Ancel Keys Lecture

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When I was a young doctor, we used to explain to our patients with atherosclerotic problems that unfortunately their arteries were wearing out; We did not need to seek causes because it was a result of old age. We were vaguely aware that the incidence rate varied in different populations, but no one saw this as an intellectual challenge; we were fatalists.

It is to the Framingham group that we owe our understanding that this disease does not strike individuals haphazardly like lightning; rather, it strikes very selectively and is drawn by identifiable risk factors. But it was Ancel Keys who led us to confront the more fundamental question, namely, why did the western epidemic of heart disease occur in the first place? Why do population incidence rates vary?

Keys raised the debate regarding these questions in cardiology and preventive medicine to a new level. He did not merely provide some of the main answers; he also taught us to investigate the problems of a mass disease from a new viewpoint—that of the sick population. To honor his achievement by giving this first Ancel Keys Lecture is a weighty and anxious responsibility. My qualification for attempting the task is simply a keen awareness of the importance of his contribution.

I shall first examine the preventive approach to individuals based on identifying and correcting their risk factors; then, I shall turn to the more basic and powerful population approach, which tackles the underlying causes of high incidence rates, and I shall explore the implications of some new data. My principal conclusion is that the two approaches are neither opposite nor even independent but rather highly interactive.

Prevention in Individuals

Medicine is concerned primarily with patients, and preventive medicine is concerned with preventing people from becoming patients. Our profession is strongly oriented toward the problems of individuals and a wish to prevent them from changing from normal, healthy people into sick people. This leads us to think of the sick as a distinct group and of disease as a defined entity that is separate from normalcy. Indeed, the basis of clinical diagnosis is the assumption that with respect to each disease, the world is divided into just two classes—those who have it and those who do not.

This dichotomous thinking carries over into many areas. We speak of a risk factor as being present or absent, and we count the number of risk factors that a patient possesses. We say that a patient either has coronary heart disease or is free of it. We speak of two- or three-vessel coronary disease as though coronary artery narrowing is either present or absent. We say that an effect is either statistically significant or nonsignificant. In all of these ways, we prefer to recognize only black and white because shades of grey introduce confusion and uncertainty. We prefer to suppose that normalcy and deviance can be clearly separated because that confines our worries to a defined minority of deviants: Most people are all right, really!

In 1954, I was working as a physician for my teacher and father in medicine, George Pickering. In that year, he published his articles on the nature of hypertension, in which he introduced the revolutionary notions that the diagnosis of hypertension is a man-made artifact; that the distribution of blood pressure is continuous, with normalcy merging imperceptibly into deviance; and that hypertension is thus not a naturally defined entity. The fact seemed irrefutable, but its implications have never really been accepted.

In clinical care, we draw an arbitrary boundary to what we know is really a continuous distribution. This is inevitable when dealing with individual patients because management decisions are dichotomous—a decision must be reached that treatment will be either given or withheld. Risk is a continuum, disease is usually a continuum, but treatment is an all-or-none affair and, hence, diagnosis must also be.

So far, so good. Regarding screening, it is quite appropriate to pick out individuals who qualify for special care and then treat them as a distinct group, provided we recognize the limitations of what we are doing. These individuals are not really a distinct group; we have made them so by the artifact of labeling. In the general population, these individuals are simply one end of a continuous distribution, and what we are trying to do is truncate the risk factor distribution by removing the high tail while leaving the remainder of the distribution intact.

Let me suggest four important restraints or guiding principles for the risk factor screening approach. First, screening without adequate advice and treatment has been shown to be a waste of time. It can do positive harm by labeling people who previously thought that they were healthy. We are in danger of forgetting this lesson. There are strong pressures by lipidologists and some pharmaceutical companies to institute mass screening for serum cholesterol, regardless of whether there are resources with which to deal adequately with the positive cases, but the

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first principle is "No screening without adequate resources for long-term care."

The second principle is that "selective screening and care are far more cost-effective than mass screening." It would cost 100 times as much to prevent one heart attack by cholesterol screening in 40-year-old women than it would in 60-year-old men.2

The third principle is that "screening for a multifactorial disease should be multifactorial." For cholesterol screening, this means that the aim should not be to identify those with the highest cholesterol values but rather to identify those with the highest cholesterol-associated risk because they are the ones who will derive the most benefit from intervention. Thus, in the population screened by the MRFIT investigators,3 the 6-year follow-up found that the excess mortality associated with being in the top tertile of cholesterol values was more than five times greater for a smoker whose blood pressure was in the top tertile than for a nonsmoker whose blood pressure was in the lowest tertile. The importance of one risk factor or exposure depends on its context; isolated elevation of one factor may be relatively benign in individuals who are otherwise at low risk. Our aim should be to identify risk, not individual risk factors. It makes little sense to define fixed action cutoff points for cholesterol or blood pressure.

