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RELATIONSHIPS OF DIET AND CHRONIC DISEASES

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INTRODUCTION

I will summarize here the relationship between nutrition and chronic degenerative diseases, mainly cancer and cardiovascular diseases. For greater detail, I refer you to the National Research Council's report on Diet, Nutrition and Cancer and the latest U.S. Department of Agriculture and Department of Health and Human Services "Dietary Guidelines" just released in October 1985, as well as to recommendations of a number of official parties including the American Heart Association, American Cancer Society, and Intersociety Report (Circulation, 1984). Then, I would like to summarize what I see as a rapid resolution of controversy about diet and chronic disease, within the profession and between the profession and the food industry and agriculture. I will indicate how close I believe these recommendations are now to a single, generic diet recommendation for the public health, one which is adequate nutritionally for growth and development, which is vastly improved in regard to chronic disease prevention in a high risk society, and which is optimal for the promotion of health and reduction of high risk in the general population, and for the prevention of high risk in the first place.

DIET - CANCER

There are important population differences in the frequency of cancer by site. There are also important changes in the population frequency of cancers and in the frequency and the risk of cancer in migrants whose risk very rapidly approaches that of their adopted culture. There are important dietary differences between these populations having different cancer rates, and there are strong group correlations of habitual diet and cancer rates. Generally, high fat, low carbohydrate diets, and the high consumption of salted and

smoke-cured foods are associated with high risk of cancer. Generally, high carbohydrate, low fat diets, high in vegetables, fruits, grains and plant foods are associated with low cancer risk. These population, group or ecological correlations tend to exaggerate differences associated with diet but provide clues to public health influences. Science correctly gives more credence to correlations between diet and disease for individuals within populations. Such studies in cohorts followed over time are more difficult and expensive to carry out, but are important for causal inference. Relationships of specific cancers to individual diet have been found within populations. In addition, both induction and inhibition of experimental cancers have been found in laboratory studies. When individual correlations, population correlations and laboratory results are congruent, then it is highly appropriate to turn back to the population findings as an important source, perhaps the best source, of public health recommendations. Natural experiments, generations long, in which certain eating patterns are associated with relatively low cardiovascular disease rates, relatively low cancer rates, and generally favorable growth, development, longevity, infant and overall mortality, are excellent guidelines to prevention in populations. I'll briefly summarize the correlations of diet components with cancer.

TOTAL CALORIES

Total caloric intake has not been studied effectively in well designed population studies in which either the composition of diet, or body mass, or obesity have been controlled in the analysis.

Mechanisms have been studied in animals, however, and consistently animals on restricted food intakes do better than those on ad libitum diets in regard to cancer risk and survival. But even here, reduction of calories is confounded

with reduction in components of the diet such as fat. Mechanisms are, therefore, not established, and, consequently, no official recommendations are being made in regard to total calorie intake. This appears wise also from observations in the Seven Countries Study where populations that eat the most are the leanest and also have among the lowest chronic disease rates (both CVD and cancer). The average number of calories consumed by a population is one measure of its habitual physical activity, so we conclude that active populations are liable to be leaner, and have lower disease rates. (There are exceptions such as Finland.) Reduction of total calories alone, in a high risk culture, would, therefore, not necessarily be an effective approach to population obesity or to cancer or cardiovascular disease prevention unless attention is also paid to diet composition.

OBESITY

With respect to cancer, obesity and overweight, both population and individual correlations are found with prostate and colon cancer in men, with breast cancer in post-menopausal women, and perhaps with the increase in breast cancer, along with the increase in weight, of non-white women in the U.S. There is also a general relationship of obesity with gallbladder, ovarian, and uterine cancer.

However, mechanisms are not established. They are thought to have something generally to do with the total number of body cells, and something more specifically to do with estrogen production in the obese. Again, epidemiological studies of obesity and overweight are inadequately controlled for diet composition and for physical activity. Consequently, official recommendations with respect to obesity, by the American Cancer Society and USDA-DHHS Guidelines, recommend only the general avoidance of obesity and

maintenance of desirable weight.

