HISTORICAL VIGNETTE

Dr. Ancel Benjamin Keys (1904–2004): Monsieur Cholesterol and a Driven Interventionist

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Dr. Ancel Benjamin Keys was the first driven interventionist in the field of preventive cardiology. Ten years back, on his death, the tributes paid to him by the leaders of the medical world, the lay and professional media and his academic colleagues bespeak of the several fields he had pioneered during a long and very active career. "He was a giant in the field of nutrition in a variety of ways," said Walter C. Willett, Chairman of the Nutrition Department at the Harvard School of Public Health.

Our perspective on Dr. Keys is not just to enumerate his widely acclaimed contributions on: Saturated fat as a primary cause of atherosclerosis (the Seven Countries Study), high altitude human physiology, the formulation of K-rations for the American Soldiers in World War II, the Minnesota starvation experiment or the benefits shown in the Mediterranean diet. Of course, these are very important. However, we would like to understand, how Dr. Ancel and Dr. Margaret Keys searched for the keys to some of the locked up secrets of good health and longevity. An attempt to grasp how this couple's minds worked in unison, with perseverance and future creating perspicacity would be a story that would enthuse and inspire the young generation to explore the current challenges in the field of lifestyle disorders.

EARLY LIFE

The fact that Ancel Benjamin Keys had humble beginnings, born to two teenagers very much in love but struggling in Colorado Springs, bespeaks of his being a love child rooted in the American dream "if you are driven enough you shall make it in this land of opportunities." Despite the humble beginnings, young Ancel must have been very impressed by the success of his uncle Leonidas Frank Chaney, the son of Ancel's deaf grandparents. Chaney, a versatile, and powerful actor of early cinema, was renowned for "his roles of grotesque and afflicted characters, and his groundbreaking artistry with makeup." One of us (ADBV) has witnessed such histrionic and persuasive skills of Dr. Keys in his scientific lectures. Dr. Keys had a rich ancestry of English, French, Scottish, and Irish descent from his Chaney side of the family. No wonder he became a world traveler and carried out the most famous Seven Countries Study. It helps have ancestral diversity!

When he was only 2-year-old, the family moved to San Francisco in search of a better life. The very year 1906 - the devastating San Francisco struck. They moved to Berkeley where Ancel studied. There he was part of the Stanford-Binet IQ test study by Lewis Terman. Ancel Benjamin Keys had high IQ and was "identified as one of the 1528 intellectually gifted children." This must have boosted the self-esteem of Ancel to the sky! This could also have contributed to his reputation for being impatient with the less gifted and that he could be "frank to the point of blunt trauma, and critical to the point of razor slash." The story that while trying to anesthetize a fly, on his eighth birthday party, he passed out with the chloroform fumes, suggests that the audacity of experiment must have been an early acquisition. He must have also learned early the importance of experiments on human volunteers. He, while in high school, loved traveling and did odd jobs in mines and lumber camps. The wanderlust and love for manual work remained his assets throughout the life.

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ADVANCED EDUCATION

After his secondary education, he enrolled at the University of California, Berkeley, to study chemistry. As the subject did not interest him much, and he took up a job as a crew member on a ship to China. This exposure to Asian culture enriched his sensibility to the influence of lifestyle and diet on health. His advocacy for the Chinese diet was evident in the best seller, "eat well. Live long." Many Chinese restaurants, in the US, are used to display the book in their front windows. On his return from China, he changed from Chemistry to Economics and Political Science and got BA in 1925. In addition, he got MS in Zoology, in 1928.

After graduation, he worked as a management trainee at Woolworth's. His love for science and research brought him to Scripps Institute of Oceanography with a scholarship. He received a Ph.D., in 1930, in Oceanography and Biology. Keys, in his fish research, used regressions to the estimation of weight of the fish from their length. This was a foundation in biostatistics that helped much in his latter epidemiology work. In the fields of obesity and metabolic disorders, a robust knowledge of biostatistics is essential.

