Mijenja li se struktura medicinske literature: pogled jednog pretkliničara

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Current trends in scholarly communication in medicine

Mijenja li se struktura medicinske literature: pogled jednog pretkliničara

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Basic research – main challenges

- Is it waste of time and money
- Time consuming (particularly experimental biomedical research)
- Mass Production of Clinical trials, Systematic Reviews and Meta-analyses (Often Redundant, Misleading, and Conflicted)
- Difficult to publish (or to present in detail) obtained data (including negative results or replication studies)
- Pressure to publish: concern that most current published research findings are false
- Is basic science disappearing from medicine:
  - Do clinicians need their findings (are they interested in it)
  - Should clinicians be involved in basic research

Basic research – probability that a research claim is true

- study power and bias,
- the number of other studies on the same question,
- the ratio of true to no relationships among the relationships probed in scientific field.

A research finding is less likely to be true

- when the studies conducted in a field are smaller;
- when effect sizes are smaller;
- when there is a greater number and lesser preselection of tested relationships;
- where there is greater fl xibility in designs, definitions, outcomes, and analytical modes;
- when there is greater financial and other interest and prejudice;
- when more teams are involved in a scientific field in chase of statistical significance.

Simulations show that for most study designs and settings, **it is more likely for a research claim to be false than true**.

For many current scientific fields, claimed research findings may often be simply **accurate measures of the prevailing bias**.

Basic research - definition

All scientific research conducted at medical schools and teaching hospitals ultimately aims to improve health and ability.

Basic science research—often called fundamental or bench research—provides the **foundation of knowledge for the applied science that follows**.

This type of research encompasses familiar scientific disciplines such as biochemistry, microbiology, physiology, and pharmacology, and their interplay, and involves laboratory studies with cell cultures, animal studies or physiological experiments.

Basic science also increasingly extends to behavioral and social sciences as well, which have no less profound relevance for medicine and health.

Basic research - importance

Basic research can address clinical issues from a reductionist approach, including the discovery and analysis of single genes or genetic markers of diseases, or sequencing and manipulating genes.

Typically, basic science research focuses on determining the **causal mechanisms behind the functioning of the human body** in health and illness, and utilizes hypothesis-driven experimental designs that can be specifically tested and revised.

More recently, “systems biology” has focused on understanding how complex systems arise from elemental processes.

Once these **fundamental principles of the biologic processes are understood**, these **discoveries can be applied or translated into direct application to patient care**.

Basic research
absence of information

In the absence of information and insights generated from basic research,

- it is difficult to envision how future advancement in treatment of disease and disability will occur;
- physicians would increasingly be in the position of mechanics who do not know how engines work, or programmers who do not understand how computers store and compile information.

Basic research is also **a source for new tools, models, and techniques** (e.g., knockout mice, functional magnetic resonance imaging, etc.) that revolutionize research and development beyond the disciplines that give rise to them.

Translational research

Translational research is defined as

"the process of **applying ideas, insights, and discoveries** generated through basic scientific inquiry **to the treatment or prevention of human disease**",

sometimes abbreviated as

"**from bench to bedside**".

Translational research – new emphasis

1. **Political** - To demonstrate the tangible public benefit from the billions of dollars invested in scientific research, translational research is an easy sell—the testing of new treatments, vaccines, and diagnostic tests.
2. **A genuine need** – to facilitate and expedite the practical application of scientific discoveries.
3. **Increasing impatience** with the pace with which **basic scientific discovery has resulted in new products and cures**. For feared diseases such as cancer, AIDS, and Alzheimer's disease, progress toward prevention or cure has not been as rapid as many would like. Hence, some of the impetus toward translational research comes from an impatient public speaking through its political leaders, who are the ultimate source of support for most scientific investigation.
4. **Increased awareness** that **observations from animal models do not always precisely extrapolate to humans**. For this reason, more translational research in humans is believed to be essential, despite the complexities and logistical hurdles posed by such research.

Lost in Translation

Basic Science in the Era of Translational Research

- Discoveries pertinent to medical progress have **often come from remote and unexpected sources**
- Progress in the treatment of refractory diseases will be made as a result of **fundamental discoveries in subjects unrelated to those diseases**, and perhaps entirely unexpected by the investigator.
- Basic research is the **pacemaker of technological progress**.
- **New products** and new processes **do not appear full-grown**. They are founded on new principles and new conceptions, which in turn are painstakingly developed by research in the purest realms of science.

BASIC RESEARCH IS THE TYPE THAT IS NOT ALWAYS PRACTICAL BUT OFTEN LEADS TO GREAT DISCOVERIES.

APPLIED RESEARCH REFINES THESE DISCOVERIES INTO USEFUL PRODUCTS.

Lost in Translation

Basic Science in the Era of Translational Research

While there are powerful forces driving trend of translational research, **support for translational research**:

- must be accompanied by a **robust investment in basic science**,
- which **provides the essential raw material** for translation and continues to represent humanity's best hope to meet a wide range of public health challenges.

