

Ancel Keys Lecture

The Three Beauties Bench, Clinical, and Population Research

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The Three Beauties of Biomedical Research. Gaze on them admiringly:

**“The baroque beauty of biology,”¹
The modern beauty of the clinic,
The classic beauty of epidemiology!**

Ponder their individual missions: the search for universal truths and specific mechanisms at the bench; for unique phenomena, their causes and cures in the clinic; and for mass phenomena, their causes and prevention in the population at large. Seek to preserve each, that all may flourish! (*Circulation* 1992;86:1323–1331)

Ancel Keys made pioneer contributions to the basic concept of population causes of cardiovascular diseases (CVD).¹ The first lecturer, Geoffrey Rose of London, elaborated the rationale for population strategies of CVD prevention.² I want to develop further those concepts and address the pervasive influence of two views of disease—the population view and the individual view—on the thinking and activities in CVD research, policy, and practice. I propose that a narrow focus on the individual accounts for most of the professional misunderstanding and public confusion about preventing cardiovascular and other mass chronic diseases. I also will dwell on how these two views affect biomedical research in general and epidemiology and prevention in particular. To begin, I borrow from the insights of Charles Dickens in *A Tale of Two Cities*: “It was the best of times, it was the worst of times . . .,” and suggest that this may be as true today for CVD epidemiology as it was for life in 18th century London and Paris!

The Best of Times

It is the best of times when medical science can predict the risk of cardiovascular events, identify those persons at high risk, and provide clear strategies for reducing that risk; when there is strong and congruent evidence that modifying risk characteristics can reduce CVD risk in high-risk individuals and in whole populations; when the goal of prevention extends beyond high-risk individuals to the entire population and, eventually, to the prevention of elevated risk in the first place.

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

¹Term coined by Dr. Donald Fredericksen when Director of the National Institutes of Health.

It is the best of times when an informed populace demands health information, preventive services, and healthier products and environments and leadership is responsive to the demand; when death rates fall dramatically, indicating the dynamic nature of CVD processes and providing impetus to prevention research, policy, and interventions; when medical and social forces join enthusiastically in the control and prevention of elevated blood pressure and blood cholesterol levels, it is socially unacceptable for physicians to smoke, and the cultural climate evolves rapidly toward supporting healthy behaviors.

It is the best of times when the National Institutes of Health (NIH), the American Heart Association (AHA), and other health agencies establish clear policy, set goals, monitor progress, and support a broad strategy of preventive research and programs in CVD prevention.³

The Worst of Times

But it is also the worst of times when there is a major opportunity and need for research and programs in CVD prevention among many segments of society and when these are nowhere near a high government priority; when biomedical research and development, one remaining area of acknowledged national excellence and source of jobs and economic stimulus, is not among the highest government priorities; when the accelerated costs of doing research and administering programs are entrapped in a linear NIH budget, and the proportional annual increments for the National Heart, Lung, and Blood Institute (NHLBI), the leader of NIH in planning and strategy for prevention, are substantially diminished.

It is the worst of times when the long touted and essential balance of NIH research and program strategies is threatened by competition for resources and by a certain elitism about what is exciting and important in science, and “the baroque beauty of biology” threatens its counterpart, the “classic beauty of epidemiology.”

Contributions of Epidemiology

As a background to understanding, let us recount what epidemiology contributes, as a major research

method and as the basic science of prevention, to the scientific community, to preventive practice, and to the public health.

First, epidemiology is both a basic and applied science; it rigorously explores questions without an immediate application as well as addressing pragmatic issues in practice and public health.

Epidemiology contributes the evidence about population differences in disease rates and risk and documents their dynamic changes. This provides the prime evidence that mass cultural phenomena are the main determinants of population risk. This is the central fact that leads to the strong possibility of CVD prevention in whole populations.

Epidemiological monitoring offers the basic descriptors of CVD in the population—of secular changes in deaths outside and inside hospitals, of short- and long-term survival, of hospitalization and incidence rates, and of trends of cardiovascular diagnosis, classification, treatment, and care. It measures the distributions of population risk factors, their behavioral counterparts, and their changes over time. Epidemiological surveillance seeks to explain the contributions to changing CVD death rates of lifestyle changes and medical advances, and it helps predict future disease trends.

The CVD risk factors themselves are a major contribution of epidemiology to preventive practice in primary and secondary prevention through simple classifications of relative risk, evidence unobtainable from clinical studies. Furthermore, epidemiology gives estimates of the absolute risk for individuals within a class and of the proportion of excess cases in the population attributable to single and combined risk factors, indicating thereby the potential effect on public health if the risk factors were controlled.

Epidemiological studies of pathology confirm at autopsy the findings about risk factors among the living. They show the necessity that atherosclerosis be severe and widespread in a population for there to be a major population burden of CVD.

Epidemiology offers rigorous design and analysis for the observational and experimental studies crucial to causal inference in medicine. It provides clinicians with useful tools such as sensitivity, specificity, and predictive power along with biostatistical methods for clinical researches. It offers insights, training, and skills in areas little addressed by medical education, including scientific criticism of the literature, research design, and analysis and a broad population and public health view of the causes and prevention of disease.