DIETARY FAT

Population comparisons show group correlations between composition of the habitual diet in fat and cancers of the colon, breast and prostate. Individual correlations within cultures show the same, but weaker correlations, and study results are inconsistent. The correlations found are with total fat, saturated fat, and with meat and egg intake. Saturated fat shows the most consistent and powerful association. There are no good data on dietary cholesterol.

With respect to mechanisms, there are findings that colon cancer in animals is enhanced by increased production of steroles and bile acids, which goes along with a high fat diet. There has also been interest in the ultimate importance of polyunsaturated fats, at low fat intakes overall, and the apparent disappearance of their importance with higher total fat intakes in experimental animals. There has been a good deal of study of peroxidation effects of polyunsaturates, i.e. damaging DNA, as well as the effect of high fat diets on prostaglandin metabolism and on estrogen production.

The conclusion of the NRC Diet-Cancer Report is that dietary fat is the strongest of the dietary influences and the most consistent between population studies and laboratory experimental findings. They conclude that the combined evidence suggests this relationship is true and causal, and that most is likely to be gained in cancer prevention by lowering fat intake. This population recommendation is reduction to 30% calories or less.

PROTEIN

Protein intake is hopelessly confounded with fat intake; they go together--the greater the protein intake, the greater the fat. However, the conclusion is

that fat is probably more important because the correlation is stronger and a few plausible mechanisms exist. However, an independent effect of protein on cancer risk is not ruled out.

Mechanisms are unclear. Animals with borderline protein malnutrition show suppression of experimental tumor formation.

The findings taken together have resulted in no specific recommendation concerning diet protein and cancer.

CARBOHYDRATE

Carbohydrate intake is also hopelessly confounded because a high carbohydrate diet is equivalent to a low fat diet, as protein is usually constant in human diets. There is nothing known about mechanisms, even very little about sugar versus starch versus other complex carbohydrates and tumor genesis. There is no official recommendation in regard to carbohydrate intake other than the concern with total calories and obesity.

FIBER

Fiber is confounded with high carbohydrate and low fat diets. It occurs in many food groups in many forms. There is an inconsistent correlation between fiber in the diet and colon cancer. Mechanisms are obscure. The evidence suggests that there is probably a specific fiber, maybe one associated with whole wheat grain (pentosans), rather than a general beneficial effect of fiber in respect to cancer prevention.

The recommendations from the National Research Council are to increase regular consumption of whole grains, fruits and vegetables, but there is no specific mention of fiber. NIH concludes that "fiber can't hurt," and it has gone along

with the cereal industry in recommending and promoting fiber. The American Cancer Society suggests also that fiber is probably worthwhile in reduction of colon cancer risk and, at any rate, high fiber foods tend to replace fat in the diet, and that is desirable.

VITAMINS

Vitamin A

The inverse association of cancer with vitamin A is fairly widely found. The higher the consumption of carotenes (precursors of vitamin A), the lower the risk of cancer of the lung, urinary bladder and the larynx. However, vitamin A and carotenes are hopelessly confounded.

Mechanisms studied in animals suggest that vitamin A protects. But vitamin A is very toxic, so most studies have been done on retinoids, carotenes, which are found to protect against bladder, skin, lung and breast cancer in animals.

Recommendations from the National Research Council are to increase carotenes or retinoids as foods, but not to take vitamin A supplements. The American Cancer Society recommends increased green and yellow vegetables and fruits and no vitamin supplementation.

Vitamin C

Epidemiological evidence is inconsistent in regard to vitamin C and lung cancer, but it is pretty good in respect to esophagus and stomach cancers.

Mechanisms are thought to be the vitamin C effect on cells and on transformed cells, as well as in-the-stomach inhibition of nitrosomine mutagen formation such as from moldy foods.

The recommendations of the NRC are to increase whole grains, fruits and

vegetables. The American Cancer Society recommends to increase fruits and peppers.

Vitamin E

Vitamin E is badly confounded because it is so widely prevalent in human diets. There is little epidemiological study, but one suggestion of an inverse relationship to lung cancer.

Mechanisms proposed are that vitamin E inhibits nitrosomines. The evidence is insufficient for recommendations.

