Discarding Logic: 2008 Ancel Keys Memorial Lecture

Michael S. Lauer

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Special Report

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Michael S. Lauer, MD

Thank you. The comments I am about to make are my own personal views. They are not the views of the National Heart, Lung, and Blood Institute or the US Department of Health and Human Services. I have no conflicts of interest to disclose.

There once was a king who had 2 servants.[1] One day, he asked the servants to take buckets down to the well, which was located just outside the palace. He told them to draw water into the buckets and bring them back to him. The loyal servants did exactly as they were told, but when they reached the well, they noticed something rather strange. The buckets the king had given them were porous, full of holes. The first servant said, "The king must have made a mistake. It makes absolutely no sense to me why I should draw water into a porous bucket. I won't do it." The second servant said, "I agree that it does not make sense, but nonetheless I will do as the king asked." The servant drew water into the bucket, and sure enough within a few minutes all the water had drained out. When the servants returned to the king, he asked them whether they had carried out his orders. The first servant explained that he discovered holes in his bucket, and logic dictated to him that he should disobey the king's order. The second servant admitted that he too felt that it logically made sense to disobey the king's order, but he nonetheless drew water into the bucket as he was told. The king looked at the second servant and said to him, "You did right. You see, what I wanted was for you to clean my buckets."[1]

This is a story that was told over 2000 years ago. Yet, the lesson from the story is one that has plagued people throughout history. As powerful as human logic is, often it misleads us. Perhaps no area of human endeavor better illustrates the failings of human logic than modern biomedical research.

I am deeply honored to be given the opportunity to deliver the 2008 American Heart Association Ancel Keys Lecture. This honor is a testament to the many blessings that have been bestowed on me, most especially the chance to learn from and work with many outstanding people in several outstanding institutions. Over the past 30 years, I have studied and worked at institutions with long and proud histories, including Rensselaer Polytechnic Institute, Albany Medical College, Massachusetts General Hospital, Boston's Beth Israel Hospital, the Harvard School of Public Health, Lahey Clinic, Cleveland Clinic, and now the National Heart, Lung, and Blood Institute. I am grateful to the American Heart Association, another organization with a long and proud history, not only for bestowing me with this award but for providing me with my first competitive research grant. Like many investigators, a grant from the American Heart Association was my first big break.

This lecture is named after the great Ancel Keys, a major historical figure in modern cardiovascular prevention research. One might wonder why lectures like this are often named after historical figures. A simple explanation is that the organization wishes to honor the memory of a great person. True, but I think that there is a deeper message, namely recognition that we scientists should pay close attention to the lessons of history.

In many respects, biomedical science is inherently antihistoric. Nothing makes a scientist happier than to debunk conventional wisdom or to make a discovery that is truly novel. Sometimes, we think about the history of medicine and biomedical science with whimsy. Talk about the history of medicine, and this brings up images of long-discredited practices like bloodletting, leeches, snake oil, and drinking 8 glasses of water a day. Surely, we must be beyond all that. The 20th century saw the rapid rise of science as a basis for medical practice, so why should history be anything that we should care about?

It is true that the advent of medicine as a scientific field must be appreciated as a great historical movement. During the past 200 years, there have been incredible advances in medical practice, many of which were grounded in systematic scientific observations. Anesthesia, antisepsis, hand washing, antibiotics, public sewage, and vaccinations all led to dramatic improvements in health. Virtually all of these grew from observations, not logic or theory; the genius of the inventors was to note the observations and ask why.

Within our field of chronic disease prevention, we can proudly point to a number of successes, including the discovery of the link between smoking and disease,[2,3] the discovery that pharmacological treatment of high blood pressure substantially reduces the risk of stroke and heart attack,[4,5] the

From the Division of Prevention and Population Sciences, National Heart, Lung, and Blood Institute, Bethesda, Md.