Epidemiology offers “tracking” techniques that establish the precursors of atherosclerosis in youth, when they are amenable to early intervention. It provides innovative methods, including institutional and community-based trials, which bring the strength of individually randomized trials to preventive interventions in whole populations. It devises new methods, such as “postal surveys” and “mail-order trials,” that can rapidly and inexpensively generate and test new hypotheses of cause and prevention among large samples of the population.

Epidemiology provides clues to disease mechanisms and thereby stimulates whole new areas of bench and clinical science—in a healthy, continuous “to-and-fro” from the population observation, to the laboratory, to

the clinic, and back again—the essence of Ancel Keys’ concept of physiological hygiene! There is, in fact, no predicting which of the three major research methodologies—clinical, laboratory, or epidemiological—will produce the next major stimulus to medical research or to the public health. The disciplines and approaches are complementary and synergistic. They may at times reverse their usual roles with results that “directly benefit people” or that are “value free.” For these reasons, balance is needed among these research methods: balance in thinking, in responsibility and influence, and in fiscal support.

No less important than these direct contributions is the indirect role that epidemiological research plays in driving health policy and NIH funding, influencing the delicate relationship among Congress, the NIH, and the scientific community. So-called “basic research,” the presumably “value-free” scientific quest for truth without regard to applications, often comes under public attack. NHLBI directors have come to appreciate that epidemiological studies, prevention trials and demonstration projects in whole communities, and risk factor control programs among the public give them the happy opportunity to “point with pride” toward many practical outcomes of NIH research for the people. For example, prevention and control programs for hypertension and hyperlipidemia and health promotion programs in patterns of eating, exercise, and smoking are now in the federal mandate for NHLBI. All these programs are seen by Congress to directly benefit people. Epidemiological and prevention research serve a critical role to justify, preserve, and deflect criticism from “pure science” and the pursuit of mechanisms, that aspect of NIH research so highly valued by the scientific community.

Finally, epidemiology provides the sound basis for an effective and responsible public health policy, a policy based on the best available evidence at any given time. Often, it is the epidemiologist who is called on to synthesize the evidence derived from all the major research strategies, to point out its public health implications, and to formulate policy recommendations.

For all these reasons, it is increasingly important that the medical community, having as its primary mission the care of patients, and academia, concerned mainly with mechanisms, understand better the major contributions of epidemiology in the context of the rapidly changing picture of CVD. It is essential that academic leaders understand epidemiology as a necessary and complementary discipline and that they support the goals of prevention research and policy irrespective of their personal interest or participation in such undertakings. Often the sole “epidemiological type” among 20 or so members of the NHLBI Advisory Council, I find that this much understanding is essential to the proper exercise of judgment and power, the power that clinical and bench investigators derive from their numbers and status in the advisory function and direction of our research institutions. The natural tension between the views and motivations of bench and clinical investigators on the one hand and population investigators on the other is tolerable when it occurs within a framework of mutual understanding—that the three main research methods are complementary and equally necessary—and where competent peer review exists for each disci-

pline, where appropriate expertise is placed in policy-making positions, and where funding is balanced between the disciplines. Only under these conditions can leaders negotiate appropriately and fairly about what is “good science” and what research needs to be supported.

When funding judgments, increasingly made at high levels, go beyond, or counter to competent peer-review, whether driven by budgetary restrictions, derived from “formulae,” or based on some ideology or “natural law,” then questions must be asked—and redress of balance sought.

Controversy About Epidemiology and Prevention

Let me develop further some of these issues that render our times so difficult. Undoubtedly, part of the controversy about prevention is due to insufficient evidence. But I suggest that most of the scientific misunderstanding has to do with fundamental differences in intellectual orientation, the one toward the individual and the other toward the population. For example, there is confusion about the associations found among populations versus those among individuals, assuming that causation is established a priori by congruent evidence. Dietary salt intake distinguishes populations sharply in regard to the frequency of adult hypertension but not individual risk. Dietary saturated fatty acid intake almost perfectly predicts population frequency of CHD but not individual risk. Average high density lipoprotein cholesterol levels distinguish effectively individual risk of CHD but not population risk. These discordances illustrate the different force of a risk factor under different settings—as does the following question that we often put to students, “What would one be likely to conclude about the cause of bronchial cancer from studies in a population where everyone smokes cigarettes?” Of course, under this condition, everything but cigarettes would tend to discriminate cancer victims, particularly their heredity. Here the main causal factor, tobacco, eludes detection because the population exposure is heavy, widespread, and homogeneous and because variability of the factor within individuals approaches that between individuals. Dietary exposures in a population are often similarly heavy and uniform. The force of a causal factor depends, therefore, on the circumstance and setting.

