LEWIS A. CONNER MEMORIAL LECTURE

Choices That Must Not Be Made

RICHARD D. REMINGTON, PH.D.

SUMMARY Throughout our professional lifetimes, we are conditioned by the need to choose: among careers, among treatments for our patients, among health habits and lifestyles. After detailing the extent to which a choice-making orientation has dominated our lives, our society, our health system, our science, this paper describes areas in which it is crucial that choices not be made. These include the choice between basic and applied research, between targeted and investigator-initiated research, between prevention and treatment of cardiovascular disease, and between the need to know (research on mechanisms of disease) and the need to take action (intervention in the individual and the community to control disease). In each of these areas, a decision to emphasize either alternative at the expense of the other is undesirable and defeats the basic goals of understanding and controlling heart and vascular disease.

In discussing these sets of alternatives, the three major cardiovascular risk factors are discussed: cigarette smoking, high blood pressure, and diet. Examples are chosen from research investigations on risk, prevention, treatment, and community control.

THE 1980s began with uncertainty. We have made major progress toward the conquest of cardiovascular diseases. To our remarkable achievements at the laboratory bench, we can add major accomplishments in the translation of fundamental research findings into community programs that are effective — programs that work. Yet, the sobering fact is that improved health for our people is not a national priority. We live in a nation that believes it is the victim of forces weakening the economy and the national security, thereby threatening its position of world leadership. I do not argue the validity of these assumptions, but simply observe that they dominate the formation of public policy, leaving little room for concern about the conquest of major diseases.

In response to the low priority assigned to health, we might attempt to fuse a concern for cardiovascular diseases with the national preoccupation over economic issues. We might argue, as does the recent excellent report of the working group on arteriosclerosis of the National Heart, Lung, and Blood Institute,1 that heart and vascular diseases cost this country billions of dollars each year, not only in direct expenses of medical care, but also in costs attendant to lost productivity. But in a climate characterized by a fixation on dollars, this approach is likely to result simply in greater attention to the containment of costs of hospital and medical care and on a reduction in employee health benefit programs and workmen’s compensation rather than on the underlying causes of the problem, the disease processes themselves.

How do we confront this gloomy public policy situation? I believe there are two ways to do this — a bad way and a good way. The bad way is to be attracted away from our game plan, to be tempted to become amateur economists, federal policy makers or politicians. Our purpose is not economics, public policy, or politics. Our purpose, our talents, our training and our instincts are directed toward better understanding and control of diseases of the heart and blood vessels, leading to reduction of premature death and illness.

These comments should not be interpreted as a criticism of the American Heart Association’s public policy posture, the development of its Washington office, or the attempt to maintain communication with the real power structure in this country. That attempt has produced benefits and it will continue to produce benefits, particularly if it concentrates on what I consider to be the good approach to the dilemma.

How can we continue to make progress in the conquest of these killer diseases? In my opinion, by the direct approach. By doing the necessary research, by translating research into improved practice, by developing and implementing community programs in cardiovascular disease control, by speaking directly to the victims of these diseases, the general public. These activities are, after all, what we are trained to do and what we do best. Furthermore, our credibility with the public and with the professional community is our most precious asset. The public, in turn, with our sup-

From the School of Public Health, University of Michigan, Ann Arbor, Michigan.

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Address for correspondence: Richard D. Remington, Ph.D., University of Michigan School of Public Health, 109 South Observatory Street, Ann Arbor, Michigan 48109.

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port, will continue to exert its influence on the policy makers. And ultimately, the policy makers must listen.

Along this road we will face choices. Some of these choices will be of our own making and some will be externally imposed. I want to discuss choices, particularly choices that must not be made.

We’ve become accustomed to choosing. Choosing a school, a career, a mate, a home, a diagnosis, a treatment, a lifestyle, a diet, a physician, a government. We are constantly confronted with problems attendant to limited resources, whether managing our own budget or that of an organization. We respond to the problem of allocating limited resources by adopting a system of priorities. Priorities are nothing but choices. We choose to spend money on priority item A before spending it on item B. But, if we are not careful, we may be forced into choice-making situations in which choice is neither possible nor desirable.

There are choices that we must never be led to make: the choice between basic and applied research, the choice between targeted and investigator-initiated research, the choice between prevention and treatment of disease, and the choice between the need to know and the need to act.