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Correspondence to Michael S. Lauer, MD, FACC, FAHA, 6701 Rockledge Dr, Room 10122, Bethesda, MD 20892. E-mail lauerm@nhlbi.nih.gov

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discovery that aspirin reduces the risk of heart attack in older men,[6] and the discovery that administration of statins to people with elevated cholesterol levels reduces the risk of cardiovascular disease events.[7] Another major historical advance was the discovery of the value of screening, the use of noninvasive diagnostic tests for discovering asymptomatic disease well before it has a chance to cause clinical problems. We have demonstrated that a number of screening tests save lives; these include mammography,[8] fecal occult blood testing,[9,10] and within our own field of cardiovascular medicine, measurement of blood pressure and ultrasound imaging of the abdominal aorta.[11]

Unfortunately, our history also includes a number of failures, including antioxidant vitamins,[12] beta carotene,[13] postmenopausal hormone replacement therapy,[14] and antiarrhythmic drugs for the prevention of sudden cardiac death.[15] There have been prominent failures in other areas of medicine. Think about autologous bone marrow transplantation for metastatic breast cancer,[16] steroids for sepsis,[17] and episiotomy for childbirth.[18] What is common about these failures is that these are instances in which logic, not observation, was the driving force. Randomized trials were needed to discard logic.

These successes and failures constitute a small part of the recent history of "scientific medicine." Is there value in thinking of the successful and unsuccessful treatments as components of history? Why should we, as modern biomedical scientists, care about history as we go about solving the problems of the present?

I recently came across a fascinating essay by the renowned historian David McCullough, who delivered the 2003 Jefferson Lecture in the Humanities in Washington, DC.[19] McCullough wrote award-winning biographies of John Adams, Harry Truman, and Theodore Roosevelt. In his lecture, McCullough quoted Lord Bolingbroke, an 18th-century political philosopher, as defining history as "philosophy teaching by examples."[19] Thomas Jefferson "saw history as largely a chronicle of mistakes to be avoided."[19] McCullough then went on with an intriguing insight. "One might also say that history is not about the past. If you think about it, no one ever lived in the past. Washington, Jefferson, John Adams, and their contemporaries didn't walk about saying, 'Isn't this fascinating living in the past! Aren't we picturesque in our funny clothes?' They lived in the present. The difference is it was their present, not ours. They were caught up in the living moment exactly as we are, and with no more certainty of how things would turn out than we have."[19]

We can say the same for the many biomedical scientists who preceded us in trying to figure out how best to prevent chronic disease. For the scientists and physicians who hypothesized benefits from antioxidant vitamins,[12] antiarrhythmic drugs,[15] postmenopausal hormone replacement therapy,[14] and beta carotene,[13] there were extensive reasons for optimism. There were sound mechanisms based on solid basic biological science. There were robust findings derived from large epidemiological cohort studies. The logic was strong. Yet, when the trials were done, the therapies failed.

The great American humorist Mark Twain once said, "Supposing is good, but finding out is better."[20] "Supposing" in biomedical prevention research means learning from experiments performed in the laboratory and from careful observations in epidemiological studies. "Supposing" is good, but it is not great, it is not a basis for defining standard practice or policies for public health. For that we need "finding out." And "finding out" means large-scale, robust, controlled trials that focus on the ability of the strategy to prevent major clinical events. This is exactly what happened for each of our major successes: pharmacological treatment of high blood pressure[4] and high cholesterol,[7] aspirin prophylaxis,[6] and screening for certain types of cancer[8] and aortic aneurysm.[11] And, if we think about some of our failures, the same process happened. There were outstanding hypotheses, but courageous scientists proceeded to test them with robust clinical trials, only to find out that their hypotheses were wrong. So, in a way, these failures were actually successes! Because the trials were done, we spared the public from treatments and strategies that either do not work or may be actually harmful.

