, 2015 ©2015 Elsevier Inc. 161
A New Initiative on Precision Medicine

Francis S. Collins, M.D., Ph.D., and Harold Varmus, M.D.

“...this concept broadly has been dramatically improved by the recent development of large-scale biologic databases (such as the human genome sequence), powerful methods for characterizing patients (such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology), and computational tools for analyzing large...”

January 20, 2015
A paradox?

• On the threshold of “precision medicine”

• Are clinicians still interested in basic sciences?
Is basic science disappearing from medicine? The decline of biomedical research in the medical literature

Benjamin E. Steinberg,*† Neil M. Goldenberg,*† Gregory D. Fairn,†‡ Wolfgang M. Kuebler,†‡ Arthur S. Slutsky,‡§¶ and Warren L. Lee†§¶

*Department of Anesthesia, †Department of Surgery, §Interdepartmental Division of Critical Care, and ¶Department of Medicine, University of Toronto, Toronto, Ontario, Canada; and ‡Keenan Research Centre for Biomedical Science, Li Ka Shing Knowledge Institute, St. Michael’s Hospital, Toronto, Ontario, Canada
Premise

• Hypothesis:
  – Clinical journals have been reporting less basic science over the last 20 years
Goal:
Quantify the prevalence of basic science articles in specialty medical journals over the last twenty years

Using a bibliometric approach, we devised a search strategy for the National Center for Biotechnology Information PubMed database to identify basic science articles for the 20-year period spanning 1994–2013; we omitted 2014 and 2015 to avoid inclusion of incomplete PubMed records. The search was run with the following terms: (Journal Title [journal]) AND (cellular* [Title/Abstract] OR cell[Title/Abstract] OR animals[Title/Abstract] OR Biologic Markers[mh] OR mice OR Polymorphism[mh] OR pathway[Title/Abstract] OR mechanism[Title/Abstract] OR cytokine[Title/Abstract] OR signal transduction [mh] OR animal[mh] NOT clinical trial[Publication Type] NOT editorial[Publication Type] NOT Case Reports [Publication Type] NOT Practice Guideline[Publication Type] NOT Comment[Publication Type]).
Methods (continued)

• Highest-impact journals in 8 specialties
• Used *JBC, JCI, Cell* as a control (nonclinical) group
• Basic science was deliberately defined broadly
  – Disease pathogenesis, physiology, biomarkers, polymorphisms
  – Review articles were included
• Excluded:
  – Clinical trials, case reports, guidelines, editorials/commentary, letters to the editor, book reviews
• Total number of articles used as the denominator
TABLE 1. Operating characteristics of the automated PubMed search

<table>
<thead>
<tr>
<th>Journal</th>
<th>Sensitivity</th>
<th></th>
<th>Specificity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>American Journal of Respiratory and Critical Care Medicine</td>
<td>0.8</td>
<td>1.0</td>
<td>0.88</td>
<td>0.7</td>
</tr>
<tr>
<td>Diabetes Care</td>
<td>0.89</td>
<td>0.86</td>
<td>0.71</td>
<td>0.56</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>0.96</td>
<td>0.88</td>
<td>0.98</td>
<td>0.8</td>
</tr>
<tr>
<td>The Lancet Neurology</td>
<td>1.0</td>
<td>0.76</td>
<td>0.48</td>
<td>0.8</td>
</tr>
<tr>
<td>Journal of American College of Cardiology</td>
<td>0.84</td>
<td>0.83</td>
<td>0.88</td>
<td>0.62</td>
</tr>
<tr>
<td>The Lancet Infectious Diseases</td>
<td>1.0</td>
<td>0.96</td>
<td>0.34</td>
<td>0.4</td>
</tr>
<tr>
<td>Journal of the American Society of Nephrology</td>
<td>0.84</td>
<td>0.92</td>
<td>0.64</td>
<td>0.78</td>
</tr>
<tr>
<td>The Lancet Oncology</td>
<td>1.0</td>
<td>0.92</td>
<td>0.62</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Table 1. Operating characteristics of the automated PubMed search

