THE UNIVERSITY OF MICHIGAN

SCHOOL OF PUBLIC HEALTH

CENTER FOR RESEARCH IN DISEASES OF THE HEART — ANN ARBOR, MICHIGAN 48108

TECUMSEH HEALTH STUDY

130 SOUTH FIRST STREET

January 12, 1971

Answered

Dr. Henry Blackburn
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Switzerland

Dear Henry:

You will remember only too well all the trouble we had with the paper you presented at the International Atherosclerosis Symposium in Chicago when it came to "camouflaging" the Pooling Project data for publication! You will also recall that I was asked to write a review paper for the new journal "Human Pathology", that I wrote a manuscript for them on the Chicago meeting and that they replied they had wanted something else... In any case, I am now glad to report to you that this review paper was accepted for publication in "Atherosclerosis". Jerry Stamler wrote 6 pages of suggestions for various changes and revisions; these were most admirably thoughtful and cogent and I have tried to take care of them.

Some of Jerry's comments related to data taken from your own paper, specifically those dealing with the Pooling Project. I attach the two relevant pages from the "Proceedings". To my great distress, I could not reproduce the numbers which were given on page 352. I think they must have come from one of the tables which Jerry presented at our Pooling Project meeting in Ann Arbor; a copy of this table is attached. The table gives only person-years-of-experience and one cannot calculate from them the number of men in each of the 19 categories without additional information which is not on file here in Ann Arbor. There has been a delay in revising this section of my manuscript because Tom Karunas was on vacation over the Christmas holidays. When he came back and told me that he could not get the N's without going back to the tape he had sent to Jerry, I called Ancel, in the hope that he might find for me the original tables which you showed on the screen in Chicago but which we left out for reasons of "camouflage". However, Ancel could not find the copies of the slides; I was very sorry that I inflicted this time-wasting goose-chase on him. In the circumstances, I decided to reword the review rather than tackle Jerry and I attach copies of the original pages, with the corrections and changes I made.

More upsetting, really, is the part of your paper which deals with the "Multiple Regression-Type Analysis" (see attached copy of page 354). Tom Karunas had no idea where these figures came from and, certainly, it is patently impossible that there were 70 men in each of the Framingham deciles for men aged 50-59; there are just not that many men of that age in the Framingham cohort! I take full responsibility for this since it was I who re-wrote these sections of your paper, after you were so distressed -- and rightly so -- about the suggestion to take the "guts" out of it. I was so pleased that you took so kindly to my "doctoring" until just now when the ugly head raised itself again in another guise.... I suppose this is all passe now and we had better forget about it. I just hope that no one will ever quote these particular figures from your paper.... It is strange how there seems to be a hex on some manuscripts!

I am sorry to invade the privacy of your sabbatical with this communication. Obviously, you should know, I am afraid. I trust that you will forget about it as soon as it has been registered.

With all good wishes,

Sincerely yours,

Fred.

Frederick H. Epstein, M.D.
Director and Professor of Epidemiology

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Enclosures
cc: Dr. J. Stamler
Dr. A. Keys

risk of 10/1,000, whereas 1.7 times a large risk, say 20/1,000 in low risk men at age 60, is 34/1,000. Blood pressure seems to be relatively more important at younger (35–44) and older (55–64) ages than in the intermediate age group; most answers seem to produce new questions. Cholesterol level is most predictive in the youngest age group while the highest risk ratio for smoking is in the age range 45–54.

Combinations of Risk Factors. Other data from the Pooling Project deal with combinations of risk factors. Taking men ages 30–49, initially free of CHD, and four risk factors (serum cholesterol above 250, diastolic pressure 90 or over, a pack or more cigarettes per day, relative weight 1.21 or above), the incidence of myocardial infarction and CHD deaths is calculated. In such younger men, the upper third of the distribution is represented by blood pressure levels of 90 diastolic or more, and cholesterol above 250 mg; in terms of that fantasy used in clinical medicine, both cut-off values are well "within the normal range".

