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CORRELATION OF THE NUTRITICNAL AND PATHOLOGICAL ASPECTS OF CARDIOVASCULAR DISEASE

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Coronary heart disease (CHD), cerebrovascular disease and other manifestations of atherosclerosis, have a devastating effect on the health of the population of industrialized nations and the incidence of this disease can be expected to increase in non-industrialized nations as they gradually manage to control infections and malnutrition.

Studies of the incidence and prevalence of CHD have made it clear that apparently normal subjects differ from individuals suffering from CHD in a number of habits and traits associated with the risk of CHD (Ernst & Levy, 1980). Autopsy surveys (Strong, 1977) also illustrate the association of CHD risk factors with coronary atherosclerotic lesions. The factors most commonly associated with increased risk for CHD are elevated serum lipids (particularly cholesterol), hypertension, cigarette smoking, hyperglycemia (diabetes), obesity, sedentary living, psychosocial tension and history of premature atherosclerosis (Strong, 1977; Ernst & Levy, 1980).

As a result of epidemiologic studies (Bronte-Stewart, Keys & Brock, 1955), complemented by controlled studies in animal models (Strong & McGill, 1967), fairly long-term massive clinical trials and prospective observations made during normal times (Christakis et al, 1966) and during periods of circumstantial food restriction (Malmros, 1950; Strøm & Jensen, 1951), there is agreement that diet is associated with CHD. However, there is uncertainty as to what extent diet, as a risk factor, influences the development of atherosclerosis and CHD. If atherosclerotic lesions

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are important in determining risk of CHD as commonly believed, it would be desirable to directly relate suspected environmental agents to lesions and not to CHD (McGill, 1968). In this paper I present a summary of our findings in exploring, on a case-related basis, the correlation of selected dietary variables with estimates of coronary involvement with advanced atherosclerotic lesions.

BACKGROUND

These studies were initiated as part of the International Atherosclerosis Project (IAP), a cooperative effort for the study of the geographic pathology of atherosclerosis, sponsored jointly by the Institute of Nutrition of Central America and Panama (INCAP) and the Louisiana State University, School of Medicine (McGill, 1968a).

One of the objectives of the IAP was to test current hypotheses of relationships among dietary variables and the extent and severity of atherosclerosis. Using rank correlation methods, Scrimshaw and Guzmán (1968) examined the association of selected nutrition related variables measured in the living population from which the autopsied cases in the IAP were drawn with an index of advanced lesion involvement at autopsy. The results showed significant positive correlations ($P \leq .01$) of the lesion index with serum cholesterol levels ($r=.755$) and with percent calories from fat ($r=.668$). The latter two variables were also highly correlated ($r=.741$). The correlations of the lesion index with the other nutrition related variables considered, were small and without significance, possibly because of limitations inherent in the procedures employed. In this connection, a case-related analytical approach, using measures of lesions and diet in the same subjects, might be more sensitive for detecting diet-lesion correlations.

The New Orleans sample of the IAP (McGill, 1968a) and related studies in the same locality on the relationship of cigarette smoking and atherosclerosis (Strong et al, 1969), provided a unique opportunity for the study of diet and lesions on a case-related basis. The collection, processing and evaluation of arterial specimens for lesion involvement followed the standard methods of the IAP (Guzmán et al 1968; Guzmán, McMahan & Strong, 1974). Raised coronary lesions (RCL), the measure of atherosclerosis used in these

studies, is the percent of coronary intimal surface with advanced lesions (fibrous plaques, complicated and calcified lesions).

For case-related diet-lesion studies, however, it was necessary to develop appropriate methodology for assessing retrospectively the dietary patterns of deceased subjects using information provided by surviving associates. A group of research nutritionists, under the direction of Margaret C. Moore (Moore et al, 1970) established that it was possible to obtain satisfactory estimates of the usual 28-day pattern of food intake during the terminal year of life of a deceased adult male by questioning a consenting female associate, provided a) the respondent and case shared the same household for at least one year prior to death, b) the respondent bought, prepared and served the food eaten by the subject and c) for detailed nutrient studies, the deceased, while alive, must have eaten two-thirds of his meals in the home. The use of food models in quantitating food intakes (Moore, Judlin & Kennemur 1967) reduced the range of variability, over all foods, to approximately one half of that found without the models. An updated extended table of nutrient values (available from the International Dietary Information Foundation Inc., of Atlanta, Ga) was used in calculating the nutrient data.