RESEARCH CONTRIBUTIONS

For his postdoctoral fellowship, he traveled to Copenhagen under August Krogh. Krogh was a pioneer in gas exchanges in respiration. In 1920, Krogh was awarded the Nobel for his work on capillaries and gas exchange. Krogh was a student of Christian Bohr – the father of the famous Niels Bohr. It is not known whether Dr. Keys had any interaction with Niels Bohr. These sort of trans-discipline interactions have a deep impact on young minds, expanding their horizons. The laboratory was small, and the restless mind of young Ancel was in search of a more challenging milieu. After this fellowship, he went to Cambridge. Dr. Keys wrote, "it was fairly common in those days to move around a lot. Not so much nowadays, perhaps, but it used to be shopping around from one school to the other as a postdoctoral fellow. If you had the wherewithal to hold body and soul together, that's what you did. I was just about to accept a permanent job at Cambridge, however, when I got a cable from Harvard. Hence, I said to myself, "okay, go to Harvard and see what's happening in the states." I taught biochemistry at Harvard and stayed for 3 years." He returned to Cambridge and earned a second Ph.D. in Physiology (1936).

Later Keys wrote about his job offer at the Mayo Foundation in Rochester. "They offered me twice my miserable salary at Harvard and an opportunity to set up a new division of biochemical research on human beings, human physiology, and biochemistry. However, after I'd been there a year, I found it a little confining. With my background, it just seemed to me awfully provincial, if you don't mind my saying so. All the docs talked nothing but doc business and the evenings were devoted to bridge." It was a blessing that he hired Margaret Haney as a chemistry technician, whom he married, in 1939. She was his research collaborator, co-author, and co-traveler for life.

He joined John Barcroft's Fatigue Laboratory at the Harvard University. In a landmark study, the effects of high altitude, in Andes, on the human body were shown on oxygen carrying capacity of the blood and body's ability to adapt. Two volunteers were serious. Keys wrote, "One of them was John Talbott, who later was editor of the Journal of the American Medical Association for many years. We had an awful time getting him down. He was not blue but black – gas pain, retching. We thought he was going to die. You see, Brian and I had the advantage of having lived at 10,000 feet for a couple of months beforehand." The temperature was 50 C at 20,000 feet. Keys wrote, "We had expected to go to the Himalayan region in Asia at the latitude of 25 or 30 north. Instead of we ended up being 22 south in July, which is the middle of winter." This work changed the attitude of the science establishment and the US War Department toward Dr. Keys. At the age of 29, he had finally found his true passion; research in human physiology.

At the University of Minnesota, he was invited to develop and test food ration for paratroopers. The aim was to develop compact, nutritious food packets that could fit into a soldier's pocket. The army was so delighted with the results that eventually all the soldiers in the war received "K-ration" boxes named in honor of its founder. He also conducted human nutrition studies with vitamin supplements with placebo-controls in early forties.

World War II affected the nutrition of millions of civilians across the globe. He designed the classic Minnesota Semi-Starvation Experiment. The objective of the study was to test the impact of starvation and the methods of nutritional rehabilitation. The diet was designed to duplicate that of the occupied countries of Europe – root vegetables, bread, and simple starchy food. In addition, the volunteers had to walk 22 miles/day. As the emaciation ensued, depression, irritability, loss of libido, fatigue, and perpetual hunger set in. Remarkable changes occurred in the metabolic and cardiovascular markers. The greatest deterioration was seen in those who were most fit initially. The volunteers needed a caloric intake of 4000 kcals in the rehabilitation phase for several months to build on their wasted tissues. The fat deposition came up first, and the muscle building needed much exercise in addition to high proteins. In 1950, the study was published titled "the biology of human starvation" – a classic even today. Keys said, "Starved people cannot be taught democracy. To talk about the will of the people when you aren't feeding them is perfect hogwash." How much relevant this is for India!

Keys had an early suspicion that fat produces high blood cholesterol. He examined a Wisconsin dairy farmer, "He had big knobs on his and elbows and over his eyes, and when you opened them, it was just pure cholesterol inside. They had tried various things at Madison including giving him thyroid extract to a point where he was shaking all the time. We checked this fellow's serum cholesterol level, and the first reading was 1000. His brother, who came with him, had a reading of 600. The average level in the United States is about 220 or 230, so of course this was sky high. Hence, we put them over in the laboratory, fed them there for a week, and bang! Their cholesterol levels dropped down to 500 and 300. Essentially, we put them on a fat-free diet. Wasn't very tasty." The quote emphasizes the need not to forget the importance of single case studies in human nutrition under the glamor of randomized, double-blind placebo-controlled trials!

In the postwar Europe, there was a drop in the prevalence of heart attacks in populations deprived of high fat diet. Keys also watched the new outbreak of heart attacks in obese affluent middle-aged businessmen. He hypothesized dietary fats, particularly saturated fats having a role in clogging coronary arteries. He followed a group of up 283 middle-aged (45–55 years) businessmen for a period of 40 years. He found that men with cholesterol level above 260 mg/dl were at a higher risk of suffering from a heart attack than those with levels below 200 mg/dl.