In today's present, we face a major controversy within cardiovascular medicine on the value of screening for coronary artery disease with noninvasive imaging such as coronary calcium measurements.[21] As Mark Twain would say, "The supposing is good." There is ample biological and epidemiological evidence to suggest that measurement of coronary calcium in asymptomatic adults may lead to clinical benefit. The logic is very strong, but at this point, it is only supposing.[22] The trials have not been done to determine whether a screening strategy for coronary calcium would lead to the same kind of benefits as screening for breast or colon cancer. We have not even seen trials in which an intervention was based on the results of a screening test, that is, not until just now with the recent release of the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) results, which indicated that persons with normal low-density lipoprotein cholesterol but elevated C-reactive protein experience markedly reduced cardiovascular morbidity and all-cause mortality when treated with a statin.[23]

Absence of definitive trials has not stopped a number of people in our field from vigorously promoting coronary calcium as ready for incorporation into routine standard medical practice.[24] The so-called Screening for Heart Attack Prevention and Education (SHAPE) "guidelines," calling for routine measurement of coronary calcium in virtually all middle-aged and older adults, were written in 2006[25] and have even been endorsed for inclusion in reimbursement legislation in at least 1 state.[24]

Simply stated, we do not know whether screening with coronary calcium will prevent clinical events or improve public health. There is only 1 way to find out, and that is by performing appropriate controlled clinical trials. History should teach us that logic alone cannot be relied on, no matter how strong the basic science or epidemiological evidence is. How many more times are we going to ignore history and "get burned?"

But wait! Isn't it blatantly logical that screening is good? Coronary artery disease continues to be the number 1 killer in our country, and we know that many among us are walking around with asymptomatic disease, disease that is waiting to strike. Yes, it is true that clinical trials were performed to

assess the value of other screening tests like mammography,[8] fecal occult blood testing,[10] ultrasound imaging of the abdominal aorta,[11] and now most recently high-sensitivity C-reactive protein.[23] And right now, the National Cancer Institute is in the follow-up phase of the National Lung Screening Trial, a massive 50 000-patient trial determining whether computed tomography screening for lung disease can prevent premature deaths.[26] Why is it necessary to hold coronary calcium to the same high standard?[24] Isn't this 1 case when "supposing" is good enough, when we can completely rely on logic?

The only honest answer can be, "We don't know." There has been extensive work showing that screening can be harmful.[27] By converting a person who thinks he is healthy into a patient, the medical profession causes a meaningful decline in quality of life. This has been well demonstrated, for example, in the case of the diagnosis of hypertension. There are other harms as well, such as subjecting people to unnecessary tests with attendant radiation exposure, anxiety, and procedures. This is exactly what happened when mass screening was instituted in several places around the world for early diagnosis of neuroblastoma, a serious cancer in children. In both Germany[28] and Canada,[29] mass screening led to more cases of neuroblastoma diagnosed (no surprise), more surgeries to remove neuroblastomas (again no surprise), but also no reduction in deaths from neuroblastoma. If screening was working, removing all those neuroblastomas at an early stage should have reduced death rates. But that did not happen. Why not? Perhaps because the technology was diagnosing "pseudodisease," that is, disease that was unlikely to cause clinical problems.[30] Like many other diseases, including coronary artery disease, neuroblastoma exists on a spectrum from subclinical and benign to deadly. It appears that our imaging technologies are highly sensitive for detecting disease but not for detecting the kind of disease that will kill if not treated early.[30]

It is interesting how coronary artery screening is being promoted. It is widely advertised in the media, especially when a celebrity dies or has a heart attack.[31] Lobbyists are pushing it in state legislatures.[24] The late Senator Paul Simon from the state of Illinois became an advocate for coronary calcium screening after he had a strongly positive scan, one that led to coronary artery bypass surgery. Senator Simon said, "Without the heart scan I was headed for serious stroke or heart attack. So now I am an evangelist for older people and those with a genetic inclination for heart trouble to get a heart scan."[32] He became an evangelist. Coronary artery screening is being promoted in the media, in politics, and even in the language of religion.