The absolute risk of CHD in that analysis is given as the rate of new CHD events per person years of exposure. It shows a stepwise increase from the rate when all four factors are low to the situation where all are high, with an eleven-fold gradient in relative risk. Some 13% of the healthy population at this age in the Pooling Project has all three or four factors high, and this 13% of men develop almost one-third of the new events in a given period. Also 70% of these North American men have one or more of the four factors high and develop, in a given period, almost 90% of the CHD cases. When two factors are considered, the combined elevation of serum cholesterol and blood pressure give the greatest excess risk; for the same end points, combined blood pressure and relative weight give the lowest, little more than blood pressure alone. This indicates what we know otherwise, that they are highly interrelated. This sort of information is essential to preventive approaches which are most effectively concentrated among the persons most susceptible.

Life Table Analysis. Another biostatistical approach in the Pooling Project uses the actuarial life table function at five-year intervals and gives the probability of surviving from one five-year period to the next between ages 35 and 65 while remaining free of a CHD event. The advantage of this analysis is that each individual contributes a person-year of experience at each year of age so long as he is in the exposed population and does not withdraw by having a CHD event, or is not lost by dropping out of the study or dying from a competing risk. This is the only way to take into account all the experience for persons entering at various ages and being followed for different durations. When these data are displayed as decrement curves in Fig. 1, clearly, each of the four factors is of value in predicting coronary risk and offers more in combination than separately. The curves show a remarkable, orderly progression so that almost 90% of men aged 35 remain free of CHD by the time they reach age 65, while only half of the men who are "not low" on all four factors are still unaffected over the same time span.

Sensitivity-specificity of Risk Factors. The table presents another approach to the analysis of multiple risks, based on the clinical concept of sensitivity and specificity of a predictive test, and was compiled by Epstein [437] on the Framingham data. The predictive power of the presence of two out of three risk factors is described in terms of CHD experience in eight years of follow-up.

By this particular combination of factors 23% of the cases were predicted, while only 6% of cases who remained free of CHD were "incorrectly" labelled positive. This is a severe, though realistic, and useful test of a predictive method in a chronic disease.

Multiple Regression-Type Analyses. The multiple logistic analysis of Truett and Cornfield [1477], has also been applied to the Pooling Project data in one of the first attempts to test the logistic in material largely independent of the data from which the coefficients were computed. A risk score was calculated for the Framingham age group 50–59 on the basis of coefficients computed from the Pooled Project as a whole, to which the Framingham group contributed only 20% of the experience in that age range. The end points in this instance are angina pectoris, as well as myocardial infarction and CHD death.

There is an equal number of people (actually 70) in each decile of the risk score. Only one new CHD case was observed in 12 years among the lowest 10% of scores, 21 in the highest 10%. The risk turns up rather sharply at the upper extreme. Almost 40% of the new cases occurred among the 20% of the population in the two upper deciles. The prediction fits the observed data well, it separates categories of risk as well as or better than the simple cross-classifications seen so far, and it provides a numerical risk score and rank for every individual.

Other Developments. There is much current interest in North America in describing the risk characteristics related to sudden death, and to other individual CHD manifestations. There is also now good evidence that behavioral characteristics are associated with CHD risk in North American men. These, along with the role of physical activity and a number of other possible risk factors, are subjects of continued investigation.

FUTURE NEEDS

This information is a central contribution of the long-term observational studies of North American men, first examined in a state of health. Continuation of these studies at a minimum level of follow-up on death and major disability would be the most economic way to obtain information on the risk characteristics and course of many less frequent but important diseases such as stroke, peripheral vascular disease and noncardiovascular maladies.

Long-term studies are still needed concerning atherosclerosis in women and in children. However, there is no major new hypothesis or methodological advance in North America giving impetus to new observational studies. Rather, attention is currently turned to application of current knowledge in clinical trials and pilot studies attempting to modify elevated factors of CHD risk. These will be detailed later in this symposium by their investigators.

PREVENTION

Suffice it to say here that results of the first generation of trials and pilot studies are now in the hands of the scientific leadership, public health agencies and funding bodies of this country. They provide good evidence that substantial numbers of people can be induced to modify their elevated risk factors, and that substantial reductions in the levels are attainable. The early evidence is