In 1951, Keys, on a sabbatical at the Oxford, heard from an Italian colleague about the low incidence of heart diseases in that region. The Keys moved to Naples and set up a portable laboratory. The population showed low levels of blood cholesterol. The low prevalence of CAD too was verified. The diet had a high consumption of pulses, legumes, whole cereals, fruits, and vegetables; a moderate consumption of fish, dairy products, red wine, and low consumption red meat. The main source of fat was from vegetable sources like olive oil. He concluded that the Mediterranean style diet, which was lower in saturated fats and higher in monounsaturated fats was responsible for the reduction in the incidence of heart diseases. Keys, like other pioneers, was challenged for these findings at an international WHO meeting by several eminent physiologists. They found a lack of evidence. The young investigators should never get disheartened by the ridicule of the seniors when their new data are shifting a paradigm.

Ancel Keys designed, in 1958, the now famous Seven Countries study, with 12,763 men (40–59 years) as cohorts in Italy, the Greek Islands, Yugoslavia, the Netherlands, Finland, Japan, and the United States. The study lasted for more than 50 years. The rest is history! The study confirmed that cholesterol, obesity, lack of exercise, and cigarette smoking increased the risk of heart disease. The fact that heart attacks were preventable became big news across the world. Dr. Henry Blackburn, the successor of Dr. Keys, said: "The Seven Countries study demonstrated the preventability of heart attacks. They were not a natural aging phenomenon, or genetically predetermined or act of God." Keys wrote, "There's a little hotel in Brussels" that my wife and I stop at now and then, and every time I go in there the maitre d', a lady in her sixties, says, "Ah, Monsieur Cholesterol!"

In 1954 Keys, with help from Paul Dudley White-the great cardiologist initiated a more serious study of cardiovascular epidemiology. As Keys concentrated on preventing cardiology vascular disease rather than curing it, time and again he was criticized by various commercial interests, particularly by the meat and dairy industries. Keys said, "There'll always be commercial interests involved in matters like this, but most of their arguments have gone by the wayside. The important thing is to make people aware of the dangers." With the massive propaganda of food and beverage industries, the task of advocacy for healthy foods and lifestyles has become uphill, even for the developing countries.

He once said, "The North American habit for making the stomach the garbage disposal unit for a long list of harmful foods…." is responsible for the heart disease. Besides foods and beverage industries, he considered that television was "doing a disservice to the nation and the individual" by promoting sedentary habits and snacks while viewing the idiot box. His advice is still relevant, "If we could find some way to make people do push-ups during commercials, then we'd all be strong as lions – the commercials are so long." He was a great advocate of mild to moderate exercise. He wrote, "Margaret and I get lots of pleasure from working in our yard. We just started the olive harvest. We have 80 olive trees and 75 citrus trees. We have oranges, tangerines, apricots, pears – lots of pears – plums, and four apple trees that produced only one apple so far." He regularly walked and swam a lot, while in Italy. He was wary of jogging, particularly by the elderly. Several cardiologists have dropped dead while jogging.

When on his 100th birthday, Dr. Keys was asked whether his diet had contributed to his long life, the quintessential scientist answered, "Very likely, but no proof." Keys died 2 months before his 101st birthday, and he was actively working till he was 97-year-old. His great message for medicine in general and cardiology, in particular, was, "Find out *before* people get sick *why* they get sick." The highlights of Ancel Keys's life are inspiring.

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RECOMMENDED READING

1. Vanitallie TB. Ancel Keys: A tribute. Nutr Metab (Lond) 2005;2:4.
2. Wright CM. Biographical notes on Ancel Keys and Salim Yusuf: Origins and significance of the seven countries study and the INTERHEART study. J Clin Lipidol 2011;5:434-40.
3. Psaty BM. Drug therapies for the primary prevention of cardiovascular events: Trials and errors: 2009 Ancel Keys Memorial lecture. Circulation 2010;121:940-5.
4. Kalm LM, Semba RD. They starved so that others be better fed: Remembering Ancel Keys and the Minnesota experiment. J Nutr 2005;135:1347-52.
5. Oransky I. Ancel Keys. Lancet 2004;364:2174.
6. Contaldo F, Scalfi L, Pasanisi F. Ancel Keys centenary and the definition of healthy diet. Clin Nutr 2004;23:435-6.
7. Blackburn H. Ancel Keys lecture. The three beauties. Bench, clinical, and population research. Circulation 1992;86:1323-31.

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