Dairy Products and Red Meat
Midwesterners Always Knew They Were Good for Something

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In this issue of Circulation, Iso et al1 report an intellectually stimulating observation from the Nurses’ Health Study Cohort linking diet with disease. The intake of saturated fat and animal protein, much maligned in this cholesterol-conscious world, were negatively associated with the risk of stroke due to intraparenchymal hemorrhage. A sigh of relief can be heard throughout the cattle-producing Midwestern states. Maybe there is something good in eating red meat after all.

Several aspects of this study deserve the thoughtful kind of postprandial reflection typically following a Thanksgiving feast, because those traditional Thanksgiving meats—turkey, pork, and lamb—are also sources of animal protein and saturated fat. A meal rich in protein takes longer to digest, and several pieces of cud must be chewed to put this study into perspective.

Four courses are on the menu: study population, dietary assessment, events, and significance. The study population, the Nurses’ Health Study Cohort, along with the companion Health Professional Cohort, offer Harvard epidemiologists uniquely large, prospective databases to link dietary intake with disease. The Nurses’ cohort is a relatively healthy, educated, predominantly white population. Follow-up is exceptional due to the compulsive nature of nurses who are both willing and able to complete and return extensive data forms. While acknowledging the phenomenal strength of this powerful and complete database, it is also important to acknowledge that the cohort represents a highly selective slice of the American public at large.

The second course is dietary assessment. The dietary assessment tool, a 61-item food frequency questionnaire, shares with the cohort a highly selective slice of the American diet. Dietary intake is quite complex, and 61 foods represent only a select few of the thousands of food entries possibly consumed. All food items on this short-item food-frequency questionnaire were carefully chosen on the basis of their ability to separate out individuals according to their intake of 18 nutrients.2 Thus, the focus of the questionnaire is not the quantitative intake of the individual, but foods that are most predictive of between-person variation in intake. The questionnaire format has been extensively adopted by epidemiologists because of its simplicity and its ability to rapidly return an analysis on dietary intake. It must be acknowledged, however, that food-frequency questionnaires provide less precise dietary information than more traditional dietary assessment methods.3 They are well-suited to populations such as the Nurses’ Health Study, where dietary intake is relatively homogeneous and common food selections can be condensed into a short list. Because the investigators limited their evaluation to areas of dietary intake for which the questionnaire was specifically designed, the study by Iso et al1 relies on the strengths of the questionnaire and not its weaknesses.

The third course is the event end point. Among the nearly 86 000 women evaluated over a 14-year period of observation, the incidence of stroke was 0.8%, and the incidence of intraparenchymal hemorrhage (the focus of the article) was 0.09%. It is, therefore, only the large data set that allows the investigators to collect a sufficient number of events (n=74) to study.

The final course completing our meal is the significance of the findings. For all types of strokes, no significant associations between dietary intake of total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and trans unsaturated fat were found. For intraparenchymal hemorrhage, a dietary association emerged only after multivariate relative risk assessment was performed. After this adjustment, low animal protein intake was significantly associated with a higher relative risk for primary intraparenchymal hemorrhage, both by trend and by comparison of the lowest quintile to all other quintiles. Low trans unsaturated fat intake, although not significant by trend, was significant by quintile analysis. The data were further analyzed regarding self-reported history of hypertension. It is only then that saturated fat intake emerged as having significance, but it was only significant among those with hypertension. In contrast, trans unsaturated fat intake was inversely associated with risk primarily among those without hypertension.

Should these findings encourage us to consume more red meat and dairy products? Before we answer, let’s become the cow and adopt its habit of calmly regurgitating each meal, rechewing the cud before allowing it to pass on to digestion. There are several issues presented in this article that deserve reconsideration.

The first issue is the findings of this article. The most striking finding is the high rates of intraparenchymal hemorrhage observed in the lowest quintile of saturated fatty acids,
animal protein, and trans fatty acids. Low intakes seem particularly bad for this unusual kind of stroke; higher intakes do not seem to differ in their incidence of stroke. Do these data describe a threshold effect, as the authors allude to, or do they represent a quirk in the data set? The confidence intervals for the conclusions are broad. Only the trans unsaturated fat finding achieved $P<0.01$, and this $P$ value refers not to trends of intake but to the comparison of the lowest quintile of intake to other quintiles. Do the results achieve clinical significance? Have the authors taken into account all potential confounding factors before reaching their conclusions?