For the diet-lesion studies on autopsied males, aged 20-59 years, it was possible to locate and interview 456 consenting respondents who satisfied the first two conditions outlined above, and qualified for eating pattern studies. A subgroup of 253 of these respondents, also satisfied the third condition and qualified for detailed nutrient studies. The respondents in these studies had been close associates of the deceased for an average of over 15 years.

EATING PATTERN AND ATHEROSCLEROSIS

The eating pattern of the 456 men in the autopsy sample was fairly stable, since 71% of the respondents indicated only minor changes through time. In a typical day and while alive, the 456 autopsied cases slept 8 hours, ate 3 meals and 3 snacks, smoked 20 cigarettes, drank one alcoholic beverage and consumed 3 to 4 caffeine-containing drinks (Moore et al, 1975).

A preliminary evaluation of the associations of eating pattern and related variables with RCL, showed significant correlations of RCL with smoking rate ($r=.171$, $P\leq.01$) and frequency of ingestion of caffeine-containing drinks ($r=.133$, $P\leq.01$). These two variables were also significantly correlated ($r=.201$, $P\leq.01$). Additionally, this pair of variables, specially smoking rate, correlated significantly with seven other eating pattern variables, which were in turn highly intercorrelated. Most of the correlation coefficients reported by Moore et al (1975) were small, indicating a low percent ($r^2\leq.10$) of common variability for 90% of the variate pairs studied. Under these conditions a multivariate analysis approach, such as the discriminant function technique (Snedecor & Cochran, 1968), may yield better results.

The reference populations for our discriminant function analysis were the lower and upper quartiles of the distribution of RCL in the autopsy population. The stepwise construction of the discriminant function continued as long as each new variable significantly ($P\leq.05$) increased the power of the function to discriminate between the low and high RCL reference populations. This stepwise procedure, in their order of selection, identified five variables out of ten included in the model: number of meals and heavy snacks, frequency of caffeine drinks, frequency of alcoholic beverages, 10 year cigarette smoking rate and ingestion span. The last variable listed is the time lapse between first and last food taken in a 24 hour cycle and may reflect activity or stress conditions.

If sequence in selection of variables in the stepwise discriminant analysis is indicative of the relative importance of the selected variables for differentiating low and high RCL populations, then factors in the eating pattern that relate to a life style that may influence metabolism merit careful consideration. In other words, in studying the etiology of atherosclerosis and CHD, it may be necessary to consider when and how we eat and not just what we eat (Moore et al, 1975).

NUTRIENT INTAKE AND ATHEROSCLEROSIS (RCL)

The studies reported here examine, on a case-related basis, the association of nutrient intakes and involvement with RCL. The nutrient intakes were expressed on a calorie-

related basis to minimize distorting effects from large individual differences in calorie intake. Analysis of variance was used for detecting differences and trends in the RCL involvement of subjects included in tertile groupings of their intake of 46 specific nutrients (Moore et al, 1976; 1977).

Preliminary analyses showed that the composition of the nutrient tertile groupings was not determined by either race or age, both strong associates of RCL (McGill, 1968a). Accordingly, a significant difference in RCL involvement among the tertile groupings for a given nutrient, accompanied by a significant increasing or decreasing trend, may be interpreted as evidence of association of that nutrient with lesion involvement.

Among the 46 nutrients included in the RCL analyses by nutrient tertile groups, 29 gave some evidence of trends in lesion involvement. These trends were significant in the case of 14 of the nutrients considered. A summary of significant results is presented in Table 1.