The fourth principle is a consequence of the third: "Prevention of multifactorial disease must be multifactorial, not unifactorial." Physicians treating hypertension are often satisfied if they can normalize the patient's blood pressure. Lipid clinics concentrate on controlling blood lipid levels, and diabetes clinics concentrate on controlling blood sugar. However, in the Medical Research Council hypertension trial,4 we found that the difference in the incidence of stroke between smokers and nonsmokers was greater than the difference between treated and control patients. Risk factors interact. To control smoking in a hypertensive patient or cholesterol in a diabetic patient may be as important as controlling the presenting problem. Management of multifactorial diseases should be multifactorial, but this is often not the case.

Limitations of High-Risk Strategy of Prevention

Physicians cannot treat everybody in a population, so the clinical approach to preventing heart disease implies focusing care on a minority of individuals at special risk. This is excellent for the individuals concerned, but to suppose—as some do—that it is a sufficient response to the problem implies some serious misconceptions.

In the Whitehall study,5 we calculated a multivariate coronary risk score for each participant. Between men with high scores and men with low scores, there was indeed a large difference in subsequent coronary mortality, but when we looked at the causes of death in those men whose scores put them in the lowest 10% risk category, we found that the single most frequent cause of death was still coronary heart disease. In western populations, we cannot define any sizable low-risk group. The large majority of coronary deaths do not occur in the high-risk sector that would be picked out for medical care but rather in the far larger number of people with average levels of risk factors. Prognostically speaking, average cholesterol is high cholesterol, average blood pressure is hypertension, and average weight is obesity. It is not just the deviant minority of people who have a problem.

The individual or clinical approach to prevention is the equivalent of sending emergency aid for famine relief in the Third World: It is greatly needed, it is life saving for the recipients, but it does not change the underlying causes of famine—for that to happen, there must be a radical, populationwide effort to identify and tackle the underlying causes. And so it is with preventive cardiology. Help for high-risk individuals is greatly needed, it can be life saving, and it rescues susceptible individuals from the consequences of unhealthy exposures, but it does not attack the underlying causes of mass cardiovascular disease. That requires us to stand farther back and ask, "Why is this population sick?"

Sick Populations

Pickering1 recognized that sick individuals are just the extreme of a continuous distribution, but he failed to recognize the idea of a sick population. That came with Keys. His famous diagram (Figure 1) marked a historical step forward. It tells us that every population has its quota of relative hypercholesterolemia, largely reflecting, one presumes, individual genetic variations, but no amount of research into individuals can tell us anything about the essential difference between the Finnish and Japanese situations. That difference lies in a characteristic of the populations as a whole, and it can be studied only by research that considers entire populations.

How exceptional was Keys' observation of a whole-population shift of cholesterol values? Does it apply to other populations? And to other variables?
Consider studies of systolic blood pressure in Norwegian women (Figure 3'). Again, aging involves the entire population, those with low blood pressure as well as those with high blood pressure, but this time skewing is seen to increase, and the coefficient of variation rises by 50%. In other words, aging affects people at all levels of blood pressure but especially those at higher levels.

Each of these examples (cholesterol and blood pressure) presents an age-related phenomenon that is being driven by potentially avoidable environmental factors—they are not intrinsic effects of aging, but there may, of course, be age-related differences in susceptibility to these factors.

I return now to international comparisons. Our INTERSALT study\(^8\) provided us with high-quality standardized data on blood pressure and some related variables from 52 different population groups in 32 countries; the entire gamut of man’s amazing range of geographical, social, and economic circumstances has been covered. (Keys’ Seven Countries Study pointed the way, and it has become inflated into our 32 countries study.) To simplify the presentation, I have aggregated the blood pressure data into five groups (Figure 4), ranked according to their mean values.

This shows several important points. The distributions shift up or down as a whole; populations behave coherently. Something constrains the range of difference between individuals, so few get unduly far from their society’s norm; the coefficients of variation are approximately constant. Next, the whole-population shifts are large (more than 20 mm Hg); as a result, the prevalence of hypertension varies enormously (in single populations, from 0% in Yanomamo Indians to 33% in Mississippi blacks).

