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Dr. William J. Zukel
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Dear Bill:

Per our conversation in Pittsburgh, attached is a copy of Kiang Liu's paper to be presented (in much abbreviated form) at the forthcoming AHA Scientific Sessions in Miami Beach, and accepted for publication by the Journal of Chronic Diseases. As I told you, I regard this as a very creative contribution, which essentially puts quantitative "flesh and blood" on the bones long lying around of the issue of the role of intra- and inter-individual variability and its effect in obscuring relationships between such variables as dietary lipid and serum cholesterol of individuals, and also tells us what is necessary to minimize this problem for various kinds of statistical analyses of such questions. I believe this essentially solves the problem of the paradox that in population studies over and over again dietary lipid is shown to relate to serum cholesterol, this is confirmed in metabolic ward studies showing changes of dietary lipid relating to changes in serum cholesterol, and in similar intervention studies of groups of free-living people (ND-HS, CPEP, MRFIT, etc.), yet the anomalous finding is repeatedly recorded of little or no apparent association between lipid intakes of individuals and their serum cholesterol levels. Of course, the problem of too limited periods of collection of diet data to overcome this problem of intra- and inter-individual variability is not the only component of this problem, as Dr. Liu's paper makes clear. There is also the matter that the diet is not the only factor influencing serum cholesterol (as shown by the sizeable persistent standard deviation of the mean serum cholesterol for groups of people when fed identically in a metabolic ward), i.e., endogenous metabolic factors are involved, with a significant genetic component certainly, and there is no current way yet found to "plug in" an estimate of these and control for them, since we do not know the specific metabolic mechanisms and therefore cannot make a measurement of them to be used as a covariate. I might note in passing that Dr. Liu is attempting to wrestle with this problem statistically. Finally, there is the fact that under the best of circumstances dietary assessments on free-living people are limited in validity. This is even true with chemical analyses, since the virtually insoluble problem is almost always present that once people know they are being observed, they can in unpredictable and non-random ways change their diets to meet their image of what is

expected of them. This is all the more true for 24-hour recalls, 7-day food records, the Bertha Burke "long method" for getting at habitual eating pattern, and applies even when the attempt is merely to characterize people, without any intervention. As we all know, from the National Diet-Heart Study, our Coronary Prevention Evaluation Program and MRFIT experiences, once people are involved in an active intervention study, this problem of their reporting distortedly becomes even more serious. Speculatively, if the error is non-random in a consistent fashion, one could still minimize the problem of distinguishing one person from another; however, it is very likely that not only is the error non-random, but also that it is an inconsistent one, i.e., not all people respond in the same way in terms of their image of what is "expected" of them. Thus, diet assessment by any methods we now know must be somewhat limited in validity, even when many measurements are made to minimize the problem of intra-individual variability. Finally, it should be noted that there is a very important implication in Dr. Liu's work in regard to methods to be used in dietary studies involving an effort to distinguish one person from another, rather than merely using data to characterize a whole group, i.e., there must be a measure of intra-individual variability, and collection of enough days of data to "get a handle" on this, and to minimize its obscuring effect. This means that methods like that of Bertha Burke -- characterizing habitual pattern, and therefore not yielding any measure of intra-individual variability -- are not suitable for this type of study, as useful as they may be for getting a description of an individual for use only in calculating a population group mean.

This adds up to the grim conclusion that data of the type collected in Tecumseh (24-hour recall) are virtually unless for any evaluation of the relationship of individual diet patterns to individual serum cholesterol levels, as useful as such data may be for characterizing the entire population or subgroups of it (e.g., men versus women, blue collar versus white collar people, different ethnic groups). Correspondingly, data of the Bertha Burke type collected in the Western Electric Study have the same limitation, for the other reason noted above.