Table 1 SUMMARY OF SIGNIFICANT RESULTS OF F TESTS FOR LINEAR TRENDS IN PERCENT RAISED CORONARY LESIONS (RCL) IN TERTILES (T_i) DEFINED BY CALORIE-RELATED NUTRIENT INTAKES

Nutrient	MEAN RCL			F tests for	
	T_1(84)	T_2(85)	T_3(84)	Means	Trends
Animal protein	26	29	39	$P \leq .01$	$P \leq .01$
Vegetal protein	39	30	25	$P \leq .01$	$P \leq .01$
Lysine	29	27	38	$P \leq .05$	$P \leq .05$
Total fat	25	35	35	$P \leq .05$	$P \leq .05$
Myristic acid	27	28	39	$P \leq .01$	$P \leq .01$
Oleic acid	25	35	34	$P \leq .05$	$P \leq .05$
Starch	42	29	23	$P \leq .001$	$P \leq .001$
Fructose	24	31	39	$P \leq .01$	$P \leq .01$
Thiamine	41	26	27	$P \leq .001$	$P \leq .005$
Riboflavin	26	30	38	$P \leq .05$	$P \leq .05$
Niacin	24	28	43	$P \leq .0001$	$P \leq .0001$
Calcium	25	33	37	$P \leq .05$	$P \leq .05$
Sodium	40	30	25	$P \leq .01$	$P \leq .01$
Iodine	24	32	38	$P \leq .01$	$P \leq .01$

The positive association of animal protein intake, in parallel with the negative association of the intake of proteins of vegetal origin and of starch with RCL, suggests that an increased consumption of foods of vegetal origin may help in protecting against atherosclerosis. Whether the protective effect results from specific elements in plant foods, or is simply an indication that persons who consume more foods of vegetal origin, in general, eat less of the rich foods that contain substances commonly regarded as atherogenic, is a question that remains to be answered. Our case-related results in a sample of deceased individuals, however, agree with other studies which suggest that higher consumption of plant foods and particularly of starch, may be associated with lower serum cholesterol (Grande, Anderson & Keys, 1974; Garcia-Palmieri et al, 1980) which is generally accepted as related to less atherosclerosis and CHD (Epstein, 1965; Christakis et al, 1966).

Some of the more specific nutrient-lesion associations presented in Table 1, may be the result of the relations already described in terms of major nutrient classifications or general food sources. Thus, the positive association of lesions with lysine, riboflavin, calcium and iodine are not surprising since foods of animal origin were the principal sources of these nutrients. Similarly, fairly large amounts of common salt are used in cooking foods of plant origin, and therefore the negative sodium-lesion association may reflect a carrier effect - in this case starchy foods, legumes and vegetables. Given the fairly high content of niacin in coffee (Bressani & Navarrete, 1959), the positive association of niacin intake with lesions may result from the positive association of RCL with frequency of consumption of caffeine-containing beverages. Nevertheless, the possibility that these associations also reflect direct effects cannot be discarded; these hypotheses merit further investigation.

The positive association of the intake of myristic acid with RCL is compatible with results of other studies that have identified the intake of saturated fats as a risk factor for CHD (Epstein, 1965; Ernst & Levy, 1980) because of the association of these rats, and particularly of myristic acid (Hegsted et al, 1965), with high serum cholesterol values. In our studies, two other saturated fatty acids, palmitic and stearic, were also positively but not significantly, related to lesions; there was no

evidence of association of the intake of polyunsaturated fatty acids with RCL. The intake of oleic acid was positively related to atherosclerotic lesions, but this result may be only a reflection of the overall positive association of total fat intake with RCL.

The association of lesions with the intakes of thiamine (negative), and fructose (positive), at present cannot be explained on the basis of their known nutrient and food-source associations.

COMMENT

The consistency of our results with current knowledge of the association of nutritional factors with atherosclerosis and CHD, points to the desirability of extending these studies to include other populations with different life styles and nutritional conditions. The results from such studies may help in identifying the factors that are contributing to the declining trends in CHD mortality reported for the United States (Epstein, 1965; Cooper, Stamler, Dyer & Garside, 1978) and other countries (Morris, 1979). In this connection, Strong and Guzmán (1980) have recently reported an apparent reduction in RCL involvement which parallels a reduction in CHD mortality and on such basis suggest that the surveillance of atherosclerotic lesions at autopsy may be an effective indicator of secular trends in CHD. Our results indicate that surveillance of lesions in parallel with surveillance of risk factors, will contribute to the better understanding of the pathogenesis of CHD. This, in turn, will make possible the definition of better preventive measures relating to diet, smoking, exercise and medical control of elevated blood pressure. Meanwhile, as Morris (1979) has pointed out, "the preventive measures currently proposed are all beneficial in themselves", and their sensible application may produce immediate benefits in terms of reductions in CHD mortality.

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