The Choice Between Basic and Applied Research

Basic research is the basis of the conquest of cardiovascular disease. Fundamental research at the cellular and molecular level has enhanced our understanding of basic disease processes, leading to improved diagnosis and therapy. Although such research often seems far removed from any practical application, most medical and surgical technology can be traced to fundamental discoveries, often in seemingly unrelated areas. Comroe and Dripps made this point forcefully by studying the 10 most important clinical advances in the cardiovascular field between 1945 and 1975, stating that 41% of the 529 key research articles in these fields “reported work that, at the time it was done, had no relation whatever to the disease it later helped to prevent, diagnose, treat or alleviate.” The 1979 Conner lecturer, Richard Ross, in commenting upon the work of Comroe and Dripps, said, “The list of 529 key articles can be further broken down to show that all kinds of research are important to the progress we are concerned with today . . . about two-thirds of the key articles were considered to be basic. If you were a betting person and wanted to pick a winner, you would bet on basic research.” The 1981 report of the Working Group on Arteriosclerosis said, “Support provided by the National Heart, Lung, and Blood Institute has made possible many important advances in basic research during the last ten years. Many of these discoveries are already having an impact on clinical care and approaches to the prevention of disease. In several instances, the initial research that led to these discoveries had no apparent relation to the study of atherosclerosis.”

When we speak of basic or fundamental research, we should not only be discussing research at the cellular or molecular level, but basic clinical, epidemiologic or behavioral research as well. Scarcity of resources can induce a conflict between bench or wet research and clinical, community or population research. This conflict is ultimately destructive of all research and leads toward a choice — a choice that must not be made.

Fundamental research on cardiovascular diseases should not be conducted in a vacuum. Although the way to improved diagnosis and treatment may not always be clear, basic scientists need some concept, however general, of the place of their work. Furthermore, clinical investigators and practitioners require some appreciation, at whatever depth, of developments in the underlying basic sciences contributing to their field of application. The development of new treatments and the testing of safety and efficacy is often the product of years of scientific effort. The implementation of specific advice on lifestyle improvements leading to maintenance of health and prevention of disease requires knowledge, attitudes, beliefs and skills that are the product of many years of basic behavioral and epidemiologic research.

Applied research is the means whereby basic discoveries can be translated into improved care of patients, improved lifestyles for patients and their families, and prevention of disease. Ten years ago, the Hypertension Detection and Follow-up Program (HDFP) was designed. That program, whose results have been widely publicized, showed, in 14 communities across the United States, that the identification of hypertensives and the provision of an intensive program of stepped care designed to reduce the blood pressures of even the most mild hypertensives to diastolic levels below 90 mm Hg saved lives. The HDFP has been hailed as a landmark medical research investigation. It received the Lasker Award. Its findings are beginning to have an impact on the management of millions of patients formerly labeled mild hypertensives.

Of course, this piece of applied research was important. But let us examine its roots. Basic physiologic, biochemical and pharmacologic research over several decades produced a broad array of drugs that made possible a stepped-care program. Without this fundamental research, the HDFP could not have been contemplated. Basic biostatistical, epidemiologic and behavioral research made it possible to design a study of adequate size and power and with adequate response rates to permit the efficient screening of 159,000 persons, leading to the identification of 11,000 hypertensives with high levels of response, participation and achievement of goal blood pressure. Without fundamental work on sample size determination, modern techniques of demographic and statistical analysis, efficient management of large data files, careful attention to epidemiologic principles of standardization of measurements and assessment of competing and confounding variables, together with application of modern knowledge guaranteeing high rates of patient compliance with therapeutic advice, the HDFP would not have been successful.
Hypertension, however, remains a dilemma. HDFP data suggest that 99% of cases of high blood pressure identified in the community are secondary to no known cause. Thus, as has typically been the case in the history of conquest of major diseases, whether Jenner’s work on smallpox before the elucidation of the germ theory of disease or Lind’s work on scurvy before the identification of any vitamin, to the successful use of insulin to treat juvenile diabetes with little knowledge of the basic disease process, we have been able to control disease long before a full understanding of etiology, natural history or fundamental mechanisms was available. An admonition that we must not diagnose and treat disease until we thoroughly understand its etiology becomes impractical. The HDFP has taught us that we can identify a life-threatening condition, administer effective and safe treatment, and save thousands of lives. We cannot await full understanding before applying the results of such investigations, for the approach to full understanding is an asymptotic limiting process that involves a slowly rising level of knowledge punctuated by occasional quantum jumps, at times and in environments which cannot be predicted in advance. To quote Stamler, from the 1981 report of the Bethesda Conference on Prevention of Coronary Heart Disease, “Our purpose is humanism — longer life with better health, in the best Hippocratic traditions of medicine, in the spirit that Pasteur put so well in these inspiring words: ‘To him who devotes his life to science, nothing can give more happiness than increasing the number of discoveries, but his cup of joy is full when the results of his studies immediately find practical applications.’”

