

# Poor Science; Poorly Trained Scientists; Poor Policies: Major Deterrents to the War on Cancer

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**Abstract:** Although the availability of funding has been described as the major limitation on advances in cancer, the progress in the war on cancer has been deterred mainly by poor science, poorly trained scientists, and poor NIH policies. This is the result of NIH policies of its extreme focus on molecular biology (genomics, molecular genetics, molecular biology) identification of the molecular factors and pathways; which are required for the acceptability of treatment and preventive protocols. As such, this has influenced virtually all agencies that provide grants for medical research to adopt the NIH policies. This has impacted the funding of the research as well as the focus of the training of scientists. Directors of NCI Dr. Varmus (also Nobel Prize awardee) and Dr. Zerhouni had addressed this issue; and they rejected the necessity of molecular biology studies and information. NIH should return to the holistic physiological/pathophysiological approach to studies of cancer issues. This would provide the best approach for winning the war on cancer.

**Keywords:** Cancer, NIH policies, training of scientists, excessive molecular biology, holistic physiological/pathophysiological approach.

## 1. INTRODUCTION

Of all the issues regarding the progress in the war on cancer, the issue that is rarely considered and discussed is the scientific and clinical quality of the funded medical research; i.e. “the return on the investment”. Five years following being Director of NIH (2002-2008), Dr. Elias Zerhouni [1] highlighted this issue that the *“Federal investment needs to be tied to the societal needs of the day. Otherwise you risk academic isolation, or living in some theoretical realm...Patients measure, better than anybody, the value of research...Any consideration of the value of research that does not take the customer into account is doomed. You’ve lost the debate if you lose sight of the taxpayers and the patients.”* This highlights the focus of this presentation.

He further identified that the dominant focus on “molecular biology” (which I will include molecular genetics, molecular signaling, and related areas) as a major issue. He stated *“We have moved away from studying human disease in humans. We all drank the Kool-Aid on that one, me included. With the ability to knock in or knock out any gene in a mouse—which can’t sue us, researchers have over-relied on animal data. “The problem is that it hasn’t worked, and it’s time we stopped dancing around the problem...We need to refocus and adapt new methodologies for use in humans to understand disease biology in humans.”*

This is a major issue in the 2004 article [2], “Why We’re Losing The War On Cancer (And How to Win it)”; which presents the following; *“a prevailing attitude exists that pushes tens of thousands of physicians and scientists toward the goal of finding the tiniest improvements in treatment rather than genuine breakthroughs... investigators rely on models that are consistently lousy at predicting success.”* The article reveals that PubMed identified 1.56 million published papers; largely on this circuitry and its related genes in hundreds of journals over the years. When including articles not listed in PubMed, this number is more than 2 million. PubMed also identified an extraordinary 150,855 experimental studies on mice... Open any major journal and 80% of it is mice or drosophila or nematodes...few if any having an impact on human cancer.

This dominance by NIH of its extreme focus on molecular biology has had a major impact on the training and background of the contemporary generations of clinicians and biomedical investigators, and on the training of future generations. However, it is abundantly obvious that these concerns have been largely rejected by NIH and the medical community. In 2009 and 2010 [3,4], I addressed some of these issues. Indeed, I had provided my article [4] to the office of the Director of NCI; to which I received a response that justified their policies and rejected my presentation. These adverse policies of NIH continue to expand, and the dominance of molecular biology funding and training of young investigators become more deeply rooted in today’s cancer research. It is imperative and in the best interest of the health and welfare of the public to address this critical issue.

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## **2. NIH POLICIES AND FOCUS DICTATE THE DIRECTION OF CANCER (AND ALL AREAS OF MEDICINE) RESEARCH AND THE TRAINING OF MEDICAL INVESTIGATORS**

In 1946, NIH instituted a subdivision (now represented by the Office of Extramural Research) with the responsibility to receive, review, and fund extramural medical research grant proposals (notably the R01 grants). This became the major source of funding for medical research. This dominance of NIH funding is accompanied by its determination to focus on the direction of nearly all funding of clinical and biomedical research. This transcends into the focus of graduate and post-doctoral training of young investigators. As such, generations of like-minded clinicians and investigators dominate the review and funding of research; the review and decisions of publications; and most importantly, they become the architects and supporters of the NIH policies.

### **3. NIH POLICIES THAT “NO LONGER FUND THE BEST SCIENCE BY THE BEST SCIENTISTS”**

For ~60 years since 1946, the policies and guidelines for the dedication of R01 funds for medical research were well described in the NIH 2010 report “*Enhancing Peer Review at NIH*” [5]. The face page states “*Fund the best science, by the best scientist...*”; and the *longstanding history of supporting the most promising and meritorious research*. The report further emphasizes that “*The excellence of peer review is directly correlated to our ability to recruit and retain the most accomplished, broad-thinking and creative scientists to serve on study sections... Peer review must consistently identify an application’s relative merit, potential for scientific and/or public health impact, and feasibility. Peer review should fairly evaluate proposals from all scientists, regardless of their career stage or discipline*”

I experienced these conditions by having received my first NIH grants in 1962, followed by 50 years of multiple funded grants; and having served on NIH study sections. These guidelines, policies, and dedications for the review and funding of R01 research grants had exceptionally served and benefited progress in medicine and the public welfare.

