Ancel Keys Lecture

Introduction to Ancel Keys Lecture
Ancel Keys, Pioneer

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It is fitting that the American Heart Association now has a lecture named for Ancel Keys. Keys was a pioneer in cardiovascular disease research and a founding father of cardiovascular disease epidemiology and prevention. He is the consummate cardiovascular investigator. His first doctoral thesis, written in 1928 in the field of physiology at the Scripps Institute, discussed the arterial circulation of elasmobranchs. He used regression equations to relate the weight to the length of fish! After his second doctorate in biochemistry at Cambridge, he studied the oxygen dissociation curve of hemoglobin at 20,000 ft in the Andes, working out of the Harvard Fatigue Laboratory. His studies during World War II on metabolic and circulatory functions and their deterioration under the stress of bed rest, heat, postural tilting, cold immersion, exercise, and semistarvation culminated in a classic work: The Biology of Human Starvation. In that series of studies, Keys demonstrated the remarkable change resulting from experimental manipulation of the environment of factors previously considered constitutional, such as Sheldonian body types, work capacity, blood pressure, and blood cholesterol levels. During the 1940s and 1950s, he basically redefined human biology, providing the distributions of most biological variables in healthy adult men in classic presentations that have affected our thinking, research, and daily lives 40 and 50 years later.

If there is still an issue regarding the priority for the concept of life-style and risk characteristics in the causation and prevention of cardiovascular disease, it should be settled by a 1948 presentation by Keys to the Chicago Heart Association entitled "Mode of Life and the Development of Heart Disease: Research for a Preventive Hygiene."

Keys probably knows more than anyone about body composition and the relation among diet, physical activity, and body compartments. He established the intrinsic differences in individual blood lipid responses to diet, and with colleagues Francisco Grande and Joseph Anderson followed this by a series of elegant isocaloric experiments that substituted different fats and fatty acids for carbohydrates. Keys had the insight, scientific rigor, computing savvy, and prodigious energy to tie these relations into a simple regression equation that has stood the test of 30 years—the Keys equation. It remains the more valid mathematical construction of the relation between change in dietary lipid composition and blood total cholesterol level, representing a body of work worthy of a lifetime of accomplishment by a productive investigator.

Keys was the earliest to put forth hypotheses about the population, or mass, causes as well as individual causes of cardiovascular risk and disease. This seminal idea derived from his observations of population differences in diet, risk factors, and disease and was honed over a decade of peripatetic rounds in exotic places with Paul Dudley White and other medical colleagues such as Martti Karvonen, Noboru Kimura, Christ Aravanis, Vittorio Puddu, and Flaminio Fidanza. Their informal observations led Keys to design the classic Seven Countries Study, which has stimulated major ongoing research projects and provided the base of evidence for

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the population strategy of coronary disease prevention through diet and behavioral patterns. Keys also initiated much of the field and laboratory methodologies that have led to this demonstration of wide differences in coronary heart disease incidence, which is in turn related to population differences in habitual diet and to the mass phenomenon of population differences in distributions of the major risk factors. His findings indicated that for public health measures to be effective, they must deal with mass cultural phenomena, whereas medicine is concerned with individual susceptibilities to cardiovascular disease.

In the Seven Countries Study as well as earlier, Keys demonstrated the correlations of habitual diet, average blood lipid levels, and disease rates among populations. These ecological associations were derided for many years by those who could not grasp their meaning. Now they are understood for their overriding importance in indicating the population causes of disease and the potential population effects of prevention once causation is otherwise established by congruent evidence.

Keys was the first to apply multiple logistic regressions developed in one population to another, showing that the risk factor concept is universal because of the ability to discriminate individual risk within different cultures but also showing that there are large differences in the force of single and combined risk factors according to the environmental setting.

Keys was the first to use a longitudinal cohort study in cardiovascular disease epidemiology in a Minnesota study initiated in fall 1947 and variously called the Minnesota Business and Professional Men's Study, the Cardiovascular Disease Study, and the Twin Cities Prospective Study. During the late 1940s and the 1950s, he recruited his longer-term US colleagues in the new enterprise of cardiovascular disease epidemiology—Henry Longstreet Taylor and myself. In the 1960s, he was a central member of the Diet-Heart Study, the "Club of Five" that produced another classic report that also led to major new research. It contributed directly to the 1970s being the decade of preventive trials (trials of everything, that is, except diet). In the Diet-Heart Study report and related activities, Keys was central to the emerging scientific and public recognition of the "diet-heart hypothesis" as well as the diet-health relation in general. During this period, he acquired other new and long-term colleagues, including Jerry Stamler.

Thus, Keys basically "started it all"—clinical studies, laboratory diet experiments, population surveys and their ecological analyses, longitudinal cohort studies, and preventive trials. He brought the field together, building a new physiological, experimental, and epidemiological science as he went along that he called "physiological hygiene." Its center was in a laboratory of the same name, under gate 27 of Memorial Stadium at the University of Minnesota. Keys not only was central to the development of cardiovascular disease epidemiology but also helped to make it the important bridge it is today among biology, preventive practice, and public health.

Few people realize Keys' remarkable contribution to international cardiology through his teamwork with White and other distinguished cardiologists. During the days of his early wanderings with White, the International Society of Cardiology was an elite club that held small meetings in pleasant places and organized the World Congresses of Cardiology, the first being held in Paris in 1950. The International
Society of Cardiology was not successful, however, in stimulating research directions of the international community, collaborative research, or research in epidemiology and prevention. Keys' activities with White and colleagues resulted in the formation of the research committee of the society, which proposed the present structure of the International Society and Federation of Cardiology (ISFC). The first major report and international visibility of cardiovascular disease epidemiology occurred on center stage at the Second World Congress of Cardiology in Washington, D.C., in 1954 and was headed by a panel made up of Keys, White, Kimura, and Gunnar Björk. This was the real launching of international cardiovascular disease epidemiology, which, along with developments in North America and Europe, led to the full flowering of a new and recognized field. The efforts of Keys and White led to the formalization of scientific councils and a lay executive board for the ISFC at the Fifth World Congress of Cardiology in Delhi in 1966. The present ISFC Council on Epidemiology and Prevention was a direct outgrowth of these activities, and the leadership of Keys extends through a connected chain to the present.

Keys' contribution to training in cardiovascular disease investigation was profound, primarily in inviting the younger colleagues of his distinguished investigator friends from around the world to come to Stadium Gate 27 for a period of months or years. He also was cofounder of the ISFC International Ten Day Seminar in Cardiovascular Epidemiology, which has exposed hundreds of young cardiologists and investigators to the rigorous concepts of criticism and design.

The American Heart Association's Council on Epidemiology and the association's leaders who are here today are to be commended for developing this named lectureship that so well represents the field. You have established a fine new tradition for the council and for the association with the Ancel Keys Lecture. All of us thank you, and we all thank particularly our colleague and friend, Ancel Keys!

**KEY WORDS** • coronary heart disease • epidemiology • prevention
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