Arguments in support of basic research require some care. Mosteller pointed out that the findings of Comroe and Dripps can be characterized as retrospective; that is, they proceed from important applications backward in time to their origins in basic science. An important question concerns the expected rate of yield of investments in the basic sciences. In quoting a number of studies of the place of basic science in other areas as well as in medicine, Mosteller said, “We need basic research for new developments. The problems must be what basic research is needed, and how much is worthwhile in a given area. Can evidence be adduced which would help with the funding and educational and occupational decisions that must be made? It is one thing to say that nobody knows, but another to face the fact that someone has to decide how much money to provide and how to spend it for the public good.” Ross said, “It would be interesting to know how many blind alleys had to be explored before the 529 key papers cited by Comroe were produced; I would guess that the number would be 2,000 to 5,000. But this in itself is no indictment of basic or fundamental science. To the dismay of relatively uninformed policy makers, we cannot program scientific innovation, discovery, and break through.”

Some of us remember the ill-starred attempts by the National Cancer Chemotherapy Screening Program in the early 1960s to force, by a mass approach, results that were not ready to break. This is not to say that no useful information was forthcoming from that approach, but that with 20/20 hindsight, the investment may not have been well advised.

Applied research has similar problems. Good thoughts and high motivation by the investigator will not necessarily produce effective study design, careful data collection and believable conclusions. There can be no shortcut to improved scientific understanding, whether in basic or applied science. There can be no substitute for interdisciplinary involvement in applied research.

As for the policy makers discussed earlier, we must remind ourselves that their attention is on economics and other global issues. With such an orientation, they can be expected to exert downward pressure on the available pool of funding for research, both basic and applied. An important tactical device in accomplishing this cost-containment strategy is to pit basic against applied research in a desperate competition for funds that are inadequate. In fact, allocations to all research and development in this country are declining, placing us almost alone among developed countries. The tendency in recent years has been for countries such as West Germany, the Soviet Union and Japan to increase the percentage of their gross national product allocated to research and development. Our percentage has decreased. (Misery loves company and it is interesting to note that France at least is with us in this decline.) Thus, it is critical that we keep our eye on the fundamental change that is occurring. This is not a targeted decline in basic research funding or a focused reduction in applied research. It is a systematic movement toward national expenditures for purposes other than research and development. All research is suffering. It has become established national policy in this country of both Democratic and Republican administrations to invest less and less of our total economic resource to the acquisition, development and dissemination of new knowledge.

In this context, we can see that a conflict between basic and applied scientists operates in service to a national policy which would not be defended consciously by members of either group. If we can be forced to choose between basic and applied research, the result will be a net decrease in total research expenditure. The outcome of this conflict will ultimately be less research of all types, basic and applied. A choice that must not be made — the choice between basic and applied research. We must have both. We must do both. We must fund and support both.

The Choice Between Targeted and Investigator-initiated Research

The HDFP was targeted research. But just what does targeting mean in that context? Is this a case of the federal government pitted against the investigative community? Is this another case of bureaucracy grinding down individual initiative? As noted earlier, for several decades, investigator-initiated activity was producing new agents, truly effective in lowering the blood pressure. In the 1960s, the Veterans Administration Cooperative Study
program, having made landmark contributions in investigations of tuberculosis, other infectious diseases, cancer, psychiatric disability and alcoholism, turned its attention to the implications in severe, fixed hypertension of pharmacologic reduction of the blood pressure.\textsuperscript{10-12} This investigation was targeted, but with little evident reduction of initiative on the part of its principal investigator, Edward Freis and his colleagues. But several questions were left unanswered by these trials, critically important as they were. No conclusive information was provided about women, about mild hypertensives, or about the influence of antihypertensive therapy on the incidence of coronary heart disease. Furthermore, the role of management of high blood pressure occurring in the general population was unknown. Because of these gaps in knowledge, the NHLBI appointed a special panel in 1970 to recommend further studies. The panel, chaired by Edward Kass, was composed of distinguished scientists outside the government. The group recommended investigations along the general lines of the HDFP. This recommendation was approved by NHLBI with the concurrence of its National Advisory Council, also composed of distinguished scientists and nonscientists outside the government. Requests for Proposals were issued late in 1970 and a review panel of nongovernmental scientists was convened to review responses to the Requests for Proposals. From this process, a complex study evolved. But the HDFP was designed to be effective, and in terms of process and outcome it generally was. That it had an impact on our view of the identification, treatment and control of hypertension, particularly at lower levels of diastolic blood pressure elevation, cannot be doubted. This, then, is targeted research. Often, we act as if targeted research is initiated, designed and conducted by the federal government. Nothing could be further from the truth. My experience does not permit informed comment about all medical funding entities within the federal government, but the NHLBI has sought and followed informed opinion from the investigative community in conducting its program initiatives. The argument that a better or more far-reaching result could have been reached if a single investigator had initiated and conducted the HDFP cannot be defended. I doubt that any of us associated with this program would have serious criticism of the basic process followed by the NHLBI.