Vitamin B

On B vitamins there are inadequate studies and no recommendations in regard to cancer.

MINERALS

Selenium is the trace element most studied, but the epidemiological evidence is not strong, e.g. mainly contrasting populations having different selenium content of their soils. The results suggest that there may be associated differences in lung and GI cancer in selenium deficient areas. Selenium also has distinct anti-tumor effects in animals, at levels bordering on toxic. Thus, selenium supplements are not advised and no general diet recommendations are made as yet.

Molybdenum is thought to be important because of its deficiency in diets of the region in mainland China where the major cause of all adult deaths is esophageal cancer. Molybdenum reduces nitrosomine tumorigenesis, however, there are no recommendations on diet intake other than the RDA.

Iodine deficiency is associated with thyroid cancer.

Salt, nitrites and smoke curing of meats all appear to relate to risk of esophageal and stomach cancer. The mechanisms are thought to do with the production of nitrosomines as well as the aromatic hydrocarbons which act as mutagens.

Recommendations are to minimize intake of salt and smoke-cured materials and for food processors to reduce the occurrence of these in processing and preservation.

ALCOHOL

There is a general relationship between alcohol and breast cancer, but study results are inconsistent. There is a strong synergistic relationship between alcohol and smoking (or chewing tobacco) with cancer of the lung, mouth, larynx, and esophagus. A specific relationship is found between heavy beer drinking and rectal cancer, but this finding is inconsistent and the mechanisms are quite unknown.

Recommendations include "moderation," without specifying what moderation is, along with a strong recommendation not to combine smoking or chewing tobacco with alcohol drinking.

MUTAGENS

Intake of mutagens from charring, broiling, smoking of meats and other naturally occurring mutagens in food are the subject of broad interest and experimentation. However, there are apparently as many natural cancer inhibitors as there are mutagens which alter DNA. The recommendation is to avoid mutagens and consume inhibitors.

COFFEE

The epidemiological evidence is weak and inconsistent concerning coffee and pancreatic cancer, and there are no official recommendations on coffee and cancer risk.

CARDIOVASCULAR DISEASES

Briefly, in regard to cardiovascular diseases, there are long demonstrated correlations between diet, blood lipoproteins which are precursors for atherosclerosis, and disease. The epidemiologic observations are largely consistent with clinical and laboratory findings. These are summarized here.

DIET FAT

With respect to dietary fat, particularly saturated fat, the population correlations are high, on the order of 0.8 between intake and coronary disease (CHD). This is the most consistent of all diet correlations, and dietary fat intake and serum cholesterol average levels explain (statistically) most of the population differences in coronary heart disease rates. Individual correlations within populations are weaker, presumably related to homogeneously high fat intakes, as well as weak methods of diet assessment. These individual correlations, to which science properly gives most credence, are greatly enhanced by methodological attempts to reduce variance, and are found to be significant in the Boston Irish Brothers Study and The Western Electric Study in Chicago.

Monounsaturated fat may have an inverse relationship to coronary disease as well as to total mortality rates in populations. That fact will be reported in detail in November 1985 at a New York Academy of Science meeting on monounsaturates. Polyunsaturated fats show no correlations with CHD at the

population level.

Congruence of population and individual correlations, and clinical and laboratory studies lead to conclusions in regard to dietary fat and vascular disease that a high intake of saturated fat is probably a necessary factor for the occurrence of mass atherosclerosis and CHD. In the presence of low saturated fat intake, that is less than 10%, there is no mass atherosclerosis, even in the exceptional circumstance where the diet overall is relatively high in fats (the Greek Islands). So it is not necessary that a diet be low in fat to be low in cardiovascular disease risk if the fat is mainly monounsaturated. It is also not necessary that the diet be high in polyunsaturated fat in order to avoid high population rates of atherosclerotic diseases.

Mechanisms of saturated fat have to do with total and LDL cholesterol levels and mass hypercholesterolemia. Diet is the major population determinant of LDL average levels. LDL is the major mass pathogen and shows the most dietary responsiveness. In addition, HDL is individually predictive of low risk in high incidence populations, but is less responsive to environment. Low LDL is the necessary factor for low individual and population risk; HDL contributes to low risk in the individual but has little to do with population risk. Dietary cholesterol is important in that it raises blood LDL as a square root function of dietary intake.