Training

These two globally different views of disease—the individual and population views—derive, in turn, from the different training, experience, and responsibility of physicians, bench scientists, and epidemiologists. The usual purview is the patient—to understand and appropriately deal with the individual—or it is the cell—to understand the specific mechanism. This predominantly individual view of the world, in which most of us are trained (and in which lie most of the earthly rewards of good works!), is the major reason for failure to join minds among the clinic, the bench, and the field—to make that needed leap of logic “from the genes, to the bedside, to the population outside!”

These different views also translate into a different tolerance for uncertainty and sometimes even to a different ability to take rational health actions in the face of ongoing uncertainty, for example, the “do-

nothing school” of preventive practice bases its views on the fact that we “don’t know enough” (in fact, we rarely ever know “enough”). This exclusively individual focus translates further into an opinion that epidemiology is only “statistics,” not “mechanisms,” and therefore, is not “science.” It is expressed by the attitude that current measures of CVD risk and ways of lowering risk are “crude and simplistic.” At best, this attitude translates into the position I have heard expressed that population preventive strategies may be “all right for now, but, just around the corner, when we are able to know the locus of each defect in each individual, then we can return to a more rational, sophisticated strategy, one that discriminates individual risk and avoids bludgeoning the whole population with lifestyle changes!” In fact, science moves forward by progressively exposing, then adding new layers; knowledge is never finite or complete.

I submit that it does not deprecate the important and exciting role of genetics and microbiology in bringing improved risk detection in the individual to suggest that this precision cannot obviate the wide-ranging effects of multiple genes and exposures, acting together through multiple body systems, to regulate the multiple physiological risk characteristics involved in the pathogenesis of CVD. Clearly, knowledge of the population distribution of genes and their epidemiological associations will enhance understanding of the genetic contribution to mass diseases. But this new and fundamental knowledge cannot account for the many health behaviors, due to multiple cultural influences, that interact with multiple genes to produce elevated disease risk—both in individuals and in populations. The “precious” view that science will eventually know and control the locus for every defect cannot, in fact, embrace whole generations of youth or set them on a healthy behavioral pathway—to a healthy metabolic pathway—to a low risk of disease as adults. The specific, individual approach to CVD cause and prevention cannot create the professional and societal attitudes needed to change the mass determinants of CVD risk. I suggest that the current intellectual excitement about genetic precision is in no way reduced by the fact that such precision cannot account for the predominantly social determinants of the frequency of major risk phenotypes or for the large population burden of the common chronic diseases. Finally, high-tech, high-cost, cardiological strategies, individually accurate and lifesaving as they have now become, cannot enhance personal lifestyles—or create a healthy society—or prevent high risk in the first place!

Value Systems

There are other major influences of the different value systems that surround the population and the individual approaches to disease. One system, from a view of the whole over time, believes that humanity can better itself through changes in behavior and changes in its institutions. The other, from a strong sense of the complexity of life and its substantial individual predestination by genes, resists any preventive action that affects private behavior, even when it is democratically achieved.

These different values can result in conceptual inconsistencies in otherwise steadfast people. For example, the views of Dr. C. Everett Koop, “the family practi-

tioner of America," evolved dramatically while in office toward a broad public health view of disease in many areas, save one. On the day the *Surgeon General's Report on Diet and Health for the Nation* was released in 1988, he quite missed the point of, and largely discredited, his own report by indicating that he personally pays little attention to diet and eats as he pleases—because of an excellent heredity!

The 1991 Report of the NHLBI Task Force on Atherosclerosis Research⁴ is a classic result of the two different value systems, the individual versus the population. There could hardly have been a more prestigious group assembled for this task, including its one and only distinguished epidemiologist, Al Tyroler. But many of us recall the remarkable impetus to CVD research of the 1970 Inter-Society Commission Report,⁵ followed by the landmark 1971 and 1981 NHLBI Task Force Reports on Arteriosclerosis.^{6,7} These reports brought to bear all of the skills and views necessary on the broad research needs in atherosclerosis and provided clear and specific recommendations. They proposed a rational and balanced program of NHLBI research with the vigorous pursuit of common goals, using all three major research methodologies.

Quite something else happened in the 1991 Task Force Report on Atherosclerosis Research. Although the report is surely among the richer and more elegant in pointing out new opportunities in molecular biology and mechanisms, the Task Force in its deliberations employed no working groups made up of multiple disciplines. Moreover, it was staffed from all branches at NHLBI except the Division of Epidemiology and Clinical Applications, the one branch concerned with epidemiological strategies and prevention research. There was, in addition, no clear set of recommendations across all research methods in atherosclerosis and, in fact, no executive summary to bring all the strategic recommendations together and in balance, a balance highly regarded until now by the scientific community, the Congress, and the public. Rather, the 1991 report focused explicitly on mechanisms and individual care—departing from the broad spectrum actually needed for the future NHLBI research program in atherosclerosis.

There is, of course, nothing wrong in being excited about the new opportunities for research on molecular mechanisms. There is, however, something very wrong in failure to recognize the need for research strategies appropriate to the stage of knowledge and for study designs appropriate to the scientific question. Particularly in such a far-reaching report, which attempts to provide guidelines for the next decade of atherosclerosis research, the broadest grasp of cardiovascular problems is required, along with all the appropriate research methods to address them.