Lost in Translation

Basic Science in the Era of Translational Research

History has taught us that the path from basic discoveries to scientific and technological applications is seldom a straight line. **Marie Curie described how her discovery of radium**, which presaged the therapeutic use of radioisotopes, was purely serendipitous:
“When radium was discovered no one know that it would prove useful in hospitals. The work was one of pure science. And this is a proof that scientific work must not be considered from the point of view of the direct usefulness of it”.

More recently, we have seen studies of **insect embryogenesis lead to a revolution in innate immunity, resulting in innumerable applications in drug and vaccine development**. In her Nobel banquet speech, Christiane Nüsslein-Vollhard recalled her discovery of the Toll gene in Drosophila:
“We started out in our research with a deep interest in understanding the origin and development of pattern during embryogenesis. None of us expected that our work would be so successful or that our findings would ever have relevance to medicine”.

And when American Society for Microbiology member Carol Greider learned that she had been awarded the Nobel Prize for **her groundbreaking work on telomeres, which may lead to advances in the treatment of cancer or the amelioration of aging,** she emphasized the following:
“We didn't know at the time that there were any particular disease implications. We were just interested in the fundamental questions… [this] is really a tribute to curiosity-driven basic science” .

Her words require no translation.

Basic research by clinicians

NATURE | EDITORIAL

More surgeons must start doing basic science

They say they don't have the time or incentives to do research — and that’s dangerous for translational medicine.

21 April 2017

Basic research by clinicians

In Steven Soderbergh’s classy television show The Knick, set in a New York City hospital in the early 1900s, competitive and obsessively driven surgeon-scientists work on the burning medical issues of the day — identification of blood groups to allow blood transfusions, for example, and facial reconstruction surgery that returns dignity to those disfigured by syphilis.

Would-be healers have been testing surgical procedures since the Iron Age first delivered the necessary cutting tools. And the need for surgical advances remains. From the first heart transplant in 1967 to the emergence of deep brain stimulation and hopes for regenerative medicine, research is needed to transfer benchside discoveries to the bedside.

Basic research by clinicians

It is a problem, then, to find that surgeons are increasingly turning their backs on research. Evidence suggests that, compared with a decade or two ago, surgeons apply for and receive fewer grants, publish less, and — perhaps most perniciously — feel that research is not part of their role. Anecdotal reports suggest the trend is widespread, and not restricted to the United States — where it is best documented.

What is behind this dismaying trend?

In a survey conducted among academic surgeons in 2000, the majority of respondents reported a belief in the value of basic scientific research, even if they were finding that growing clinical and administrative duties hindered their success.

In a survey conducted among academic surgeons in 2015 more than half said that basic research was a priority in their departments — but just one-third said that it was realistic to expect surgeons to succeed in basic research. Most respondents said they had neither the time nor the motivation for research, and in any case lacked adequate departmental support and funding.

Nearly two-thirds believed that basic research among trainees should be limited to a select few residents with the ambition and talent to be successful in future research activities.

Basic research by clinicians

Transplantation and transplant immunology have always been dominated by surgeons, and these areas are set to embrace a future that includes regenerative medicine and possibly xenotransplantation (transplantation of tissues and organs from other species).

They are also much needed for crucial research into surgically treated diseases that only rarely hit the headlines — particularly in the correction of congenital birth defects, but also in adult disorders that rely on surgical skills, such as pancreatic cancers.

Involvement in research also allows surgeons to develop rigour in their everyday work, and to judge — and so maintain and improve — the quality of the work done by their peers.

The Rise and Fall of Basic Science

Scientists typically **direct their basic research according to internal drives** that are modulated by the scientific community.

The **preservation of independence of research among individual scientists** allows a wide coverage of the search field that is available to human research at a given time.

In basic science, individual investigators follow their intuition, knowledge, and creative thinking along fine-grained gradients, converging as a group toward the underlying principles of nature.

Public funding should aim to recognize those lines of research that promise to follow positive gradients.