Our good friend and colleague Ancel Keys put his finger on this whole problem of variability years ago, but it was left lying there as a qualitatively pinpointed problem, without anyone working out its quantitative details and indicating the full implications and the ways to solve it. This whole problem has been gnawing me for years, more so as time went by, not only because I don't like to have apparent paradoxes lying around unsolved, on straight intellectual grounds, but because assorted grinders of axes for special interests have used these paradoxes in a scurrilous fashion deliberately to obscure the whole diet-heart relationship. About all I contributed to the solution of this matter is to present the problem clearly to Alan Dyer and Kiang Liu, and to take advantage of the availability of brillant young statisticians to put them to work on the problem. Incidentally it should be clearly and explicitly stated that Dr. Liu has been with us only thanks to the NHLBI Training Program in Cardiovascular Epidemiology, Biostatistics, Nutrition, Preventive Cardiology that we have here.

Finally, as I told you verbally, it now becomes easy to apply these methods to the related problem of characterizing individuals in regard to habitual sodium intake, for studies to test the hypothesis that within population individual differences in that variable are related to individual differences in blood pressure, another unsolved problem lying around in a similar muddle for years. With use of data on two groups of men we are studying at the American Oil Company and the International Harvester Company, with multiple 24-hour urines and multiple blood pressure measurements on each man, we are getting Dr. Liu the body of data he needs for the empirical analyses to determine how many days of 24-hour urines are required on each person to distinguish one from another for these kinds of analyses and hypothesis testing.

As I further told you, we are also tackling the question, is the overnight urine adequate to characterize the individual, so that the much more difficult task of collecting multiple 24-hour urines could be avoided. As you know, Drs. Langford and Watson worked on this, but more refined statistical analyses are needed, and Dr. Liu is developing these. In the work at AMOCO and International Harvester, we deliberately have the people collect their 24-hour urines in three bottles, to have separate samples for the overnight, arising to lunch, and lunch to retiring portions of the output. Thus we are getting data on the overnight and the total 24-hour values for sodium, potassium and creatinine, and Dr. Liu will do the computations on the comparative reliability of each of these, and the validity of the overnight (compared to the 24-hour) in ranking people. He already has informed me that from first looks the overnight may well be satisfactory to distinguish reliably between people in the lowest quintile of sodium output compared to those in the highest. Our work on these two problems will be pursued, slowly I fear, since it's with minimal support. If indeed several overnight urines on an individual will enable us to distinguish one from the other, at least to make a reliable contrast between the lowest and the highest quintiles of sodium intake, then it becomes possibly feasible on sizeable numbers of people to test the hypothesis that habitual sodium intake relates to habitual blood pressure. We would hope to go on to do this, as well as our effort to prevent development of high blood pressure in hypertension-prone people, and to treat "mild" hypertension by such non-pharmacologic means as correction of overweight and moderation in sodium intake. Since I regard these as the most important unsolved challenges before us in cardiovascular epidemiology, prevention and control at the present time, and the problems long lying fallow because of the foregoing types of difficultues, I am determined with this breakthrough to pursue these vigorously, and to pursue efforts to get support for these. These are on my list of key things to get done, with the highest priority, "come Hell or high water"!

I hope you share with me a feeling of excitement about these developments. Again, I repeat, my contribution has been the important but limited one of clearly identifying the problems, a tremendous amount of credit goes to this fine young statistician for having finally solved them, and to Alan Dyer for his aid.

I hope you will pass this paper on to Max, and both of you will send us your comments. You may also show it to Tavia as well, particularly since the Framingham data on the very limited relationship of dietary factors of individuals to their serum cholesterol levels has been one of the challenges in this area, and Dr. George V. Mann has used these data in distorted fashion, while ignoring other data, to push the absurd claim that diet has no relationship to serum cholesterol. I would be grateful also for Tavia's comment on Dr. Liu's paper.

Finally, per our discussion, I would very much like for us to have a chance to study Abe Kagan's paper in this area, to be presented at the AHA meeting.

It was good seeing you in Pittsburgh. All the best.

Cordially,

Jerry

Jeremiah Stamler, M.D.

JS/nd

att.

Best to Marjorie. She — as well as Marilyn Farnand + Jeanne Tillotson — might also like to see this.