'High-Tech' Medicine

Value differences between the individual and population orientation to science come into play in other dramatic examples of high-tech research and development in cardiovascular medicine. The prevailing attitude in academia, in industry, and at the NIH is to explore knowledge and develop technology wherever curiosity and opportunity lead. A prime goal of technology is to develop first a working prototype. It is claimed that then society can take up social questions

about producing and disseminating the high-tech development, that later on there will be "time enough" to go into the important social, ethical, and legal issues of the new technology, such as cost-effectiveness, access, and allocation of resources. The totally implantable artificial heart (TIAH) is a classic example of scientific technology and enterprise focusing on the individual, irrespective of the population need.

History provides few examples, I suspect, where the essential social concerns are ever considered adequately—after a high-tech prototype is available. By then, all forces tend toward mass production and marketing. By then, industry has made such a considerable investment that all its forces push toward realizing profit. By then, NIH is committed with new staff and program. By then, an NIH industrial complex is in place; careers and money are on the line. With such strong forces in play, society has no real opportunity to deliberate or to make objective evaluations of any high-tech, high-cost innovation. When "the genie is out of the bottle," there is, in fact, not "time enough" to consider the cost benefits or the larger ethical and legal issues.

Now, 30 years after major funding was first provided the TIAH, a 1991 Institute of Medicine (IOM) Report has recommended anew that the project continue to be funded until it develops a workable prototype. The IOM report provided little discussion, and no guidance, on the legal, ethical, social, and economic issues that should be addressed before the prototype is developed. The scientific community and the public must, I believe, inquire more actively about the broad social issues in all high-tech research and development and about who will evaluate the needs, benefit and cost, by what processes, and on what schedule. The IOM chose not to grapple with the population-wide issues, proposing rather that the development of the TIAH should continue, based on rough estimates that the device might provide selected recipients 3 years of "reasonable life quality" at a cost in today's dollars of \$105,000 a year.

Controversies Over Health Recommendations

This fundamental cause of scientific misunderstanding, that is, the individual versus the population view of causality, spills over into confusion between population and individual health recommendations. Official preventive recommendations are directed almost uniformly toward the individual, not the population. Consider the 25-year-old litany of dietary recommendations of the American Heart Association: 30% fat calories and 10% each saturated, monounsaturated, and polyunsaturated fatty acids. Aside from the fact that it is difficult to implement such a recommendation for an individual—neither the physician nor the patient has any idea what these proportions mean in respect to foods, quantities, or menus—the individual prescription is actually meant to be a population prescription. But the investigators themselves and the reporters disseminating their recommendations are unlikely to have a population view of what is important for the public health or of what is needed to prevent disease in the general population (Figure 1).

The National Research Council's recent report on diet and health was the first to put forward separate goals for populations and individuals, in this case, for serum cholesterol levels.⁸ The "desirable" goal for

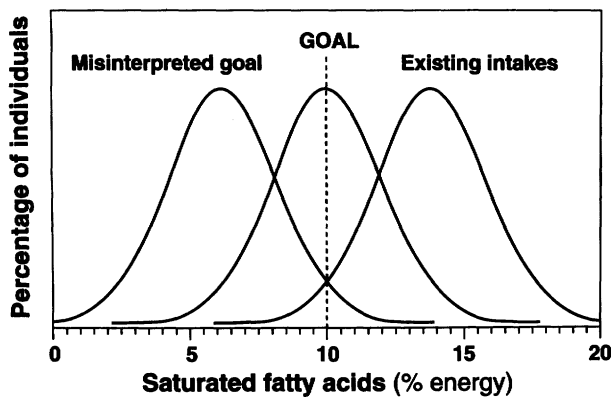


FIGURE 1. Individual dietary goal. Reproduced by permission.¹⁰ Prepared by G. Beaton.

blood cholesterol level (200 mg/dl) of the National Cholesterol Education Program (NCEP) implies that every physician should seek to achieve that level for every patient.⁹ This fails to consider that not everyone is able to achieve this by manipulation of the environment because of large individual differences in the intrinsic regulation of blood cholesterol level. The goal of 200 mg/dl represents rather an average cholesterol level for the adult U.S. population, a goal that is feasible to achieve in the next decade and is likely to be associated with a significant reduction of population risk, an interim population goal applicable to adult populations of affluent societies. Recently, a WHO Technical Report on Nutrition and Chronic Disease was the first to break down dietary recommendations successfully into individual and population goals.¹⁰ Figure 1 from that report shows an individual dietary goal of less than 10% saturated fatty acid calories, called the “misinterpreted goal,” as contrasted with the existing average population intake of saturated fat calories, and recommends an appropriate “population goal” that would result in a shift downward in the mean and distribution of saturated fatty acid intake from the current mean of 14% to 10% of daily calories. In the future, all such health recommendations would do well to separate the goals, and ranges of desirable values, for application both to individuals and to populations.