BLOOD LIPOPROTEINS

LDL is considered from vast evidence as the mass pathogen, while HDL is considered the individual protector in high risk cultures. Individual correlations of LDL and CHD are strong and continuous. The experimental trial evidence parallels the observational study evidence. A 1% difference in LDL is

associated with 2% difference in coronary heart disease rates. This concordance between the trial data and observational data confirms the causal relationship as well as the potential for prevention in populations from public health recommendations on diet for healthy persons.

Mechanisms for blood lipids and atherosclerosis are well demonstrated by induction and regression experiments in animals.

Official recommendations have to do with lowering total blood cholesterol average in whole populations, lowering LDL in individuals and in populations, and increasing the HDL level in individuals, all with a combined public health and medical approach.

COMPLEX CARBOHYDRATES & FIBER

These are totally confounded between high carbohydrate, low fat diets. They have slight contributory effects to total cholesterol level, body mass and glucose tolerance in individuals.

In summary, it is generally concluded that saturated fats are the major determinant of population levels of low density lipoprotein and thus the major population influence on atherosclerosis and CHD. Monounsaturated fats probably have no specific effect and allow a wider flexibility of total fat intake in regard to atherosclerosis risk. Polyunsaturated fats are not necessary, and probably not desirable, beyond the small amounts required as essential fatty acids, somewhere in the neighborhood of 3% to 5% of calories.

There are many official recommendations regarding nutrition and cardiovascular disease. Most of them center around the prudence of decreasing total fat to 30% of calories, decreasing dietary cholesterol to 300 mg, increasing complex

carbohydrates and fiber. There are no specific recommendations at this time on fish oils. There are many recommendations for various food choices to achieve these nutrient recommendations.

INDEPENDENT EFFECTS

There are very likely effects of diet on CVD independent of the blood lipoprotein mechanisms of atherogenesis, but, if so, they are poorly understood. They may have to do with coagulation, platelet agglutination, thrombosis and prostaglandin metabolism, such as with fish oil effects. They also may have to do with blood pressure levels and related polyunsaturated fat intake, salt, potassium, calcium and magnesium intake.

SALT

There are strong correlations between salt intake in populations and mean blood pressure levels, or the frequency of adult hypertension. Within populations, individual salt-BP correlations are weak, largely explained by the homogeneously high intake of salt in western cultures and the weak methods of measuring salt intake. Dietary calcium is apparently unrelated to blood pressure levels in populations or individuals.

With respect to mechanisms, sodium restriction lowers blood pressure and sodium raises blood pressure in some nonhypertensives. Sodium effect is in part suppressed by potassium. The mechanisms are obscure and related to blood volume and arteriolar resistance. Calcium blood levels are important but are independent of diet intake of calcium.

Official recommendations are for decreased salt in food processing, less eating of salty foods and added salt, and an increased intake of potassium containing foods.

DIABETES

Diabetes is mentioned here because of its frequency and its relationship to diet. Adult onset, Type 2, noninsulin dependent diabetes may be considered a complication of mass obesity, or at least of truncal obesity. The epidemiology is not complete in this field, but in geographic comparisons, low frequency of noninsulin dependent diabetes is associated with high carbohydrate and low fat diets. The most blatant example is east Pakistan with 2% diabetes and 83% carbohydrate diet. West Pakistan has 17% diabetes and a low carbohydrate, high fat diet, 47% carbohydrate. In addition, high fat diets are generally associated with high atherosclerosis complication rates, such as coronary disease in diabetics who are free of these in low fat consuming cultures.

CIRRHOSIS

Hepatic cirrhosis is the only major disease prominently related to alcohol and is responsible for the mass phenomenon. Certain HLA types may be responsible for individual susceptibility to cirrhotic effects of alcohol.

DISCUSSION

Diet-disease controversy is frequent when there is a lack of concordance between population and individual correlations. When correlations are concordant there is a tendency to think they are due to a common factor and that the common factor is probably diet composition. However, when they are discordant, there is need to go further in research to find whether and why the factor important in populations is unimportant in individuals or vice versa. This discordance is often explained by homogeneous conditions within the

population and by great measurement variability.