But targeting cannot be generalized to all areas of research. We must protect the individual investigator following his or her own scientific conscience, attentive to leads generated by his or her prior investigations, and responsive to his or her own fundamental intellectual curiosity. In a democracy, we place high value on the free flow of ideas, whether economic, political or scientific. Furthermore, as the cancer chemotherapy program demonstrates, we cannot program innovation. We cannot say to an investigator or even to a group of investigators, Here is the money, now go out and make a scientific breakthrough. We must guarantee through diverse and adequate funding of the best ideas of the best investigators a steady flow of basic research results, initiated by individual scientists.

Both targeted and investigator-initiated research can have imperfections. Targeted research can be pedestrian, plodding, noninnovative, costly and ultimately ineffective. Investigator-initiated research (and here my favorite example is the history of investigation of the relationship between dietary sodium chloride intake and blood pressure level) can be idiosyncratic, poorly designed, inconclusive, erratic, and can create as many problems as it solves. This, however, does not suggest that either type of research is bad per se. Bad research is bad, whether targeted or investigator-initiated. Good research producing good results with an impact on science or practice or both can arise through either funding mechanism. Again, a choice that must not be made: the choice between targeted and investigator-initiated research.

The Choice Between Prevention and Treatment

Many of us were pleasantly surprised by Richard Ross's presidential address to the American Heart Association in 1974.\textsuperscript{13} In this address, Dr. Ross outlined his personal transition in philosophical approach to cardiology and medicine. He said, "Today's physician has a responsibility to his individual patients who are by and large the symptomatic patients in the later stages of their disease, but he also has an obligation to the rest of the population who have not yet developed symptomatic severe disease. He must work by whatever means are required to prevent the development of atherosclerosis and retard its progress in the population as a whole."

It makes basic sense that prevention is less costly than treatment. If we are truly interested in cost containment in medical care, what better way to contain costs than to avoid them altogether by keeping potential patients healthy and out of the hospital. But cost containment is not our most important concern. Preventive strategies lead to a higher quality of life as well as to a longer life. The lifestyle interventions reflected in the American Heart Association's program of risk factor control produce life of higher quality. The cigarette addict may not agree with us, at least as he or she is moving through the throes of withdrawal, but there can be little doubt that the unhitched exsmoker has a higher quality of life as a result of kicking the habit. There can be no doubt that the Mediterranean diet, long advocated by Stamler, Blackburn, Keys and their associates, is both highly palatable, highly nutritious, and altogether rather classy.

Furthermore, our prevention and intervention technology is improving dramatically. What we used to call health education has now become a much more sophisticated program of health behavioral change involving an alliance between a teacher providing individual techniques and skills and a learner truly motivated to improve his or her lifestyle in a manner consistent with increased vigor, increased happiness, fewer medical bills, and longer life. Consider some examples. The Multiple Risk Factor Intervention Trial (MRFIT) recently reported\textsuperscript{14} that of 4103 MRFIT special intervention participants who were smokers at the first screening visit, 46% said that they were not cur-
recently smoking cigarettes 48 months after entry to the trial. These results were more favorable than initially anticipated in the design. Data on changes in lifestyle of adult Americans indicate lower frequency of cigarette smoking, reduced intake of butter fat, lard and eggs, and increased frequency of detection, treatment and control of high blood pressure. 7 The comment that preventive and interventional strategies do not work is simply unjustified in the light of recent experience using modern intervention techniques.

Deaths from coronary heart disease in this country have fallen, both in percentage and absolute number. We are, for the first time in many years, observing fewer than 1 million deaths from cardiovascular disease each year. In addition, all-cause mortality is decreasing, as is mortality from all cardiovascular disease. 1 Finally, between 1969 and 1977, the mortality rate for coronary heart disease in the United States for men 35–75 years old declined 23%, the largest decrease among 27 industrialized countries reporting to the World Health Organization. This decrease moved us out of the lead position in these 27 countries in 1969, at a rate of 865 deaths per 100,000, into seventh place, with a rate of 670 in 1977. Australia, Finland, Scotland, New Zealand, Northern Ireland, Ireland, and England and Wales all now have higher mortality rates. The results for women are roughly comparable, though the rates remain at a lower level. Our efforts at prevention and intervention are clearly bearing fruit, although we cannot assign accurately the proportion of the decline in mortality attendant to prevention and to improved treatment. Most observers agree that a substantial part of the reduction is due to preventive efforts.