As many of you know, I am a religious person and place great value in faith. In the course of examining religious texts in preparation for this lecture, I came across a discussion among the ancient rabbis who, as recorded in the Babylonian Talmud, were arguing about the therapeutic value of amulets in animals.[33] In the course of discussing whether amulets deemed to be effective in humans could be used in animals, the question came up as to whether such a case could even exist. Wasn't it absolutely logical that if an amulet works and can cure disease in humans, it for sure would work in animals? In fact, the rabbis noted, there can be cases in which something that works in humans will not work in animals, perhaps because humans know that they are receiving treatment, what we might refer to today as the placebo effect. The conversation then shifted to determining how one knows whether an amulet is therapeutically effective. The answer given is that one must observe a complete cure in at least 3 people. This fascinating discussion occurred among religious men, not men of science and certainly not men of medicine. And yet, they recognized that ascertainment of therapeutic benefit is not a matter of faith or logic but rather depends on active experimentation and replication. Even for the rabbis of the Talmud, faith does not supplant the value of experimental evidence.

Fast forward 2000 years. One of the great successes, although only a partial one, of 20th-century medicine is the advent of "evidence-based medicine." An excellent description of the evidence-based movement was given by Drs Richard Deyo and Donald Patrick from the University of Washington School of Medicine. They wrote, "The evidence-based approach argues that it isn't enough to know that a particular treatment ought to work, that it makes sense, that it's common practice, that we learned it in medical school, that we've always done it that way, that an expert vouches for it, or that it works in mice. Even further, this approach says that it's nice, but not enough, to know that treatment lowers blood pressure, improves cholesterol, normalizes heart rhythms, or has similar physiological benefits. The newer evidence-based approach asks instead, what's the best evidence that a new treatment actually extends lives or improves quality of life, and what are the risks? Advocates of evidence-based medicine argue that the best evidence available to answer questions about effectiveness comes from multiple randomized controlled trials. When these aren't available, we still have to make clinical decisions, but they're based on less rigorous information and may be prone to error."[34]

There are 2 critical elements, I think, to the success of evidence-based medicine. First, we recognize the limitations of human logic. We have seen plenty of times when the basic science evidence was strong, when observational epidemiological observations were consistent and seemingly robust, yet careful experimentation by means of randomized controlled trials demonstrated otherwise. Second, we recognize that in nearly all cases the only way to know whether a treatment or strategy is worthwhile is by performing controlled trials. Yes, there are a few exceptions when randomized trials were not needed to demonstrate causal associations between exposures and outcomes; we did not need trials to link diethylstilbestrol with clear cell carcinoma or smoking with lung cancer or to require working parachutes for sky jumpers.[35] But, these exceptions are cases when effect sizes are huge—hazard ratios well above 10, even 100, 200—cases that are very rare. Nearly all interventions we are currently considering have modest effect sizes, if they have any; therefore, the requirements for evidence-based medicine hold. When we fail to follow the 2 components of evidence-based medicine, acknowledging the limitations of human logic and insisting on the performance of robust large-scale

trials, we open ourselves up to serious and arguably wholly justified criticism.

Unfortunately, coronary artery screening is not the only area of preventive medicine in which policies or standards of care have been promoted in the absence of evidence from robust large-scale trials. Many of you, I am sure, are familiar with the pointed criticism of Gary Taubes,[36] a well-known award-winning print journalist. In his recent book *Good Calories, Bad Calories: Challenging the Conventional Wisdom on Diet, Weight Control, and Disease*, a detailed critique of obesity research, Taubes writes, "This is how functioning science works. Outstanding questions are identified or hypotheses proposed; experimental tests are then established either to answer the questions or to refute hypotheses, regardless of how obviously true they might appear to be. If assertions are made without the empirical evidence to defend them, they are vigorously rebuked." He then goes on to write, "Practical consideration of what is too loosely defined as the 'public health' have [sic] consistently been allowed to take precedence over the dispassionate, critical evaluation of evidence and the rigorous and meticulous experimentation that are required to establish reliable knowledge. The urge to simplify a complex scientific situation so that physicians can apply it and their patients and the public embrace it has taken precedence over the scientific obligation of presenting the evidence with relentless honesty."

