ABOUT ANCEL KEYS*

by

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There's something more than a little ironic about being asked to speak at a dinner honoring an old friend and teacher on the occasion of his retirement when, in actual fact, the great influence of his contributions in science and in medicine, far from beginning to decline, is only just beginning to come into its own. The course of Ancel Keys' influence is not proceeding according to the ordinary pattern; but then, Ancel Keys is not an ordinary man.

I propose, in fifteen minutes or so to try to make my meaning clear, drawing both from the record and from personal knowledge. I also propose to demonstrate to you that Ancel Keys' work and thought are reaching into the lives of western man probably more than the work and thought of any other contemporary scientist: a startling conclusion but, one that within its own framework and context is not difficult to substantiate.

All because he is, and always has been, a very unusual person in many respects. For one thing, he was the son of a bookbinder, a fact that appeals to me who am a bibliophile to the extent that my income permits. Then, if the record is to be believed, Ancel and the Keys family arrived in San Francisco, where he spent his so-called formative years, just in time for the great earthquake of 18 April 1906. That in itself was unusual to say the least. The family fled to Los Angeles for a time, then came back and settled in Berkeley.

What happened in the years between the great earthquake and 1930 is available to me only in the printed record (3,5). Somehow, I never got round to asking the subject himself about it. But I get the impression of considerable restlessness and rebellion against the standard academic sequence; combined unmistakably with great intellectual and academic competence when he chose to bring them to bear. There was a spell of living in the desert and working at shovelling bat manure in Arizona caves. It's not exactly the sort of thing the usual conformist high school lad is likely to undertake. But he finished high school nonetheless, a bit late perhaps, but no doubt creditably.

And so to the University of California at Berkeley where he started off in Chemistry, Physics and foreign languages, worked 30 hours a week in the library, and picked up adequate spending money by applying his agile mind to the noble game of bridge. But the old restlessness would not die. Within a year or so, we find him serving as an oiler on the U.S.S. President Wilson, China-bound and allegedly living mainly off a diet of alcohol. Then back to the University and a new major, this time Economics, with a bachelor's degree, despite the interruptions, in two years (1925). Then an eight month stink working for Woolworths's; and then boredom.

If I may make a few somewhat educated assumptions at this point, the story so far is that of a highly competent mind and great physical stamina; of a vigorous, youthful searching for goals and activities that might fit the particular, and most unusual, combination. Most of us in this room have at one time or another sat on selection committees, Boards of Review, and the like, for the purpose of choosing between applicants for scholarships, awards, and honors of various sorts. What might we have said if, somewhere around 1923 or '24, we had found ourselves facing Ancel Keys? Would we have recognized then, as it is so easy to do now, the meaning, the cost and the inestimable value of the search; or would we have dismissed the applicant as "unconvincing, confused?" The question, or course, is rhetorical. But somebody on an admissions committee had the good sense to recognize that some searches are worth gambling on: the University of California admitted Ancel Keys to graduate work in Zoology. It was a switch - in a candidate who to that point had done a fair amount of switching - back to science.

And it was obviously a massive turning point. Thenceforth there was to be restlessness of a highly purposive and constructive sort, something which has so constantly characterized the man as I have known him. And credit is to be assigned not only to the honest searcher himself, but also to a few officials who were sensitive enough to recognize that all rebels are not evil; that all those who decline to follow standard educational sequences are not merely dropouts at heart.

The rest of the story, educationally at least, is almost anti-climactic. The masters degree in Zoology in 1928, the Ph.D. in Biology and Oceanography in 1930, and the all-important three years in Copenhagen with Krogh and at Kings College Cambridge; all this followed without a break, and in due course. The impulsive thrusts into non-academic activity in the middle of an academic year were no more. They weren't now necessary. An extraordinary talent and a brilliant mind had, by age 22 or 23, found themselves.