Controversy Because of Vested Interests

Perhaps the most venal of all sources of controversy surrounding prevention is that instigated by the writer, lobbyist, or consultant who uses his or her intelligence or authority to foster, for personal profit, the views of a vested interest. Some may be acting in what they believe to be the best interest of the profession or the public health, as well as their own pocketbooks. And none of us, of course, is free of errors in judgment. It may be, however, that we are witnessing these days a renaissance of distortions about lifestyle, health, and prevention, with the deliberate creation of controversy and confusion, tending to reduce the credibility of science and weaken the support systems that science requires to flourish.

The Economy

But today the major source of concern and controversy over epidemiological studies and preventive trials, and the central question for cardiovascular disease

research, is the U.S. economy, the NIH budget, and the competition for resources. These related issues threaten the entire cardiovascular disease community. I suggest that they threaten epidemiological and preventive undertakings especially.

The NHLBI budget grew from \$560 million in 1982 to \$1.07 billion in 1990, most of which was between 1982 and 1987 when there was an annual 10% increment. NHLBI funding since that time has lagged behind NIH funding and, until 1992, increased at only 3%–4% a year (ignoring inflation), much less than the increasing cost of research.

First, costs of new grant proposals have escalated. Commendable NIH efforts to increase the stability and productivity of researchers and institutions by longer-term awards have increased the cost of research, as have other mechanisms such as Merit Awards.

Congressionally mandated NIH programs have stimulated specially needed research activities but often have not been accompanied by commensurate augmentations of the NIH budget. The current Women’s Health Initiative reflects only the more recent of a series of such important mandates. This “mother of all trials” appears likely to be funded adequately during Dr. Bernadine Healy’s “honeymoon.” It will, however, profoundly affect NIH awards available for all other women’s health studies in the considerable future.

Congress has mandated that a given, high number of grant awards be issued annually by NIH, which, in effect, reduces the amount of money available per grant award. Congress has mandated also that NIH cannot in the future reduce the grant amounts recommended by peer review. Formerly, “downward negotiation” was a customary way of redistributing funds.

The research pot, boiling high now in a competitive stew, has a new influx of ingredients; the numbers of grant applications have soared, as have the costs of review, and of re-review.

A \$1 million federal cap has been placed on all program projects and a 4% cap on grant budget augmentations after the first year with a 10% cap on renewal budget increases. But fully operational, later-year budgets for epidemiological studies and clinical trials are characteristically and necessarily 50–100% greater than their earlier year budgets that cover only protocol development, observational and pilot activity. These caps and rules apply only to new awards, but existing large awards have been cut as much as 25% on continuation, severely jeopardizing their scientific integrity and feasibility. A whole class of research activity is selectively and severely crippled by such arbitrary blanket regulations.

Furthermore, proposed federal caps on indirect cost allocations to research institutions will, at the very least, eliminate the sole source of developmental funds and new research enterprise in many departments of universities. It will have an equally serious effect on research facilities.

Federal fiscal “games,” to defer current NIH awards to reduce the apparent national deficit, will have serious consequences including delayed funding, 10-month instead of 12-month funding, a 2-month period without local authority, and a potential nightmare of excess funds for NIH to manage come the end of the fiscal year.

TABLE 1. The NHLBI 'Value Function'

Total cost 1st year (\$1,000)	Cost \times $^{\wedge}0.25$	Priority percentile \times cost $^{\wedge}0.25$ Priority percentile			
		10	20	25	30
150	3.50	35	70	87	105
250	3.98	40	80	99	119
300	4.16	42	83	104	125
400	4.47	45	89	112	134
500	4.73	47	95	118	142
600	4.95	49	99	124	148
750	5.23	52	105	131	157
1,000	5.62	56	112	141	169
2,000	6.69	67	134	167	201
3,000	7.40	74	148	185	222

The NHLBI Value Function is computed from total costs of a grant raised to the 1/4th power, multiplied by the percentile priority from peer review.

NIH Administrative Reactions

Administrative reactions by NHLBI to these and other fiscal strains have generally been thoughtful, well-intended efforts to keep the research establishment afloat, to maintain a balanced research program, and to reconcile the monies available with the number of grants mandated. But all of these administrative reactions affect the whole scientific community profoundly. I voice the particular concern here that these changes selectively affect epidemiological and prevention researches that, because of their nature, organization, and costs, are especially vulnerable. Larger and long-term grants, characteristic of epidemiological studies in sizable human populations, present a particular problem for NHLBI. Overall, less than 6% of awards consume one third of its grant resources. In consequence, NHLBI now computes and applies a "value function" that enters the total cost of a grant proposal, as well as its scientific merit, into the funding decisions for the main lines of research grants and program projects. This is another well-intentioned effort to match the mandated number of grants with the funds available in those budget lines, but it will have major consequences for larger grants. Because grant awards can no longer be reduced in dollar amount by NIH staff or councils, again due to Congressional mandate, the value function is employed, taking into consideration the first year total cost of a proposal with its priority percentile rank:

$$\text{Value function} = (\text{priority percentile}) \times (\text{total cost})^{1/4}$$

In Table 1, if the cutoff for funding occurred at a value function of 88, for example, all \$150,000 grants would be funded up to the 25th percentile and all \$400,000 grants excluded above the 20th percentile. A \$1 million grant would require a 20th percentile rank to compete with a \$250,000 grant at the 30th percentile of merit, and so on. The upshot of this model is that for value functions falling around the funding cutoff, peer review is bypassed and smaller grants are awarded in preference to larger ones at the same or superior scientific merit.

