

Commentary on Ancel Keys' Career

The precocity, the depth of perception, the creativity and productivity of Ancel Keys were early apparent. However, the breadth of his grasp of human health questions extended as his career matured. Early researches on serum osmolality led into researches on the oxygen dissociation curve and high altitude explorations with the distinguished Cambridge physiologist Barcroft. The direction toward physiological hygiene became apparent in the Harvard Fatigue Laboratory where Dr. Keys' collaboration with Henderson and others began to bring together work physiology, metabolism, nutrition, and body composition. In turn, these considerations began to touch on questions of lifestyle and stresses on human performance which provided a central theme to physiological hygiene and Dr. Keys' career.

With this distinguished background and two doctoral degrees, in physiology and biochemistry, along with many professional associations as a young investigator, it was perhaps natural that Dr. Keys was called upon to respond to wartime needs in the study of heat stress, semi-starvation and human performance. This call resulted in the gathering together of the first distinguished investigative crew in Physiological Hygiene, Taylor, Brozek, Henschel, Mickelsen, Anderson and Simonson, at the height of WWII. The classic experiments on semi-starvation brought together many disciplines, and in the course of developing survival rations and performance recommendations for wartime stresses, also produced the standard 2 volume scholarly work, Human Starvation.

The immediate and direct outgrowth of these efforts included observations of changes in serum lipids and blood pressure on semi-starvation and re-feeding, changes in body composition with the classical monograph, Body Fat in Adult Man, as well as the standard measuring tool for aerobic capacity in man, the maximal oxygen uptake developed with H.L. Taylor. This carries us to the late 40's and this experience resulted in change in emphasis of the laboratory to consider disease and impaired performance as well as norms in human physiology.

The first longterm longitudinal observational study in adult men oriented towards measuring physical and psychological characteristics and subsequent cardiovascular disease risk was begun in 1947 and is known as the Minnesota CVD Study, of Minnesota professional and business men. This study antedated Framingham and all other efforts in this field. Though the CVD study was surpassed in numbers by the other population studies in the U.S., concepts and methodology were not, and the publication of its results in the early 60's demonstrated as did the other studies, the major significance of primary risk characteristics for coronary disease, as measured within homogeneous U.S. populations.

Going back to the early 50's it became clear to Dr. Keys that the quantitative and objective demonstration of cultural differences in coronary disease risk, and the population characteristics associated with these differences, was important to physiological hygiene and to significant preventive approaches. In addition there was the opportunity to test hypotheses about the essential role of habitual diet in the populations with differing burden of atherosclerotic diseases and different "natural experiments" of habitual diet.

Ancel Keys' Career (continued)

The Seven Countries Study was a remarkable exhibition of simple design, multiple disciplines in professional collaboration, good field operation and elegant analysis. The publication of the Seven Countries Study 5-year results in Circulation 1970 provided, finally, evidence acceptable to the scientific community that some cultures do very well without clinical coronary disease and others have as much or more than we. The study further supports the hypothesis that saturated fats on the order of 15% of calories or more is probably an essential factor to a significant population burden of coronary disease, in contrast to diet as an individual risk factor which may not be essential. It thus provided a key to mass preventive efforts in atherosclerosis.

In the period between the onset of the CVD longitudinal observations and the beginning of the Seven Countries Study there was initiated a period of precise, objective and powerful experiments which established mathematically the relationship between changes in individual components of diet (other factors held constant) and change in serum cholesterol level. These collaborative studies of Keys, Anderson and Grande greatly contributed to understanding of the role of nutrition influencing serum lipids and the potential of mass preventive efforts through diet. These studies have been confirmed, with remarkably similar regression equations, by independent investigators around the world.

In the several periods of Ancel Keys' researches he has attracted young and mature investigators whose careers have been permanently influenced by his many qualities including 1) directness and simplicity of thought, 2) intensity of pursuit in testing hypotheses, 3) rigorous use of validated methods, 4) simplicity and elegance of analyses, and 5) clarity of expression of ideas and conclusions. Probably because he was ahead of his time in cardiovascular epidemiology and prevention, and possibly because of the directness of his language and criticism, Ancel Keys has become a controversial figure. To those who have worked with him, recognize the rigor of his thinking and the absence of fanaticism, along with the industry and effectiveness in testing hypotheses, they find much less of controversy than of good sense. To those who take the trouble to read his work, rather than what others say of them, they will find much scholarly substance and intellectual stimulation.

Finally, Ancel Keys has given great impetus to past and current efforts at intervening on populations, as experimental tests of preventive hypotheses. He was an active participant in the Diet-Heart Study and is a helpful collaborator in the MRFIT study.