Figure 5 shows the situation for body mass index. Again, populations shift as a whole (although now with more variation in skewing). The prevalence of overweight, like hypertension, varies enormously (this time, the Mississippi blacks yielded first place to

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**FIGURE 2.** Distribution plots of serum cholesterol in US men 18–24 and 35–44 years old.\(^6\)

Anyone who tries to answer those questions will at once encounter extreme frustration! Researchers rarely publish their data on distributions; they do not think in those terms. Rather, they think in terms of cases, so they report prevalence rates; or they look at means and standard deviations. They do not stand back and look at whole distributions. With much difficulty, therefore, I have managed to gather a few examples with which to test the generalizability of Keys’ finding.

Recent NHANES reports were no help, but the US National Health Survey in 1971–1974\(^6\) gave cholesterol distributions at different ages (Figure 2). As men get older, we see a replica of the Keys phenomenon: The distribution shifts upward as a coherent entity. The coefficients of variation of these two distributions are identical, with the increase in the low-cholesterol individuals being proportionately the same as in the high-cholesterol individuals. The effect is across the board; that is, the effect of age on cholesterol involves all levels similarly.

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**FIGURE 3.** Distribution plots of systolic blood pressure in Norwegian women 20–24, 35–39, 50–54, and 65–69 years old.\(^7\)
Hawaii); again, this simply reflects a shift involving the entire population. The same pattern also holds true for alcohol intake.

It is apparent from these illustrations that a small shift in the population mean is associated with a large change in prevalence of high values. Applied to the cholesterol distribution, this predicts that if the population mean decreases by 6–7%, then the prevalence of hypercholesterolemia (defined by the top decile point) will be halved. When compared with the expected impact of a screen-and-treat approach, such a population-based change in prevalence is likely to be larger, cheaper, safer, and better sustained.

INTERSALT data permit similar predictions for other risk factors (Table 1). This tells us that concern for the population and concern for high-risk individuals represent one concept, not two concepts, and a change in the population may be the best way to help the high-risk or deviant individuals.

**Prevalence of Deviance Reflects General Population Mean**

Surprisingly, this close link between population mean and prevalence of deviance has received little attention. It is impressively demonstrated by the INTERSALT findings. Mean blood pressure of a population accurately predicts the number of hypertensives; mean body weight predicts the number of obese people; and prevalence of heavy drinking precisely reflects average consumption of alcohol (Figure 6).

There are some powerful implications. First, the prevalence of a high-risk state (hypercholesterolemia, hypertension, obesity, excessive alcohol) is largely a secondary reflection of the life-styles and attitudes of the masses. The problems of deviant individuals and their possible solutions can be studied properly only in their population and societal contexts. They cannot be understood in isolation. Our research has been too narrow.

Second, explanations of incidence rates and the key to control of cardiovascular diseases must be sought in characteristics of the whole population. The study of individual susceptibility is important, but the fundamental questions are, "What determines the population's mean blood pressure, cholesterol, body weight, and alcohol intake? And how might that mean be changed?" This calls for a different kind of research as well as a different approach to prevention. Populationwide prevention is essential because we are dealing with mass diseases and sick populations; it is the radical approach because it corrects the underlying causes of the epidemic; it is cheaper, safer, and much more cost-effective than the high-risk approach; and it is often the best way to help high-risk individuals.

Third, the medical approach to identifying and helping high-risk individuals is obviously vital for those individuals—and there are many of them. But it may well be that the most important role for physicians' advice and practice lies in its powerful effect on public knowledge, attitudes, and behavior. What is aimed primarily at needy individuals has a potent spillover effect throughout the entire population. These two strategies are mutually supportive, not rivals.

Fourth, success in preventing heart disease calls for establishing healthier life-styles as norms for the entire population. Physicians have key roles as expert advisers, opinion formers, and (we hope) good personal examples. Governments, the agriculture and

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition of high values</th>
<th>Necessary change in population mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>≥140</td>
<td>8</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>≥90</td>
<td>4</td>
</tr>
<tr>
<td>Overweight</td>
<td>Body mass index, ≥30 kg/m²</td>
<td>2 kg</td>
</tr>
</tbody>
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From References 8 and 9.

**FIGURE 4.** Distribution plots of systolic blood pressure in five aggregated populations of men and women 20–59 years old grouped according to increasing levels of average pressure.
food industries, the mass media, educators, and many other community groups and agencies constitute an even greater force than physicians. However, regardless of how much we may all long to move those risk factor distributions in a favorable direction, we must always respect the right of the public to make their own choices. In a democracy, success in preventing heart disease ultimately depends on what the public chooses to do. Our responsibility is to see that their choice is informed and free.

References

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