Back in the United States, Ancel Keys proceeded, via Harvard and a short stay at the Mayo Clinic (as a Biochemist) to the University of Minnesota at Minneapolis. In between, there was an expedition to the Andes to study individual variations in adaptations to altitude. The work and the report give evidence of mature physiologic and biochemical expertise; but, just as important, of inquiry well beyond the usual questions having to do with average changes in hemoglobin and adjustment in acid-base balance (1).

Wartime service and the development of the Stadium Laboratory filled the early forties. He's alleged to have developed the scientifically laudable but virtually inedible K-ration of WW II fame. If the K really stands for Keys (and I've never been able to get him to admit it), it may rank as the most dubious of the many efforts at public service to which he has lent his name. Most GI's of WW II vintage would, in any case, have given the achievement very low marks. Yet even this has to be judged in context:

what was needed at the time, and what specifications were laid down by the Quartermaster Corps before the work began?

None of this, however, is germane to our main theme. What is relevant just now is a fuller understanding of research, and academic attitudes toward research, in the mid - and late forties. Beginning in the late forties, and carrying on through the fifties and most of the sixties, there was a growing and beguiling view that research wasn't respectable unless it was done with test tubes, chemicals, spectrophotometers, radioisotopes, and (usually) experimental animals. Bedside research, or research carried out among thousands and millions of living, breathing and feeling human beings outside the confines of the laboratory wasn't actually the real thing. Somehow during this period the importance of framing questions - many questions - with conscientious clarity, and then of attacking those questions with any methods that might logically be expected to yield the desired answers; somehow these two things became partly submerged. The inference of it all was quite clear: the young investigator might work on a vaguely defined problem in a laboratory - but he must not go into the field. One type of data - that gleaned from test tubes and microbalances - was clean; data coming from multiple human beings in the field was suspect. And the way to greatest recognition and reward was mostly via the test-tube route.

It's very difficult, in retrospect, to see how the bio-academic world, including its medical segment, fell quite so completely into such an artificial and puristic state of mind. Bioacademics prided themselves on freedom of thought and inquiry; yet methodologically they set very rigid guidelines. Some of the work that emerged was indeed brilliant. But the system ignored huge and important areas of vital human concern and, no doubt without specific intent, made it quite difficult for those areas of human concern to be examined at all.

Israel Shenker, in last Sunday's New York Times Book Review Section, attacked intellectuals by saying that they "... like fish, often move in schools, following a leader. Where he goes, they go; and where he goes wrong, they are often close behind." Parenthetically, I might add that Shenker ought to know: he is one of us. And he's also indulging in that old pastime of setting up a scarecrow so that he can dramatically knock it down. The schooling phenomenon is by no means limited to the intellectuals; they may, in fact school less readily than other groups. But it has to be admitted that the intellectuals of the bioacademic world did indeed, after World War II, follow a certain leadership into a sort of cul de sac. By defining research in such a rigid and narrow way, the leadership created an impasse and a partial polarization that, although partly understood by quite a few, were extraordinarily difficult to modify.

It's my purpose, in painting in this particular mise en scène, to set in stark relief one of the several main services to humankind Ancel Keys has rendered and continues to render. It might be made more vivid if I specifically designated the bioacademic intellectual of the forties and fifties the devils of the piece; devils that somehow had to be countered and overcome. But to do so would be to distort the record very dangerously and irresponsibly. The bioacademic intellectual community, passionately believing that research is another fundamental type of service, has justified its existence - and the billions of federal funds allocated to it through the National Institutes of Health - quite adequately; and it still does so. But I think the leadership of that community fell into serious error when it virtually refused to acknowledge the existence of numerous gray areas; of interfaces and overlaps between laboratory science and sociopolitical considerations; and of the need to train young scientists who were not precise duplicates of their teachers and mentors.

And no member of the bioscientific intellectual community understood all this as clearly - or any more clearly - than Ancel Keys, in the mid and late forties. Some few suggestions of his line of thoughtcame out in the first interview I had with him - it was in the fall of 1946 in the old Copley Plaze Hotel (now the Sheraton-Plaza) in Boston. But it was a few years later that he developed his basic line of thought - in print - for his peers in bioscience (2).