MASS PHENOMENA

There is long appreciation in the scientific community for the fact that individual, intrinsic, genetic differences are the important determinants of individual risk, within high risk cultures where the cultural influences are strong and widely distributed. On the other hand, there is increasing appreciation of the fact that population cultural differences probably determine most of the population risk, where individual susceptibility is widely or similarly distributed. The relative force of a risk factor may be greater for the population than the individual.

Another source of diet-disease controversy is the confusion of population and individual changes and their import. A clinician considers a 10 mg/dl change in blood cholesterol of no significance. He can't measure it in an individual and it probably has very little biologic significance in an adult patient. On the other hand, a 10 mg% difference in mean value, and a downward shift in the distribution of cholesterol level for a whole population has a tremendous estimated public health impact.

These parts of controversy are being resolved by increased understanding of the public health importance of a small benefit acting over a large number of people. A change from 230 to 210 mg/dl average total cholesterol (TC), where we now are on the distribution, is associated with a 30% reduction in coronary deaths in this country in 15 years. A change of another 10% to an average of 190 mg/dl would be estimated to be associated with another 20% drop in CHD deaths, by populations having that level. In the Mediterannean Basin, for example, 50% of U.S. rates of the '60s and '70s obtain. A fall to a mean of

160, only another 10% drop, would be associated with the virtual absence of coronary disease based on observed population differences. There are similar estimates for the public health impact of small changes in average blood pressure in populations. These observations conform well to experimental evidence.

Another controversy being resolved, perhaps not as rapidly, is the issue of a medical approach versus a public health or population approach to prevention. Some academic clinical investigators say we must detect and treat "all those with high risk," but leave the rest of the people alone. In addition to the difficulty of defining high risk, with a continuous risk measurement, and the difficulty of screening and referring all such people and then caring for them, there is the greater problem for prevention. Most disease events attributable to high cholesterol or high blood pressure levels occur in the central part of the population distribution of values rather than at the extremes. Seventy five percent of CHD cases attributable to elevated cholesterol are in 45% of people in the so-called "normal range" of 220 mg/dl to 310 mg/dl.

Therefore, we are dealing with mass disease in which whole cultures differ from each other by a factor of tenfold in the frequency of cardiovascular disease or cancer. Coronary disease rates are very low in Japan and the Greek Islands, very high in northern Europe and the U.S. Populations also differ from each other in distribution of mass characteristics associated with these diseases. For example, there is almost no overlap between the east Finns and the southern Japanese in blood cholesterol values, a vast difference which cannot be explained by differences in their genetic composition. We are dealing with mass phenomena; genetic heterogeneity accounting much for the rank of an individual within the population, but mass socio-cultural factors (e.g. diet)

accounting for the position of the distribution in space and for the large average differences in risk factors.

Consider the idea further, that mass diseases result from the interaction of powerful cultural factors on widespread population susceptibility. It would seem that a favorable environment should encourage minimal exhibition of susceptible phenotypes and minimal disease.

MODERN HUNTER-GATHERERS

Let me suggest that modern humans are basically hunter-gatherers metabolically. The hunter-gatherer diet and lifestyle, to which we are undoubtedly adapted by survival characteristics over the major phases of evolution, consisted of alternate scarcity and abundance of calories, a variety of foods, predominantly plant in origin, high in vegetable protein and complex carbohydrates, low in simple sugars, high in minerals, vitamins and fiber, high in potassium, low in sodium and low in fat and saturated fat. We probably have an evolutionary legacy then of survival to scarcity, a mainly plant diet, and to opportunistic, not obligatory, low fat meat eating from wild game.

RESOLUTION OF CONTROVERSY

Many lines of evidence are converging in the current resolution of diet-disease controversy. As well, public eating behavior and change in the agricultural establishment are tending toward an eating pattern lower in fat, higher in carbohydrate, fiber, vitamins, and minerals, and lower in sodium. They tend toward a Mediterannean or an Oriental eating pattern in composition. The Mediterannean style has been lightly characterized as follows: "Many vegetables mixed together, plenty of cereals, olive oil, lots of herbs, few animal fats, not much meat, quite alot of fish, little sugar, a variety of

fruits, a relaxed atmosphere at table, a little wine but not too much, a few thousand year's experience, and boundless love."