In other developments, NHLBI Program Project applications just failing the payline are now being "disag-

gregated" into their fundable meritorious components, to the competitive disadvantage of RO1 grants and other program projects. Moreover, all new grants of \$400,000 or more now require "prior consultation" with NHLBI staff in their preparation. The "constitutional-ity" of this requirement has not been tested, but most investigators comply with and generally profit from discussions with NHLBI staff. If, however, an investigator-initiated effort does not succeed in peer review, yet is considered sufficiently important by staff and council, NHLBI may then take the research initiative. This, in effect, puts the NIH in competition with the community of investigators. Even though such institute initiatives fall within a separate NHLBI budget allocation, in the end, "everything competes with everything else" for the limited funds. The investigators who made the original proposal are, in effect, blocked from pursuing investigator-initiated enterprise of a similar nature.

Another new, across-the-board regulation by NHLBI requires that all epidemiological-type proposals specifically costing \$500,000 or more be placed under "cooperative agreements" rather than being awarded as grants. This rule was born out of an NIH-perceived need for large-grant accountability and presumably some occasions of inadequate performance of clinical trials, for example. The rule, in fact, increases NIH control and direction of research and selectively affects the freedom of investigators involved in epidemiological and prevention pursuits. Though there are valid reasons for cooperative agreements, and many of them function very well, the need for such a blanket rule should be thoroughly documented by NHLBI and discussed beforehand with that part of the scientific community most affected. The regulation was passed by the NHLBI Advisory Council and not recognized as yet another incursion into the independence of all CVD investigators.

All in the CVD research community would likely agree that it is essential and past due that epidemiological researches address a number of relatively neglected areas in women's and minority health. All would likely agree that a research agenda dominated by white male subjects is inappropriate and incomplete. But a blanket rule now affects the feasibility and cost of all epidemiological studies, quite independent of the scientific questions addressed. All epidemiological studies and clinical trials of \$500,000 or more, unless clearly justified, are required, in effect, to have sufficient numbers of minorities and women in which to test subgroup hypotheses, with profound consequences on the cost, feasibility, and competitiveness of grants in the field. NIH research into these critical health issues should be vigorously pursued and rigorously planned with the goal to achieve the best answers, through the most appropriate populations, within the strongest study designs. But this simply cannot occur under such a blanket regulation for all epidemiological studies, which amounts to "politically correct" science.

"Programmatic review" by the NHLBI Advisory Council is now mandatory on all grants of \$500,000 or more. This added level of review, again, tends to select against large proposals, therefore, against many epidemiological study proposals.

There is reason for concern, in addition, about administrative tampering with the excellent NIH peer-review process. Parent review committees, individual

institute review groups, and site visits to applicants' institutions are being abolished. These and other major changes are underway or under consideration by the Division of Research Grants and by an NIH Task Force on Peer Review. It has taken years to develop experienced and skilled review in many fields of research, particularly in epidemiology, prevention, and behavioral researches. The ongoing changes threaten this competence. Needs for change in the NIH peer-review process should be most carefully documented and widely and consultatively considered and actual changes initiated very cautiously.

Discussion

All these trends involving the U.S. economy and the NIH budget, congressional mandates, and public stewardship of resources, along with the administrative responses of NIH, originate from different value systems, enthusiasms, and pressures. They create a major challenge for those of the "epidemiological persuasion" as well as for the larger scientific community. In observing these trends, some have suspected a mindset, even a "conspiracy" against epidemiology, large grants, and program projects. But a conspiracy takes a great deal of planning! In fact, it is rare that NIH Council reviewers exchange views at all on individual grants or on substantive policy issues. Even in the small NHLBI Committee on Working Program, which I like to characterize as the "Gang of Four," opinions are expressed openly, no agenda are set, and no one goes to Council with a strategy for who will talk first or who will support what. On the other hand, informal views of members of Council are widely heard in NIH corridors at meeting time: "I couldn't care less about these epidemiological studies!" "Is that community trial going to go on forever?" "Don't those guys know that it is 1991!" "This isn't science! Well, if it's science, it isn't research!" "Epidemiology had its heyday in the 1960s and 1970s; other things are more interesting now." No, there is no conspiracy; perhaps there is only ignorance of the broad spectrum of research needed, and bias against certain colors of that spectrum!