If we think about the history of preventive medicine, we have a number of successes we can point to in which the requirement to develop evidence with relentless honesty led to improved public health. In some cases, the hypotheses turned out to be true. Pharmacological lowering of blood pressure prevents strokes and heart attacks.[4,5] Lowering cholesterol levels with statins prevents heart attacks and other major clinical events.[7] Screening for breast cancer,[8] colon cancer,[9,10] and abdominal aortic aneurysm prevents premature death.[11] In other cases, the hypotheses were refuted. Antioxidant vitamins,[12] beta carotene,[13] antiarrhythmic drugs,[15] and postmenopausal hormone replacement therapy[14] do not improve health. But all of these cases, whether the original hypothesis turned out to be true or false, were scientific successes. The process of science took us beyond just supposing to actually finding out.

Beyond cardiology and preventive medicine, the focus of healthcare debates has shifted to unsustainable cost increases, so much so that if current trends continue, 100% of all government expenditures in 2040 will go to health care.[37,38] Policy makers and many politicians have identified advances in technology, especially diagnostic technologies like coronary calcium scanning, as the major driver of cost increases.[39] They note that there is little, if any, evidence showing that newer technologies lead to substantially better patient outcomes or public health. There is evidence that one third or more of health care is wasteful, unneeded, or even harmful.[40]

On Capitol Hill, there is a vigorous debate about establishing a special entity devoted to comparative effectiveness research, research that aims to figure out how we ensure that the right treatments are being given to the right patients under the right circumstances.[37,41] Some supporters of comparative effectiveness legislation foresee a "learning healthcare system"[42,43] in which sophisticated, electronically derived observations of treatments and outcomes will enable rapid development of guidelines and policies without the need for large-scale robust controlled trials. We in cardiovascular medicine and cardiovascular prevention have to watch this debate closely and become actively engaged in it. Yes, electronic medical records may make it possible to make high-quality epidemiological observations faster and to generate the right hypotheses, but information technology cannot negate a fundamental tenet that we should have learned from history: To make the right judgments about optimal practice and public policy, we almost always need to perform robust, controlled trials that test the impact of interventions or policies on hard clinical end points.

Much of the Capitol Hill debate focuses on clinical practice, but we in cardiovascular prevention also focus on public policy. Should we have a public policy that favors screening for coronary artery disease with coronary calcium tests?[21] Should we, as a matter of policy, largely on the basis of observational studies and relatively small surrogate-outcome trials, favor 1 kind of diet over another? Should we advocate a certain level of moderate to vigorous physical activity? Should risk stratification be the bedrock for targeting specific patients or populations? When we allow observational findings to dictate public policy, we institutionalize a societal value and make it difficult (some would say unethical) to obtain proper trial evidence and to change ingrained beliefs. We need to have an even higher standard for what is enthroned in public policy.

I am sure that most of you are familiar with the quote of the Spanish philosopher George Santayana, who said, "Those who cannot remember the past are condemned to repeat it."[44] We typically think of this relative to political or military history. In the modern biomedical world, with the advent of scientific, evidence-based medicine, I think we should engage this idea in a positive way. When we do accept the fallibility of human logic and when we have the discipline to require evidence from large-scale robust controlled trials, we accomplish great things. We must appreciate that the essential lesson of history is not limited to determining the value, or lack of value, of a particular therapy, intervention, or public policy, but the categorical imperative of basing them on strong experimental evidence whenever possible. Those of us who succeed and learn the lessons of history are bound not only to repeat them but to benefit from them. "Supposing is good, but finding out is better."[20] Let us proceed.

Disclosures

Dr Lauer is an employee of the National Heart, Lung, and Blood Institute, National Institutes of Health.

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