With respect to treatment of cardiovascular diseases, we are in another era of remarkable advance. We can offer improved longevity to the hypertensive with modest elevations of blood pressure. We can, through the use of β blockers, improve the rate of survival of patients already experiencing a heart attack. 15, 16 Noninvasive diagnostic techniques have reduced the risks and discomforts of identification of the location and size of lesions. Patient monitoring and automatic control have improved the survival experience of even the most severely impaired cardiac patients.

But there are problems in both areas. As we seek to emphasize improved lifestyle and prevention of cardiovascular disease, we stress the importance of positive health habits. Yet, some persons who do not smoke, who do not have high blood pressure, who eat a prudent diet, and who exercise regularly will develop cardiovascular disease. In such persons, our efforts at prevention and our emphasis on self care may induce feelings of guilt. It seems wise to inculcate a sense of responsibility for one's own health, but we have not yet worked out a fully adequate approach to doing so while avoiding guilt and self-recrimination in the patient and family. Here, prevention must join with treatment, for the best line of defense is surely the humane physician. With respect to treatment, we must note with Ross that there is no real cure for the most dramat-ic manifestations of cardiovascular disease. 13 Prevention and treatment are under dynamic tension. As our therapeutic discoveries proliferate, there is the danger that the public will be lulled away from a healthy lifestyle consistent with disease prevention in the false belief that they should not worry, the miracles of modern medicine can fix them up if something goes wrong.

We must maintain an emphasis both on the prevention of disease and on the treatment of that disease. We run the risk of de-emphasizing prevention in favor of costly treatment and unfortunately, our most common system of paying for health care is partly to blame. Third-party payers seldom reimburse for prevention or intervention programs. On the other hand, if our attraction to preventive strategies becomes entirely economic, there will be a problem. We must again recognize that our goal is highest possible quality of life. Finally, we must worry that the decline in cardiovascular mortality will be interpreted by policy makers as indicating that the battle is over and we have won. Cardiovascular disease is still our number 1 killer. More people continue to die in this country each year from cardiovascular disease than from all other causes combined. Another choice that must not be made: prevention vs treatment.

The Choice Between the Need to Know and the Need to Act

We must have an uninterrupted flow of facts and information to guide the formulation of public programs in the prevention and treatment of cardiovascular disease. Research must continue. But at an appropriate time, we must make recommendations for public programming and action. There is, as noted earlier, no such thing as total or perfect knowledge. A relatively safe and efficacious smallpox vaccination was available before the smallpox virus or any other infectious microorganism had been identified. British sailors were prevented from developing scurvy long before the identification of vitamin C. Hypertensives with relatively modest elevations of diastolic blood pressure can profit from blood pressure reduction by pharmacologic intervention, even though we rarely have any idea what caused their blood pressure to become high in the first place. It is almost always true in programming for disease control in the general population that we must act before complete knowledge is available. Louis Katz, 17 speaking as Duff lecturer for this Association in 1970 stated, "How complete must knowledge be before it is applied in developing a prevention program? I believe it is not essential to have every 'i' crossed and every 't' dotted. When the shape of the program becomes fairly clear from the state of developing knowledge, then the value of the prevention program should be explored. The particular program may have to be modified or dropped as new knowledge appears, just as unexpected problems arising during the course of applying the prevention program may lead to these possibilities." Yet, as Katz also says, this is no excuse for recklessness, no excuse for delaying or de-emphasizing continued acquisition of research knowledge. Upon the introduction of com-
munity intervention programs, it is important to evaluate these programs to determine their safety and effectiveness in mass application. Another choice that must not be made—the choice to continue to develop new knowledge, the need to know, and the choice to apply that knowledge through public programming, the need to act.

In conclusion, we have looked at choices and choice-making behavior. We have considered areas in which choices must be made and areas in which choices must not be made. Our great goal of improved health for all members of the population through the reduction of premature mortality and unnecessary morbidity from heart and vascular disease requires an emphasis not necessarily consistent with current public policy. By working together, by emphasizing good research, both basic and applied, both targeted and investigator-initiated, both public and private, we can avoid a posture which may make us not only less than we need to be but less than we are. The best way to continue to serve the public and its health and to continue the impressive gains toward the conquest of cardiovascular disease is to refuse to make choices that must not be made.

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R D Remington

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