A critical point required to accept the authors’ conclusions rests on the certainty with which individuals can be classified according to nutrient intake. Two articles have been published validating the adequacy of the dietary questionnaire used in this investigation. In the first validation article, the accuracy of the food-frequency questionnaire was compared with the accuracy of a 7-day food record; the latter is considered the gold standard for recording dietary intake. Data were collected from 173 nurses who filled out four 7-day food records and 2 food frequency questionnaires throughout a 1-year period. The raw data showed comparable mean intakes, but the standard deviation of most values determined by the questionnaire was twice that determined by the food record. Specifically, mean total protein intake by food record was $68.4 \pm 12.0$ g and by food frequency questionnaire, $78.2 \pm 28.6$ g; likewise, saturated fat intake by food record was $24.9 \pm 6.8$ g and by food frequency questionnaire, it was $22.8 \pm 10.6$ g. Log-transformed total protein intake, after adjustment for caloric intake, was correlated with food record protein intake with Pearson $r$ values between 0.26 and 0.33. Saturated fat intake achieved slightly better correlations between 0.32 and 0.53. Because the purpose of the dietary questionnaire was to rank individuals on the basis of protein intake and not to quantitate protein intake, a comparison was made of the classification of lowest quintile of intake by food-frequency questionnaire versus lowest quintile of intake by dietary records. Concordance of ranking to the lowest quintile was present in only 44% of individuals for dietary protein and 47% of individuals for dietary saturated fat; 9% of individuals ranked by food-frequency questionnaire in the lowest protein group were found to be in the highest protein quintile by food records, and 3% of individuals ranked by food-frequency questionnaire in the highest saturated fat intake group were found to be in the lowest saturated fat quintile by food record. Thus, the certainty by which a given individual is classified into the lowest single quintile of intake is near that of chance.

The validity of the food-frequency questionnaire was addressed by Iso et al. by referencing a second validation article for the food-frequency questionnaire. In this second article, previous data from the earlier validation article were combined with new data from an expanded version of the food-frequency questionnaire. Iso et al. provide more encouraging correlation coefficients between food records and food frequency questionnaires but do not mention the need for log-transformation to achieve these correlations and do not explain why the values reported do not exactly match those tabulated in the second validation article. The critical issue remains the ability to correctly identify individuals according to their intake. In the second validation article, only 33% of individuals classified in one quintile of intake by food-frequency questionnaire for either total protein or saturated fat were classified in the same quintile by dietary records. In a data set such as the current one, where the major finding relies on the certainty of classification of lowest intake, this magnitude of error in misclassification could make or destroy a significant association.

Other areas of bias could have potentially confounded the results. Only female nurses were studied: this is a unique population that is at risk for unusual dietary habits, including anorexia nervosa, and unhealthy habits such as drug abuse. Anorexia nervosa, a disease traditionally viewed as an adolescent disturbance, can affect middle-aged women, and it has been associated with intercerebral hemorrhage. Substance abuse (ie, amphetamines and cocaine) has also been associated with intercerebral hemorrhage, and the nursing profession has not remained untouched by this problem. Could these lifestyle habits have confounded the interpretation of the study? One can only guess.

Does the analysis adequately adjust for other factors that are known to be associated with cerebral hemorrhage? Advancing age, a known risk factor, seems evenly distributed among intakes. Hypertension, another notable risk factor, was adjusted for by a yes/no self report. Unfortunately, this is a significant weakness because the association between blood pressure and risk seems linear, even among blood pressures in the “normal” range. Alcohol intake, another factor, may not have received its proper due. It should be noted in their Table 1 that the number of participants who consumed $>25$ g of alcohol per day were more prevalent in the lowest quintile of saturated fat intake, the lowest quintile of trans unsaturated fat intake, and the lowest quintile of animal protein intake. The Honolulu Heart Program reported a linear relationship between alcohol intake and hemorrhagic stroke, but this study only included men and the amount of alcohol associated with high risk was substantial—much higher than that reported in other articles describing alcohol intake in the Nurses’ cohort. However, a Finnish case-control study evaluating both men and women confirmed a linear association between alcohol and cerebral hemorrhage in women at far lower intakes than those for men. Specifically, the short-term intake of $>150$ g the week before a stroke or $>40$ g 24 hours before a stroke were associated with a 5- to 6-fold increase in risk. Could the Iso findings be confounded by an inability to quantitate blood pressure and/or inadequate adjustment for alcohol intake?

Another factor that the authors do not directly address is the known association between warfarin therapy and the risk of intracerebral hemorrhage. The authors report that 4 of the 74 intraparenchymal hemorrhages occurred in women taking thrombolytic agents. It is not clear whether this notation refers to the use of chronic oral anticoagulant therapy or whether this refers to short-term administration of thrombolytic therapy for myocardial infarction. Conservatively, one could argue that any event associated with anticoagulant therapy should be excluded from the analysis, because the risk for hemorrhage simply from anti-
Don’t worry, says the cow. You won’t hurt my feelings if you choose chicken.

References

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