<table>
<thead>
<tr>
<th>Journal</th>
<th>Fold change in the proportion of basic science articles, 1994–2013</th>
<th>$P$ value $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Journal of Respiratory and Critical Care Medicine</td>
<td>0.53</td>
<td>0.000001</td>
</tr>
<tr>
<td>Diabetes Care</td>
<td>1.01</td>
<td>0.62</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>0.49</td>
<td>0.00003</td>
</tr>
<tr>
<td>The Lancet Neurology</td>
<td>0.55</td>
<td>0.000004</td>
</tr>
<tr>
<td>Journal of American College of Cardiology</td>
<td>0.55</td>
<td>0.0000001</td>
</tr>
<tr>
<td>The Lancet Infectious Diseases</td>
<td>0.41</td>
<td>0.004</td>
</tr>
<tr>
<td>Journal of the American Society of Nephrology</td>
<td>0.97</td>
<td>0.28</td>
</tr>
<tr>
<td>The Lancet Oncology</td>
<td>0.50</td>
<td>0.000004</td>
</tr>
</tbody>
</table>
The decline is not due to dilution
Basic science has little presence in the top general medical journals.
Why is this occurring?

- Editorial preference
- Proliferation of journals dedicated to basic science
Does this shift have any consequences?

• Will clinicians/trainees perceive basic sciences as irrelevant to clinical practice?

• Will trainees be less likely to pursue basic science research?
Research projects in the Surgeon–Scientist and Clinician–Investigator programs at the University of Toronto (1987–2016): a cohort study

Neil M. Goldenberg MD PhD, Benjamin E. Steinberg MD PhD, James T. Rutka MD PhD, Robert Chen MBBChir, Val Cabral, Norman D. Rosenblum MD, Andras Kapus MD PhD, Warren L. Lee MD PhD

Background: Physicians have traditionally been at the forefront of medical research, bringing clinical questions to the laboratory and returning with ideas for treatment. However, we have anecdotaly observed a decline in the popularity of basic science research among trainees. We hypothesized that fewer resident physicians have been pursuing basic science research training over time.
Methods (continued)

- Reviewed all projects from 1987-2016
  - Title, supervisor, graduate department, Pubmed
- Two independently raters categorized the projects
  - Basic Science
  - Clinical Epidemiology
  - Education
- The proportion of residents pursuing basic science was determined
- Basic science defined broadly
  - Mechanisms of disease or therapy
- 583 trainees in the cohort
- 100% agreement between the raters; 9 resident projects could not be classified (1.5%)

<table>
<thead>
<tr>
<th>Period</th>
<th>Title of project</th>
<th>Basic Science</th>
<th>Clinical Epidemiology</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987-1992</td>
<td>The Development of an Integrated Care Centre for Vascular Surgery at the University of Calgary: the Western Canada Vascular Centre</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>1987-1992</td>
<td>Role of surface characteristics in the bony response to implant materials in vivo</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987-1992</td>
<td>Effective donor site on chondrogenic potential of periosteum in vitro</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987-1992</td>
<td>The role of fibrin in the pathogenesis of intraabdominal sepsis</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011-2016</td>
<td>Moral maturation and values of surgeons surrounding palliative colorectal cancer treatment</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2011-2016</td>
<td>Predicting the Risk of Medication Side-effects in the Elderly (PROMISE)</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2011-2016</td>
<td>A Qualitative Critical Appraisal of the Toronto Orthopedic Boot Camp: How to best prepare junior surgical residents for clinical duties</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>2011-2016</td>
<td>The Role of Molecular Biomarkers and miRNA in Prostate Cancer Progression</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2011-2016</td>
<td>Improving out-patient care after an in-patient episode of acute kidney injury</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>2011-2016</td>
<td>MRI- and ultrasound-based assessment of tumour response to cancer therapy</td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Decline in the proportion of residents pursuing basic research
Figure 2. Changing research interests of postgraduate residents

- **1987-1992**: 2 (Clin Epi 1, Basic Science 1, Education 1, Unclear 1)
- **1993-1998**: 24 (Clin Epi 10, Basic Science 11, Education 3, Unclear 0)
- **1999-2004**: 49 (Clin Epi 36, Basic Science 11, Education 1, Unclear 1)
- **2004-2009**: 78 (Clin Epi 62, Basic Science 17, Education 2, Unclear 1)
- **2010-2016**: 86 (Clin Epi 78, Basic Science 8, Education 1, Unclear 1)
Our data show a significant decline in both the relative and absolute numbers of clinicians obtaining training in basic science research over the last 30 years. Most (90%) of the research projects completed by trainees in the Surgeon-Scientist Program at the University of Toronto from 1987–1992 were classified as basic science. More recently, only 37% were classified as basic research.