Unfortunately, a series of new and changing NIH guidelines and policies during the current and past ~20 years have largely abandoned and violated the commitments described above.

### **3A. R01 Funds are now Utilized for “New Investigator” Scientific-Inferior Grant Awards**

Beginning ~2009, NIH initiated new and pursuant policies [5] based on a “concern” that applications from New Investigators experienced a reduced success rates in receiving new R01 grants that started in FY 2003. This initiated the policy that *The NIH strongly encourages New Investigators to apply for R01 grants when seeking first-time NIH funding . . . For FY 2009, Applications from New Investigators will be clustered during initial peer review to the extent possible; and NIH intends to support New Investigators at success rates comparable to those for established investigators submitting new applications.*”

This goal has been achieved by a series of NIH policies that include: special favorable considerations and criteria for the study section review and scoring of the New Investigator R01 applications; special submission and review of revised New Investigator applications; New Investigator applications are funded at the 25 percentile, compared to 15 percentile for others; grant awards outside the pay line are given predominantly to New Investigator applications even after these special favorable considerations.

The consequences of these policies are: 1) the funding of New Investigator scientifically-inferior grant proposals that replace the funding of better science by better established scientists; 2) the introduction of prejudicial policies in the review process, and justification for overt and covert discrimination by the reviewers; especially targeted in favor of New Investigators and against established investigators; 3) the misdirected use of dedicated R01 medical research funds as a substitute for the training and development of New Investigators.

This violates the policies for the “Implementation Goals of the Committee on Enhancing Peer Review at NIH” [4] to:

*“Improve the Quality & Transparency of Review: Peer review must consistently identify an application’s relative merit, potential for scientific and/or public health impact, and feasibility.*

*Ensure Balanced & Fair Reviews: Peer review should fairly evaluate proposals from all scientists, regardless of their career stage or discipline ...”*

For more than 60 years, New Investigators successfully competed with established investigators

for R01 grant awards based on the same considerations regarding the scientific merit of the applications. Notably, the decline in the New Investigator success rate has occurred despite the availability of several NIH programs with substantial funding, which are dedicated for the training and development of New Investigators. Those programs apparently have been largely unsuccessful in remedying this issue. Rather than addressing the reasons for this problem, the NIH solution is to award scientific-inferior R01 medical research grants to New Investigators; to achieve the designated outcome of an equal number of grant awards for New Investigators and established investigators. I would add that this purported major problem for the supply of well-trained future investigators will have little adverse impact compared to other issues regarding their training.

NIH should abandon its ill-advised policies and should return to R01 funding of the best science by the best scientists. It is in the best interest of the medical community and the public welfare for the use of medical research funds for progress in the war on cancer.

### **3b. The dominance of “Molecular Biology and Molecular Biologists” and its adverse impact on the scientific quality of medical research and its clinical application**

Until the recent past ~25 years, human organ/systems physiology and pathophysiology; cell physiology and cell metabolism; and related disciplines were the focus of medical research. This represented an integrated holistic approach and understanding of the normal and clinical implications in medical disorders, and their prevention and treatment. Since then, the onset and rapid progression of molecular biology and molecular technology became the new frontier of medical research; and was hailed as the direction that will best lead to the identification, prevention, and treatment of cancer and other medical disorders.

As recognized by Dr. Zerhouni above, the molecular biology hasn't worked, and we need to refocus on methodologies for use in humans to understand disease biology in humans [1]. In fact, NIH no longer adheres to its recognition that *“The excellence of peer review is directly correlated to our ability to recruit and retain the most accomplished, broad-thinking and creative scientists...”*; which is in direct conflict with its extreme focus on molecular biology.

I must acknowledge that the molecular technology and progress in molecular biology have provided the opportunity to study and identify organ system and cell physiological and pathophysiological relationships, which previously could not be addressed. When applied appropriately, molecular biology becomes an indispensable essential discipline to be integrated into the holistic understanding of the normal and dysfunctional operation of the human body. As such, I have employed such technology and information in many of my studies. Unfortunately, this has not been inculcated in the thinking and research of the vast majority of molecular biologists and their studies. Instead, the molecular biology and molecular technology interest has become an end unto itself, the *raison d'être*; and “the tail wagging the dog!”

Dr. Sidney Farber, Nobel Prize awardee and a past Director of NIH, had earlier testified in congressional hearings *“We cannot wait for full understanding; the 325,000 patients with cancer who are going to die in 1971 cannot wait (compared to 595,690 in 2016);... nor is it necessary, in order to make great progress in the cure of cancer, for us to have the full solution of all the problems of basic research. The decades, and even centuries before the mechanism of action was understood for these cures—from vaccination, to digitalis, to aspirin”*.