What is new in this painful and highly competitive picture today derives mainly, of course, from the economic "crunch," but it is accentuated by congressional hands-on policies and by vigorous and hasty "top-down" responses of NIH management to the federal mandates and fiscal crisis. In consequence, the entire community of biomedical investigators is now anxious and upset. What seems to be missing is an over-arching public and congressional understanding of, and mandate for expanded biomedical research in all lines, including epidemiology and prevention. What is missing also is an ongoing forum for bringing the concerned parties together to analyze and respond, to resolve issues, and to plan. Dr. Healy has attempted a worthwhile, one-of-a-kind consultative approach to the current NIH strategic plan.

Where to?

Where, then, do we go from here in respect to the special interests of epidemiology and prevention science but also in our larger obligation to biomedical research and public health policy?

First, as investigators, we would do well to document better our problems and articulate better our ideas and arguments, attempting ways of resolving important issues that are preferable to simply accepting NIH "solutions" passively, or "bellyaching" loudly about them, or, more seriously, bypassing the system to activate the "loose cannons" on the decks of Congress and in the media!

Our next priority should be to focus on doing a good job with what we now have in the NHLBI research "portfolio." The major CVD cohort studies underway must be carefully nurtured, impeccably managed, and their data fully exploited so that they may become the "new Framinghams." They present a remarkable opportunity to study new risk characteristics among cohorts of youth, adults and the elderly, women, and minorities to acquire new knowledge about etiology and about the force of risk factors in a rapidly changing U.S. culture. Indeed, there is every evidence that the current generation of studies is improved in design and is highly productive. These valuable epidemiological undertakings can best be preserved by continued good work.

We need to learn from costly happenings of the past that have contributed much to the negative attitudes of bench and clinical colleagues about trials and other epidemiological undertakings. As investigators, we clearly made mistakes and perhaps we failed to protest sufficiently some mistakes thrust upon us, in the designs, end points, and sample size estimates, for example, of the Multiple Risk Factor Intervention Trial and the Lipid Research Centers Program and conceivably of the large public health trials and community studies of the last decade. On the other hand, we have not summarized effectively the positive accomplishments, and presumably, the money well spent, of such recent successes as the CAST, SHEP, SOLVD, and TOPH trials, nor pointed out how CAST, for example, has led to a complete rethinking of generations of medical therapy directed at suppressing ectopic beats to prevent more serious arrhythmias.

For new proposals in epidemiology and prevention, we must be particularly innovative, using more objective markers of physiological and sociobehavioral characteristics studied in stronger and more efficient designs (such as case-control studies nested within population-based cohorts). Postal studies with mortality follow-up of huge cohorts might be applied more widely to occupational and social groups, even to magazine subscription populations, giving a rapid yield on simple questions and self-administered measurements. Two-staged clinical trials, recommended by the NHLBI Atherosclerosis Task Force and properly criticized as inappropriate to a general or required strategy for preventive trials, may, in fact, be highly appropriate for certain specific, short-term studies of atheroma regression, using imaging, to prepare the stage for more costly definitive clinical trials. On the other hand, such a two-stage process should not become a requirement that precludes needed complementary studies on thrombosis, arrhythmias, and heart failure, which are remote from the pathogenesis of atheroma. Nor should it exclude systematically any necessary, even costly, definitive clinical trial.

Ways should be sought to increase the power and reduce the cost of community or public health trials

through greater numbers of randomized units and with controls using iterations within populations rather than comparisons to theoretical distributions. Such major preventive undertakings should profit from the experience of the 1980s studies in which time-tested principles, using substantial numbers of randomized units, were abandoned. That generation of community studies was forced by a clinically oriented review system to carry out explanatory trials with physiological risk characteristics and disease end points rather than to test adequately the needed health promotional strategies. Cumbersome questions were posed that required costly designs that had minimal power to demonstrate whether changes in community risk could be accelerated above the rapidly downward secular trend.¹¹ We also must seek more efficient CVD surveillance, which is critically needed to measure the continuing dynamics of CVD in society, to describe, explain, and predict change in disease rates, in risk levels, and in mass behaviors, and to measure in parallel the effects of rapid change in medical diagnostic categories and therapies and hospital administrative reactions to changing health economics.

A House in Order

In epidemiology and prevention, as in science and medicine generally, we need to "put our house in order," including professional motivations and behaviors. Perhaps nothing has done more harm to the public trust, or to the stature and credibility of science, than the recent evidence of fraud and cover-up in research and the carelessness in research administration. This may have been caused in part by "bigness," with increasing lack of intimacy in research, as well as to a laissez-faire entrepreneurship that fosters academic freedom without concomitant responsibility. But nowadays, as the prestigious support of NIH shrinks in relative dollars, there is a tendency to turn to "easier" sources of funding than NIH. We have seen the effects of the growing collaboration of universities with industry under the accepted aegis of "rapid technology transfer." "Easy money," like dope, is addicting. Investigator "dependence" may develop insidiously but rapidly, first reorienting and eventually deforming academic purpose and program. Ever-increasing "doses" are needed, until traditionally principled behavior deteriorates. Investigators vigorously deny the reality that they are "hooked" on industry support, and they often maintain, sometimes until too late, that their good names, and their institutional reputations and personal integrity, are not "for sale." At best, there is a chilling effect of such industrial support on freedom of expression.