mational research over the last 30 years. If this trend continues, the participation of physicians in basic science investigation will be in jeopardy.
Historically, physician–scientists have played a key role in bringing clinical questions to the laboratory and returning with scientific advances. Because scientific discovery forms the underpinning of modern medicine, in our opinion, engagement by clinicians in basic science research is both desirable and essential.
Study limitations

• Not doing research does not necessarily mean lack of appreciation for it
• Single centre, single country

The unanswered question:

• How much basic science exposure is necessary in medical education and clinical medicine?
Getting Into Med School Without Hard Sciences

By ANEMONA HARTOCOLLIS  JULY 29, 2010

For generations of pre-med students, three things have been as certain as death and taxes: organic chemistry, physics and the Medical College Admission Test, known by its dread-inducing acronym, the MCAT.

So it came as a total shock to Elizabeth Adler when she discovered, through a singer in her favorite a cappella group at Brown University, that one of the nation’s top medical schools admits a small number of students every year who have skipped all three requirements.

Until then, despite being the daughter of a physician, she said, “I was kind of thinking medical school was not the right track for me.”

Ms. Adler became one of the lucky few in one of the best kept secrets in the cutthroat world of medical school admissions, the Humanities and Medicine Program at the Mount Sinai medical school on the Upper East Side of Manhattan.

The program promises slots to about 35 undergraduates a year if they study humanities or social sciences instead of the traditional pre-medical school curriculum and maintain a 3.5 grade-point average.

For decades, the medical profession has debated whether pre-med courses and admission tests produce doctors who know their alkyl halides but lack the sense of mission and interpersonal skills to become well-rounded, caring, inquisitive healers.

That debate is being rekindled by a study published on Thursday in Academic Medicine, the journal of the Association of American Medical Colleges. Conducted by the Mount Sinai program’s founder, Dr. Nathan Kase, and the medical school’s dean for medical education, Dr. David Muller, the peer-reviewed study compared outcomes for 85 students in the Humanities and Medicine Program with those of 606 traditionally prepared classmates from the graduating classes of 2004 through 2009, and found that their academic performance in medical school was equivalent.
Challenging Traditional Premedical Requirements as Predictors of Success in Medical School: The Mount Sinai School of Medicine Humanities and Medicine Program

David Muller, MD, and Nathan Kase, MD

Abstract

**Purpose**

Students compete aggressively as they prepare for the MCAT and fulfill traditional premedical requirements that have uncertain educational value for students of Medicine with those of their 606 traditionally prepared classmates for the 2004–2009 graduating classes. The authors analyzed basic science knowledge, clerkship performance, (P = .001), there was no difference in graduating with distinction in research (P = .281). HuMed students were more likely to have lower United States Medical Licensing Examination Step 1

- Slightly lower USMLE scores
- More likely to take personal leave
But overall performance was similar.
Trend towards psychiatry and primary care

Academic Medicine, Vol. 85, No. 8 / August 2010
Conclusion:

The role of basic science appears to be diminishing in medical literature and postgraduate research.
Potential negative consequences

• “Tradespeople” instead of “professionals”
  – Algorithmic thinking
  – Loss of leadership, respect
    • Who will advance “precision medicine”? 

• Rise of quackery?
Potential positive consequences

- “well-rounded” clinicians
- Focus on the patient experience, not the disease
Scientific Discovery and the Future of Medicine

Phil B. Fontanarosa, MD, MBA; Howard Bauchner, MD

Scienfy in clinical care, many physicians in practice and in training may be unaware of the extraordinary advances in basic and translational science and the novel discoveries in the biosciences, with the related implications for expanding medical knowledge and improving medical care—the magic of medicine.

All physicians are trained in the medical sciences and have an appreciation for the critical importance of biomedical research in advancing medical knowledge. We hope that
MEDICAL EDUCATION
IN THE
UNITED STATES AND CANADA
A REPORT TO
THE CARNEGIE FOUNDATION
FOR THE ADVANCEMENT OF TEACHING
BY
ABRAHAM FLEXNER

Is there any logical incompatibility between the science and the practice of medicine?
Summary

• Science underpins advances in medicine
• Physicians and trainees are exposed to much less basic science than previously
• The consequences of this change remain unclear
  – We speculate that a decreased appreciation of basic sciences is unhealthy for physicians
Acknowledgements

• Benjamin Steinberg
• Neil Goldenberg
• Norman Rosenblum
• James Rutka
• Andras Kapus
• Robert Chen
• Val Cabral

Funding

[Logos of various funding organizations]