For several untreatable cancers (for example: pancreatic cancer, liver cancer, and advanced prostate cancer), the >70-80% death rates and ~6% 5-year survival rates have not improved over the past 25 years. The contemporary emphasis and dominance on molecular biology is the ultimate condition that represents the deterrent to progress in the war on cancers.

## **4. POORLY TRAINED SCIENTISTS: THE MAJOR DETERRENT TO PROGRESS AGAINST CANCER.**

When Dr Zerhouni identifies that solving the puzzle of complex diseases will require the application of systems biology and holistic understanding, he has recognized that the dominance on molecular biology is a deterrent [1]. Similarly, Dr Varma's comment that great progress in the cure of cancer does not require the full identification of molecular events resolution; especially as represented by the adverse impact of the contemporary dominance of molecular biology. When NIH recognizes that the progress in medical research is directly dependent on broad-thinking scientists; and then violates this requirement, reveals its dedication to

the dominance of its focus and support of molecular biology.

Consequently, of all the conditions described as deterrents to progress in cancer other disorders, poorly trained scientists pose the major and fundamental issue that must be addressed. However, it is the most difficult to address since it involves deficiencies that exist in most contemporary biomedical investigators.

#### **4.1. Training of “Holistic, Broad-Thinking Scientists”**

The holistic approach had been achieved by focus on integration of physiology/pathophysiology and cellular metabolism; along with adjunct areas, such as anatomy, genetics, embryology. The “specialty interest and research training” was then integrated into the relevance and implications at the relevant physiological and pathophysiological approach. This training resulted in the development of “holistic, broad-thinking scientists”

#### **4.2. Current Training of “Highly Specialized Researchers” and “Supertechnologists”**

In my view, the contemporary training programs produce highly specialized “researchers” and “supertechnologists” with limited knowledge and capabilities to integrate their research into the holistic human physiological/pathological relationships. The focus of the training programs has become the major role of the trainees to plan and conduct dedicated experiments in molecular biology to advance the existing molecular biology research program of their Program Director.

More than any other factor, this training has been changed beginning about 1990, by the progress in technology and research in the molecular biology areas; which led to its extreme dominance of medical research, and the NIH focus for R01 grant awards. This new frontier was hailed as the direction that will best lead to the identification, prevention, and treatment of medical disorders. The contemporary infatuation with molecular biology accompanied with the major advances in molecular technology subverted and diminished interest and application of the holistic integrated disciplines.

These contemporary molecular biologists have dominated the decisions and focus of medical research. As such, grant proposals are dominated by molecular biology research; study sections are

dominated by molecular biology interests; and the outcome of the funding of medical research is dominated by molecular biology.

Of the more than 2 million published reports of such molecular biology studies; very few, if any, have led to the efficacious regimens for the prevention and treatment of cancer. This dominance of research funds and resources has been at the expense of funding of organ/system and cellular physiological, pathophysiological, and metabolic studies: which is due largely to NIH leadership.

#### **4.3. Training of Medical Scientists and their Responsibilities**

The training of scientists should include other important components. Scientists must be trained as “thinkers”; and as currently emphasized in the medical sciences, must be encompassed in “evidence-based medicine”. The latter requires the understanding of science and the scientific method. Such capability is lacking in contemporary biomedical graduate and post-doctoral programs.

It is essential to have an appropriate understanding of the scientific method and its application in developing and conducting the required studies, applying statistical application, interpreting the data, and reaching conclusions. An understanding of empirical versus rational approaches in relation to the scientific method is important. It is then essential to translate their observations at the holistic physiological and pathophysiological consequences. These are examples of developing the scientific mind. This is also essential to apply to the investigators who review and evaluate the appropriateness of the studies of others.

In my experience, aspiring young scientists appreciate and become involved in such discussions; which would never have been inculcated into their thinking. At most, this would take but a few hours from their training program.

The scientific method provides the evidence that leads to the identification of the physiological and pathophysiological principles and relationships, which are applied for the diagnosis, prevention, and treatment of medical disorders; and which “transformed medicine from an art to a science.”

This is described mainly by Claude Bernard (the “father of modern physiology”) in his book “An Introduction to the Study of Experimental Medicine” first

published in 1865 [7]. Bernard also describes the role and obligations of the scientist. He emphasizes that: *“The theories which embody-our scientific ideas as a whole, should serve as a basis for new ideas. But as these theories and ideas are by no means immutable-truth, one must always be ready to abandon them, to alter them or to exchange them as soon as they cease to represent the truth. If men discuss and experiment to prove a preconceived idea in spite of everything, they no longer have freedom of mind, and they no longer search for truth.”* This is extremely relevant to the issues presented herein; and these attributes should be incorporated into the training of all medical and life sciences investigators as “medical scientists.”

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