But we still encounter negative public and professional attitudes. "We can't change people's habits," is one. On the contrary, we've observed in a very short time a shift in emphasis from fatty to lean meats. We think it quite possible that the Minnesota Heart Health Program collaboration with the Minnesota Beef and Pork Council will result in a rapid spread of our "Lean Meats Make the Grade" program, a small but broad effect on eating pattern. Dealing with a mass phenomenon such as excess saturated fat consumption, a widespread but small reduction in saturated fat consumption by the consumers' choice of leaner meats can have a profound impact on mass hyperlipidemia and eventually on mass disease.

Similar "environmental programs" in restaurant menu selection are being tested in a strategy of education for mass changes in attitudes in regard to saturated fat, salt, and including the promotion of non-smoking.

ATTITUDES

Also, a public health strategy to prevention must deal with professional attitudes in which "moderation" is the goal, i.e. a legacy from the Greeks of "a healthy mind in a healthy body," or "moderation in all things." But this, in my view, is poor advice, because "moderation" is not a scientific term, and is not quantitative. On the contrary, what is moderate, as what is liked and disliked, is totally culturally determined. Thus, moderation for one group may be nauseating for another. Moderation in our culture may be gross excess in other cultures. Recommendations need to be more precise.

We also have the problem of three different professional views and experience

of disease and the study of disease. Much of the professional controversy is resolvable by appreciation of the validity of each, and the complementary nature of the evidence from each method. The clinical approach is concerned with individual differences, importantly genetic, and the tailoring of therapy to fit the individual metabolic defect. The academic view to find basic mechanisms, the mechanisms at the cell level, a never ending search in the laboratory where one is not called upon to make public health decisions. Then there is the population and public health view, based on epidemiological evidence for population-wide differences and exposures. Socio-cultural disturbances and distortions may be the "metabolic defect" for whole populations, and they require "diagnosis" and reasonable public recommendations for gradual change.

Finally, there is a prevalent attitude that all these recommendations, of NRC/NAS, the American Heart Association, USDA and HHS, etc., are somehow depriving us of an American right to live "high," and somehow deny us of something we've earned by hard work, i.e. the "natural" increase in fat intake and fall off of plant food staples with increasing affluence. Sometimes we can agree with Ogden Nash: "Progress -- might have been alright once, but it went on too long."

CONCLUSION

I would like to emphasize in closing that the profession is now clearly coming together on recommendations for diet and eating patterns for healthy Americans. These recommendations are approaching one eating pattern. I emphasize also the relevance of natural experiments in populations as guidelines to public health recommendations when the population data are congruent with clinical and laboratory findings. These are, in my view, better guidelines than clinical

and animal studies because they are tested for generations in attractive and palatable ethnic eating patterns. I'd like to emphasize that the recommendations so far made by the National Research Council, The American Heart Association, USDA/HHS, NIH, The American Cancer Society and a dozen other official agencies are on the whole quite "moderate." They are also flexible and allow wide individual variation, and permit gradual accommodation of food and agriculture. These official recommendations are parallel to ongoing change in the consumer demand for leaner red meats, more poultry and fish, more whole grains, beans, vegetables and fruits, low fat dairy products, low salt and low sugar products, and reduced mutagens in foods. These recommendations also parallel ongoing changes in agriculture associated with the increased cost of fuel and grains, the cost of obese animals, i.e. their finishing in feed lots; the inefficiency of energy transformation of grains to beef relative to fish, pork and poultry; the tendency toward husbandry and feeding for leaner breeds and lower fat carcasses; the low fat dairy dairy product marketing; the recent lean meats promotion and greater relative profits from fruits and vegetables. Finally, the profession is coming to a wider understanding of the different viewpoints and complementary evidence about disease and diet, between that from the clinic, that from the laboratory and that from the population at large.