Patterns of Health Risk

Seven Countries. A Multivariate Analysis of Death and Coronary Heart Disease. ANCEL KEYS with 15 others. Harvard University Press, Cambridge, Mass., 1980. xvi, 382 pp., illus. $25. A Commonwealth Fund Book.

This is an important book describing a monumental research effort. Enrollment of the first study subjects began in 1958, and the final 10-year examinations were completed in the mid-1970's. A total of 12,763 persons entered the study, representing 16 communities in seven countries. The place names—Zutphen, Cravalcore, Ushibuka—are to conjure with, rivaling the magical appellations of arthropod-borne viruses. The logistic, financial, and communications problems must, at times, have been appalling, and the successful completion of the program is testimony to the organizational and management skills of Keys and his colleagues.

The research was begun to test some of the concepts developed by Keys and others concerning the etiological links between diet, serum cholesterol, and coronary heart disease (CHD). A series of observations had indicated that the frequency of CHD differed greatly between different countries and that dietary customs were an attractive explanation for the variations. In collaboration with scientists in each locale, study groups of 40- to 59-year-old men were enrolled in 16 communities, including urban and rural residents, groups selected by occupation, and others chosen because they were believed to represent marked contrasts in characteristics of special interest. The study populations ranged from 2571 railroad employees in the northwestern United States to 502 inhabitants of a fishing village in Kyushu. A fairly detailed account of the experience after five years of observation has been published, and this book presents data collected over the ten-year period following the entry examinations.

The volume is organized as follows: an overview of methods; data on prevalence at entry, mortality, and incident morbidity; chapters addressing major risk correlates individually; and finally the results of multivariate analyses and some summary conclusions. This format is generally quite satisfactory, except that to compare the univariate associations with the same variables in a multivariate context requires continual cross-reference between chapters.

The single variables discussed are age, blood pressure, cholesterol, smoking, body weight, physical activity, pulse rate, respiratory function, and diet.

Age. The increase in CHD mortality with increasing age is rather less marked than the rise in mortality from all causes; nevertheless, age is the most important determinant of risk of death due to CHD, and its effect is not fully explained by age-related changes in other factors. The sharp increase in risk with age implies that fairly small differences in age structure between different populations may compromise comparisons if the age groupings that are compared or that serve as the basis for age adjustment are too broad.

Unfortunately, this analysis has followed the custom of the Framingham Study and others in reporting age-related events by age at entry. Given ten years of observation, this means that a death reported for a person who was 40 years of age at entry could have occurred at any age between 40 and 50 years. If the curve of mortality with age differs markedly between different communities in the Seven Countries Study, then comparisons are compromised, probably more seriously than will occur by age adjustment by five- or ten-year age groups. Computation of mortality and morbidity rates based on the ratio of events at the ages they occurred to person-years of observation for those ages is not difficult, and why it is not done is not clear.

Blood pressure. As in other studies, the Seven Countries report shows a consistently higher risk of CHD among persons with higher blood pressure, although the risk may not be smoothly graded across the entire range of pressure. Risk was found to be higher in some countries than in others at equivalent blood pressure values, and the association was stronger with manifest myocardial infarction than with angina pectoris.

Serum cholesterol. The most important observation in the comparison of diverse countries with respect to serum cholesterol is that the association between serum cholesterol concentration and CHD tends to disappear in those populations with the lowest frequency of CHD.

Smoking habits. In northern Europe and the United States, the risk of CHD was graded according to amount of cigarette smoking, but in southern Europe and in Japan the association was very weak or absent. As a community characteristic, the proportion of persons who smoked cigarettes was not predictive of the death rates in the communities from all causes or from CHD, or of the CHD incidence rates.

Overweight and obesity. Fatness was assessed by measures of relative weight and skinfold thickness. The relation between these indices and the risk of CHD differed markedly in different countries: a strong positive association was noted in the Netherlands, Greece, and Italy, a modest relation in the United States, and no association in Finland and Yugoslavia. This variable, then, showed an erratic pattern of association with CHD, in contrast to the tendency of cholesterol and smoking to be associated where the CHD rates were high and not associated where they were low.

Physical activity. The study subjects were allocated to one of three classes of physical activity, based on occupation and leisure-time activity. The associations are disturbingly inconsistent; except in the United States, Yugoslavia, and Finland, CHD deaths tended to decrease progressively with increasing activity. In Finland the intermediate physical activity class had the highest CHD death rate, and in Yugoslavia that group

Associations between possible etiological variables and risk of coronary heart disease by geographic area, as reported in *Seven Countries*.

Risk variable	Geographic area		
	United States	Northern Europe	Southern Europe
Systolic blood pressure	Yes	Yes	Yes
Serum cholesterol	Yes	Yes	Yes
Cigarette smoking	Yes	Yes	No
Relative weight	No	No	No
Physical activity	No	No	Yes
Resting pulse rate	No	No	Yes

had the lowest. The incidence of CHD was not consistent with the death rates in Rome and the Netherlands. I suppose the most reasonable conclusion from all of this is that physical activity may be mildly protective, but the evidence is uncertain and inconclusive. In the comparison of communities the intensity of physical activity contributed nothing to explaining the differences in CHD mortality or morbidity.