Just as the growing dependence of members of Congress on special interest funds tends to corrupt government, so, too, it corrupts the scientific process. Just as lawmakers are no longer as beholden to those who elect them, but rather to political action committees that finance them, so scientists may no longer be as beholden to the beauty of truth, but rather to a new support system in which their beliefs are subtly influenced by their instincts for survival!

It is time that Congress cleans house. So, too, it is time that medical science cleans house!

Bypassing Peer Review

The increasing practice, including that of a few epidemiologists and prevention investigators, of running right away to complain to the media or to Congressional representatives when NIH review fails to result in funding, is a most serious departure from a long academic tradition. It must be avoided until all "normal" procedures are exhausted; that is, diligent study of the peer criticisms, careful discussion with experienced colleagues, direct consultation with NIH staff and directors, regrouping and resubmission of proposals. Eventually, if called for, legitimate formal NIH appeal procedures are available. The merits of a case must be weighed very carefully against damage to the peer review process, and to NIH, when influence-peddling is thrust into the picture.

Some have suggested that these days of relatively reduced NIH funding may have a salubrious "shaking out" effect on the population of medical investigators. On the NHLBI Advisory Council I have heard frequently such calls for a return to a smaller investigative elite. Interestingly, these views usually come from an already small (and senior) elite! But a broad base for the pyramid of science is probably crucial for its summit to reach high. The base of the scientific enterprise must be maintained.

Balance (Is in the Eye of the Beholder)

Clearly, for epidemiology and prevention science, we must attempt systematically to redress the distorted balance of power in NIH and in voluntary agencies such as the AHA. It is unhealthy that epidemiology always be in an unrepresentative role and always in a posture of reaction rather than in a condition where disciplines and interests have equal weight. Only then can special interest be transcended for the greater, common good—which is a truly broad and successful national research program.

What might be an appropriate representation of the major research disciplines on scientific and governing bodies? The obvious division is $\frac{1}{3}$, $\frac{1}{3}$, $\frac{1}{3}$ for laboratory, clinical, and population approaches. What expertise would effectively represent the "population" approach and what, for example, should be the composition of the major working groups, standing committees, and councils of NIH and AHA? "Our one third" would consist not only of epidemiologists but also statisticians, sociologists, anthropologists, ecologists, clinical-trialists, health economists, and preventive practitioners; and not only these, but also health policy thinkers and communicators. As effectively as NIH has learned to put together its specialty study sections and ad hoc review groups, it has not yet succeeded in composing its major councils, working committees, task forces, and planning groups to include an appropriate representation of skills, experience, and vision from epidemiologists, preventive practitioners, or public health experts.

With a view to improving collaboration needed among such critical U.S. agencies as the NIH, USDA, IOM, and congressional staffs, useful models exist. For example, there was a particularly fruitful collaboration between NIH, HEW, and the USDA during the Carter Administration where for the first and perhaps only time in history, agencies for health and agriculture took

each other's needs and constituencies into consideration. Not only is a mechanism needed for long-term planning but for short-term responsiveness. The scientific community and its professional organizations should lead in taking up research initiatives, bringing quickly on board the institutes and, finally, the Congress, to consider needed programs, using an ongoing process of thoughtful and timely deliberations.

Back to Basics

We in epidemiology and prevention need also to return to "basic principles" of public health in applying the strong scientific evidence for health action. The population strategy seeks public education along with the promotion of healthy products, clean air and water, and on occasion it seeks regulations, passive restraints and controlled access. "Luxury" taxes and other strategies need to be applied toward industries that, in effect, manufacture excess deaths, including tobacco, chemicals and drugs, and guns. We should seek democratically, but vigorously and innovatively, to change institutions and industries and their unhealthy products, with positive efforts to promote healthy community behaviors.

Communications

We need to call attention directly, in our scientific and public communications, to the messages in our results that are relevant to other disciplines, and we need to encourage others, in turn, to point out leads and approaches for our researches. If we train ourselves and future generations of investigators to look for such clues and opportunities in each others findings, greater understanding and mutual respect would surely result.

It is also time for us to speak up, to organize, and to deal squarely with the NIH, with voluntary agencies, and with the Congress. We must be forthright, vigorous and concerted, formulating our arguments clearly so that they cannot be construed as mainly self-serving (or even disloyal to the NIH establishment that we have worked so diligently to create!). But it is time now that we speak out for much broader views of what is "real science" and "basic science," always seeking patiently to

persuade other colleagues to our view: that of "sick and well populations" as well as "sick and well individuals!"

Finally, it is time that we document carefully the opportunity, and paint attractively for the larger community, a portrait of the benefits to be expected from a greater national investment in epidemiology and prevention research, within a spectrum of generally expanded researches, illuminating all three "beauties." The effect of stimulation of biomedical research activity in our country can only be a healthy one, on jobs, on the balance of trade, on the national economy, and on the health of individuals and whole populations.

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