The Rise and Fall of Basic Science

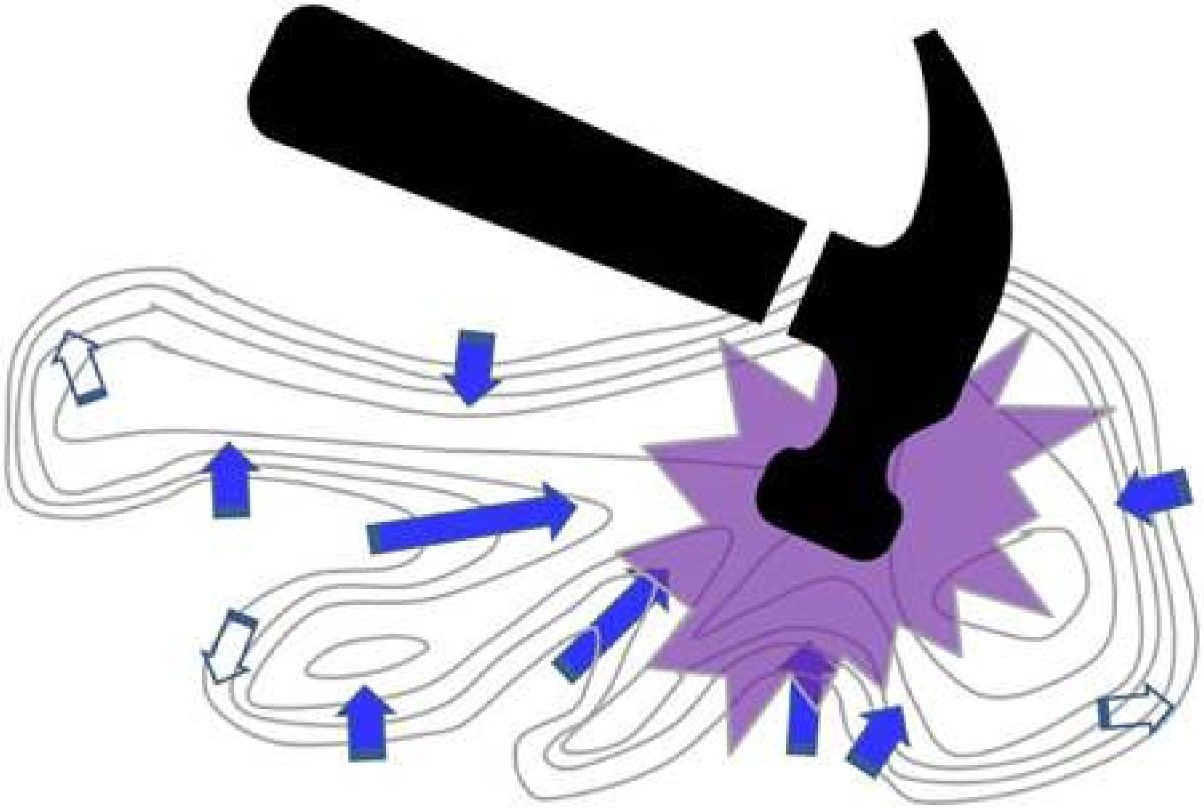
When you don't have a clue where to look for something you are interested in, such as cookies hidden in the kitchen, the best strategy may be a random search.

If that something can be remotely sensed by you, e.g., smelled, then your search would be facilitated by adding gradient-sensing—if the gradient over two or more samples taken along a path is positive don't change the path, if not—select another path (randomly).

This algorithm has been adapted by microbes while searching for food (known as chemotaxis)—it ensures that the microbes, as a community, would find any reachable food located in their vicinity.

The same algorithm appears to have **subserved scientific search for several centuries with a great success.**

The Rise and Fall of Basic Science



Individual investigators (arrows) follow their intuition, knowledge, and creative thinking along fine-grained gradients, converging as a group toward the underlying principles of nature—the centers of the contours. Public funding should aim to recognize those lines of research that promise to follow positive gradients (filled arrows).

Disproportionate top-down funding initiatives like the European Human Brain Project flagship, **symbolized by the massive hammer, <u>fail to recognize the value of individual research lines</u>** and threaten, upon impact, **to destroy the existing research fabric.**

The Rise and Fall of Basic Science

During the last years there is a trend that has gained increasing popularity among funding authorities.

The trend is characterized **by replacing independent scientific research with top-down directed focused search**.

Importantly, this trend started with projects that do not affect basic science, but it continues with projects that seriously threaten basic science.

Among the first precursors of this process were the human genome project at the US and the particle accelerator in Europe. In these projects the basic scientific principles (e.g., genetic codes and physical laws) were known, the path for scientific findings was clear and the only missing component was an intensive application of measurements.

This can be compared to the evolutionary path leading from chemotaxis to object localization; you know that the food is out there, you know how it feels and thus you can accelerate its localization by applying intensive measurements using high spatiotemporal resolution.

The Rise and Fall of Basic Science

However, the most salient recent example in this trend, the EC Human Brain Project “flagship” project, is totally out of this alley.

In this case **no principle** (e.g., neural codes, transformation laws) **is known** and **no scientific path has proven to be the right path** to the target—understanding the brain.

Thus, selecting a (any) single direction here has roughly **zero chance to hit the target**.

Thus, while “flagship” projects focusing on industrial directions make sense, there is no sense in similar projects aiming at basic science.

On the contrary, **it goes against the paradigm that proved to be successful during the last several centuries**.

THE **IMPRESSIVE PROGRESS** IN NEUROSCIENCE, RESULTING FROM THE ACCUMULATED GAINS OF THE FULL **SET OF INDIVIDUAL RESEARCHERS**, **COULD THUS BE AT RISK**.

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MICROCIRCUITRY OF HIGHER COGNITIVE FUNCTIONS

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