Resting pulse rate. Generally the resting pulse rate at initial examination showed a graded, positive association with subsequent CHD mortality. This relation was much less apparent for CHD morbidity.

Respiratory function. The association between measures of pulmonary function and the occurrence of CHD was significantly inconsistent.

Diet. Average serum cholesterol values for the different communities were strongly correlated with the fat composition of the diet. CHD mortality and morbidity rates for the populations were associated with fat, and especially saturated fat, in the diet. As in other population studies, no association was found between dietary fat and serum cholesterol of individual study subjects. Keys presents a fairly detailed discussion of this recurrent problem of intraindividual variability.

Multivariate analyses. Analyses of the predictive value of the individual variables taken jointly provided general agreement with the univariate analyses. When the study populations are grouped into larger geographic regions, evaluation of the associations between the variables and the risk of CHD is summarized as in the table on p. 1138.

Although grouping the study subjects in this way is not strongly defensible, given the lack of homogeneity within the groups, the data indicate a marked similarity in the patterns of risk between the United States and Northern Europe and a dissociation of Southern Europe from those patterns.

When the equation derived from one of these regions is used to predict the occurrence of CHD in another, the observed incidence of CHD agrees with the predicted incidence quite well in a relative sense. That is, any population may be arrayed in groups from high to low risk by use of indices of risk derived from any other population. However, the total number of cases of CHD predicted in Southern Europe from the experience of the United States is more than one and one-half the number observed; conversely, applying the Southern European coefficients to the Northern European population yields a predicted number of CHD cases that is a little more than a third of the number observed. Thus, although the same variables determine risk in the same way in the three regions, equivalence of the risk indices does not establish equivalence of risk.

The extraction of information from this book is severely restricted by the variation in format from one graph or table to another. The 16 study groups are combined in a bewildering number of ways. Occasionally the logic of a particular aggregation is presented, perhaps in a statement that the groups did not differ, but more often no justification is given and very often antecedent data indicate that the communities grouped are very different from each other. The result of this is confusion and, even more serious, concern that the patterns illustrated often conceal important elements of diversity. One cannot select a single community and follow it through the chapters to discover how it looks with respect to CHD and each of the variables of concern. The information would be much more accessible and valuable if somewhere, perhaps in an appendix, a prescribed set of analyses of the communities had been presented in a consistent format.

The most consistent presentation is a series of graphs relating some community averages of each of the important individual characteristics to the death rates for all causes and rates for coronary disease in each community. These graphs usually include a linear regression equation and a correlation coefficient, and the correlation coefficients are often strikingly high. In a few of these graphs the magnitude of the correlation is clearly a function of one or a few outlying values combined with a cluster that appears randomly distributed.

This research presents some conceptual problems whose implications are profound but that are not discussed profoundly. The primary data, physiological measurements, are characteristics of individuals and are commonly viewed as related to the likelihood that an individual will exhibit coronary heart disease. When the average values of these variables are computed for each geographically distinct population group and the averages are related to the measured risk of illness in the communities, a different order of assessment is introduced. Comparisons of the characteristics of communities cannot be equated with comparison of the characteristics of individuals, even though the community descriptors are derived from observations of individuals. This distinction is important in all epidemiological studies where the characteristics of groups are used to draw inferences about the occurrence of disease in individuals.

This book is packed with information; the inconsistencies noted between different populations suggest many interesting avenues for additional research, and the observations need to be studied in more detail than can be approached in this brief review. Keys's contributions to the epidemiology of coronary heart disease are enormous, but this report suggests that what he has begun may be far greater even than what he has done.

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History of Mathematics

The Historical Development of the Calculus. C. H. EDWARDS, JR. Springer-Verlag, New York, 1979. xii, 352 pp., illus. $28.

Edwards explores here the antecedents and origins of the fundamental techniques of differentiation, integration, and analysis by infinite series as they were understood and set forth by Euler in the mid-18th century. Although two brief concluding chapters offer sketches of the work of Bolzano, Cauchy, Riemann, and Weierstrass in the 19th century and of Lebesque and Robinson in the 20th, Edwards concentrates on the earlier development of the calculus, in large part because he wishes to emphasize computation over concepts. That is, he presents the calculus as the outcome of some two thousand years of problem-solving. From earliest antiquity the problems involve determining the areas, volumes, and surfaces of curvilinear figures, and hence bringing the discrete process of counting to bear on the continuous realms of magnitude and motion. Later are added the problems of tangents and extreme values, of rectification of curves, and of the calculation of logarithms and of trigonometric functions.

It is specific instances of those problems, and specific techniques of solution devised to handle them, that form the substance of Edwards's book. Guided by his exegesis, the reader steps through—to cite just a few examples—the details of Archimedes's quadrature of the parabola and measure of the surface of a sphere; of Fermat's, Pascal's, and Roberval's quadrature of the general curve $y = x^k$ by means of summation formulas for series of the integers raised to powers