What he said in this remarkable paper, he said gently, decently, and persuasively. He must have realized that some of his peers, already moving into their cul de sac, would either reject his thesis or be resistant to it. But he wisely declined to create a tract; a gaudy, self-righteous attack on dogma. What he really said was that the test-tube scientist likes to homogenize everything; to set up a laboratory experiment where all variables, but the one under study, are carefully controlled. The scientist who has worked in this way is all too likely, one reads between Ancel Keys' lines, to assume that any phenomenon that can't be handled in this way, cannot post hoc, by systematically studied at all. The trouble is, he points out,

> There is a very large area of human affairs in which the day-to-day operations, though concerned with human characteristics, proceed with a minimum of reference to knowledge of physiology, biochemistry [and other basic sciences].

By applying only classical scientific concepts to this "large area of human affairs," we have discerned very little that enables us to predict what might, at some future time, happen to an individual subject: would this individual age more rapidly than that one; would this one be more likely to become incapacitated by a certain type of chronic stress than another?

"Perhaps," wrote Ancel, possibly with tongue in cheek, "these applied problems should be of no concern to us." He then went on to show why they, are in fact, of very vital significance, practical as well as theoretic; to indicate that to understand very much about our species, and especially about those long-term, very subtle processes that so often lead to premature deterioration and death, we must develop ways of looking at groups of individuals with little or no expectation in advance that we can hold <u>any</u> vital variable constant, much less all but one such variable. He then took some of the data that had been collected from that famous group of 541 white men in order to illustrate his points.

"The goal of all natural science," said Ancel Keys, "is accurate quantitative prediction. In the area of human health and disease, this begins with the problem of normality and normal standards. With the extension to development with time these become ... the essential apparatus for prediction."

But in order to reach the goal, a vast amount of purely observational data must be collected and very expertly and vigorously analyzed. By inference, he was saying that many massive problems of human biology cannot be solved solely by using the rat colony approach: a though that approach certainly has its specific uses. In the free-living human subject, the natural experiment is well under way before we even start; it is not something we ourselves create and manipulate at will. With the rat colony we can play God, something which is usually quite gratifying to the ego; so gratifying, in fact, that we assume, godlike, that our rat colony results can be instantly extrapolated to man primarily perhaps because they are <u>our</u> results. The thrust of Ancel Keys' conviction was to begin to turn us into a much more complex, difficult, and long-term bioscientific direction; he applied the brake gently but persuasively, to an irrational exclusiveness in biomedical research.

All this, contained directly or by inference in the 1949 paper, amounts to a very skillful affirmation of an important philosophy of bioscientific research. It wasn't altogether new - no innovation ever is - but very few of the ranking bioscientists who, at the time, were working on human biological problems, had any real understanding of it. We were most of us still trying to work with groups of allegedly comparable human subjects under highly contrived conditions, an approach which most of the time could only yield rather limited results.

The Study of the Five Hundred and Forty-One,- now the 279 - which began in 1947, was in fact, the first major application of the Keys philosophy to a major human biologic problem; and that study is still continuing. It has already yielded information of definite predictive value which is what it set out to do; but it has also yielded a great many other ideas and by-products, things that were not foreseen at the start. It mayn't be too much to say that the whole vast change in the dietary attitudes of the Western World, initiated primarily by Ancel Keys and his Stadium Lab colleagues, stemmed one way or another from the Study of the Two Seventy-nine. The various cholesterol studies, the studies of saturated and unsaturated fats, the extension of the epidemiologic inquiries to populations overseas and to working populations in this country; all these directions received very important impetus from the Study of the Two Seventy-nine.

There was, of course, the fabulous Starvation Study that had been completed earlier and which was being published when I arrived. The two volumes, by the Stadium Lab team, are and will for years remain the authority on human starvation. But the study had a different purpose and a more limited outlook than the Study of the Two Seventy Nine.