Comments on the Contributions of Henry Blackburn

Public Health training in the Tulane University Schools of Medicine and Public Health and field experience in Oriente Province, Cuba and in the U.S. Public Health Service in the Displaced Persons camps of Austria and southern Germany as a young physician, set the background for Dr. Blackburn's later involvement in preventive medicine. A longterm interest in electrocardiography dated from student experiments under George Burch at Tulane, and led to a working relationship early as a medical fellow between Dr. Blackburn and Professor Ernst Simonson at the Laboratory of Physiological Hygiene. In the mid-50's Dr. Blackburn was presented by Dr. Keys and Henry Taylor with the challenge of rendering aspects of the clinical medical art more susceptible to objective measurement and evaluation. This led to a grounding in methodology, test--re-test repeatability studies and the development of quantitative and unambiguous criteria for classifying cardiovascular and related disorders for the Seven Countries Study. The best known example of this contribution is the Minnesota Code published in 1960 which is now standard procedure for most cardiovascular epidemiological studies and for the current series of U.S. and international large scale preventive trials. The Minnesota Code is still the only quantitative code acceptable for manual-visual application for such population studies and clinical trials. Advances in computer measurement and interpretation are ongoing, but they are still cross-validated with Minnesota Code criteria and technician performance. The latter offshoot of Minnesota Code procedure has been the systematic training of several hundreds of students and technicians in the reliable measurement and classification of electrocardiograms.

Several years of Dr. Blackburn's career were devoted to the methodology of stress electrocardiography which resulted in the Ernst Simonson Conference and a book on Measurement in Exercise Electrocardiography, a standard reference.

Though the Bruce exercise protocol has superseded that recommended by Drs. Taylor and Blackburn, the importance of skin electrode preparation and the configuration of exercise lead derivations were strongly influenced by these efforts from the Laboratory of Physiological Hygiene.

The concept of the electrocardiogram as a predictive tool both in apparent health and in post-infarction patients was a distinctive contribution of Dr. Blackburn's career. The Coronary Drug Project material published in the Annals of Internal Medicine in 1972 indicated that the presence and severity of depolarization, repolarization, rhythm and conduction defects was strongly and independently predictive of future risk of death and sudden death in infarct survivors.

In the late 60's Dr. Blackburn collaborated closely with Drs. Taylor, Stamler and Remington in the design and protocol of the Multiple Risk Factor approach to major preventive trials and tests of preventive hypotheses in cardiovascular disease. When the time was not ripe for this proposal to mature in this country, Dr. Blackburn became actively involved in individual discussions, and in W.H.O. collaborative planning for the implementation of Multiple Risk Factor Trials abroad. This started in the Yugoslavian Makarska Conference on Clinical Trials in 1968 and continued through the Rome Conference on Multiple Risk Factor Trials in 1970. The U.K.-Continental trials are a direct growth of these planning sessions. In fact, the successful implementation

Contributions of Henry Blackburn (continued)

abroad of multiple risk factor trials is importantly responsible for NHLI task force decisions to proceed in the development of our NHLBI study, MRFIT.

Dr. Blackburn serves on the MRFIT Steering Committee and served as Vice-Chairman of the U.S. MRFIT trial for its first two years, in the design and development of protocol and successful recruitment.

As a long-term and indirect result of the Seven Countries Study's Finnish investigations, community organization occurred which developed the North Karelia Study. Dr. Blackburn was on the first W.H.O. organizing team for this study in the fall of 1971, the earliest and largest-scale community intervention preventive effort in cardiovascular diseases. For the past two years, Dr. Blackburn has also been principal external advisor to the Stanford Communities Projects and from Physiological Hygiene is now directing large scale monitoring of cardiovascular morbidity-mortality experience, as correlated to health behavior and risk factor levels, in communities of Minnesota and the Upper Midwest. This monitoring approach is designed to measure ongoing spontaneous changes in the community, as well as those reflecting the influence of public health campaigns and socio-economic changes. They are also designed to establish methodology for evaluation of the impact of new mass strategies of health education being planned in the Laboratory of Physiological Hygiene.

Dr. Blackburn is the successor to Dr. Ancel Keys, taking over his chair in Physiological Hygiene in 1972 and building the laboratory into an effective team of 18 academic staff and approximately 70 employees, within what is now a larger division of Health and Human Behavior which includes Physiological Hygiene, Public Health Nutrition and Health Education programs of the University of Minnesota School of Public Health. The mission of this division is to develop the evidence on which firm preventive and public health policy can be developed. Its strategy is to test prevention hypotheses in the community and to maintain the to and fro relationship between laboratory studies and field applications in the community, to assess objectively the impact of preventive community programs.

Dr. Blackburn has become centrally involved in public policy positions on preventive measures for the major cardiovascular diseases, in part due to his efforts and offices in the American Heart Association and his being called as FTC witness in the "Egg Trial" and as witness to health subcommittees of Congress. In recent years he has made efforts to clarify and reconcile opposing views within the health professions, and among the public, about cardiovascular diseases and modification of their risk characteristics. He has attempted to indicate that many aspects of these controversies are unnecessary, due to biases in training and experience and concepts of clinicians and investigators concerned with decisions for the individual, in contrast to those concerned with observations and prescriptions appropriate to the public health. A model for these attempts at reconciliation is the joint Nutrition-Public Health Seminar held between the Agricultural Sciences and the Public Health Sciences on the University of Minnesota campus, in which an on-going dialogue has been established.