And where will that Study finally end? The total effort will never enable us to predict, for example, that a given individual will have a massive coronary attack ten years, three months, one week, and four days from the time of observation. That sort of prediction belongs in the realm of the mystic and the supernatural. But studies from the Stadium Lab have already begun to enable those of us who are forever burdened with demanding something like rational evidence to say, on the basis of multiple observations, that a given individual can expect some manifestation of coronary disease within a certain period of years and range of probability. And as this fundamental study proceeds, and others like it are undertaken, the accuracy of such predictions will undoubtedly increase greatly.

More than this, the Stadium Lab Studies collectively have provided strong suggestions, dietary and otherwise, as to measures one may take to improve his own personal prospects. This gets back to the problem of the individual. There need now be little question that a persistently high serum cholesterol is undesirable and that, whatever the mechanisms involved, dietary - not chemical - cholesterol-lowering measures should be instituted. This, despite continuing controversy, is almost universally accepted in the Western World and the knowledge has, slowly but definitely, begun to change dietary habits in many countries, especially in the Unites States. It will take years for all this to show up in the form of a lowered incidence of coronary disease; but the ultimate prospect in my view is for precisely that.

The Study of the Two Seventy-Nine has to date yielded portents but not a completely new body of knowledge (6). Yet, in the fullness of time, the Study and the activities that grew from it, in and out of Minneapolis, are almost certain to do so. By this and other work, Ancel Keys more that any other one person brought the intellectuals of the bioscientific world to realize that they had begun to box themselves in; that was one major and continuing achievement.
The other is that Ancel Keys and colleagues, plus those that have followed them, have reached and continue to reach into the lives of millions by suggestions for constructive alteration in their day-to-day patterns of living, including the diet. These suggestions are bearing fruit. The implications of the social and scientific process that had its origins largely in the Stadium Laboratory are, like a mountain seen close-up from its base, too huge to be fully perceived and understood as yet.

I am inordinately proud to have been a minor member of the Stadium group in the late forties. I was, at the time, basically a student insofar as research was concerned; but I was treated by this extraordinary group, under Ancel Keys, as a colleague. It was, for me, a time of considerable excitement and warm acceptance. Taylor

Henschel, Brozek, Simonson - and numerous others - put me forever in their debt by giving far more than they could possibly get from me. And as for Ancel Keys himself, I had the unique opportunity of learning at first-hand how a distinguished and mature scientist contrives, amid a busy and complex life, to be a masterful and sympathetic teacher. It was a grand privilege and a splendid example. In closing, I suppose I should try and dig out a few defects; no man, after all, is really a paragon. But I shan't make the effort for two very good reasons. The first is that the defects with which I am familiar are insignificant when compared to the positive themes of Ancel Keys' career. The second is that he knows <u>me</u> too well; if I , by citing any of his petty foibles, give him license to play the game in reverse, I can only come off second best.

In any case, it has been my purpose to take a macro look - not a micro one - at a macrophenomenon initiated in large measure by the intellect,competence and motivation of one man, supported down the years by unusually gifted and generous colleagues. It has not been an easy assignment and there are those who may disagree with my emphases. Yet I doubt that they can sucessfully do so. There are those who contend that Ancel Keys is an extraordinary man and a highly controversial figure. I agree with both contentions. But I trust I have shown that, from a very early age, the unusual about him led him ultimately into the acquistion of competence and expertise in a number of specific areas, most of them essential to his highly creative, subsequent career. And he is controversial mainly because he has, with growing success, begun to open up the bioscientific cul de sac of which I spoke earlier; to expand the horizons of the human biologist, and to make huge intellectual investments without expectation of early pay-off.

He is said now to be headed for retirement; and, I suppose, on the University's books, he actually is. But I detect no retirement resignation. On the contrary, he seems to be saying, as restlessly as ever:

Andiamo amicoli! Lets get going!

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