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Summary of the Conference on Nutrition in the Causation of Cancer[1]

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Sufficient information has been presented at this symposium to make it reasonable to assume that nutrition and cancer are related and that there are opportunities for prevention in this area. Many of the epidemiological associations, however, are the general ones that occur with "development" or increasing affluence. On the dietary side the common pattern includes more food, more fat, meat, cholesterol, eggs, and sugar, more additives and processed foods, and less carbohydrates, especially crude cereals. Also associated is better health in children, more rapid growth rates, and larger size, less physical activity, and less infectious disease, as well as a host of other changes in the way of life. These are the same associations that relate to coronary heart disease. Clearly, association does not mean causation. The job is to determine which factors are causally related to cancers that are more prevalent in affluent societies, or less common in the developing societies, and there is no reason to assume that there are single causes.

I can probably fulfill my function best by pointing to some of the problems and opportunities that we face in trying to determine the role of dietary factors.

Many of the associations that have been presented are based upon the food supply for different countries as developed by the Food and Agriculture Organization. While there is no doubt about the general trends, it must be emphasized that these are rather soft data and particularly that data from some countries are much softer than for others, but we are generally ignorant of the accuracy of the data from any particular country or for any particular nutrient. Thus, when Dr. Berg presents correlations between breast cancer and total fat of 0.8, but 0.6 with regard to protein and 0.5 with regard to sugar, one cannot assume that the data for each country (the food data or the prevalence data) are equally accurate or that the data with regard to fat, protein, and sugar are equally accurate. Information on local production is often poor. The values do not necessarily represent consumption values. Wastage is substantial but the degree of wastage and the kinds of food wasted differ from one country to another. Even in the United States or other developed countries, we have rather poor data on actual food consumed and we can expect, for example, that wastage of fat in this country may be large for many groups and larger than, say, for sugar.

Furthermore, we must remember that dietary patterns within countries (between regions with differing agricultural practice or between social classes) may differ as much as the differences between countries that we have been discussing. It is probably remarkable that national statistics seem to make as much sense as they do. Nevertheless, it would seem clear that what is needed are prevalence and dietary data within regions that demonstrate some consistency with regard to the factors in which we are interested.

Improvements in the dietary data, whether within countries or within regions or social classes, can presumably come only from dietary surveys. This brings us to consideration of the accuracy of the information obtained in such surveys. First, we should note that there is essentially no way to determine the true accuracy of such data. One can determine reproducibility of the technique used but an assessment of accuracy would require the collection of duplicate samples of the material actually consumed and analysis for the nutrient or other substances in question. Since food samples vary in nutrient content and dietary data are usually interpreted from food tables, we rarely know how well the food table duplicates the actual material eaten. Certainly, the order of magnitude is right but a true figure of accuracy cannot be stated for any particular survey.

It is my impression that, given a relatively homogeneous population group, well-conducted surveys of several types yield about the same estimates *on the average*. The choice is usually a 24-hr recall of the food eaten with which one can examine a large sample or a more detailed survey with fewer individuals. It should be clear that a 24-hr intake or even a 3- or 4-day intake does not necessarily characterize the intake of an individual, but most techniques yield similar estimates of the average intake of the group examined.

In any survey it must be true that the results are dependent upon the nature of the questionnaire, the expertise of the nutritionist, the cooperativeness of the respondent, his ability to recall, and other factors. Also survey data for some nutrients are inherently more accurate for some nutrients than others. For example, the protein and iron content of diets in the United States is reasonably constant per 1000 kcal, whereas the vitamin A or vitamin C content is quite variable. For the latter nutrients, as well as riboflavin, calcium, and certainly others, we obtain an adequate intake by consuming relatively small amounts on some days and quite large amounts on others. The vitamin A intake will be low on those days when green and leafy vegetables are not consumed and much higher than the requirement on the days when they are consumed. The intake of these nutrients that are consumed irregularly is much more difficult to assess than those that are evenly distributed in food. This fact alone explains why in most surveys in the United States we find fairly large proportions of the population consuming

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less than adequate amounts. The surveys simply overestimate the degree of deficiency of these nutrients. Generally speaking, nutritionists have done a rather poor statistical job of defining the degree of reproducibility of dietary data and the sources of error. I have suggested elsewhere (2) some of the things that might be done to improve the evaluation of such dietary data.

Unfortunately, very little has been done to investigate the reproducibility of *individual* dietary histories. I am personally rather pessimistic about the study of individuals, which is inherent in case studies. The dangers of such studies are exemplified by prior data on coronary artery disease, heart attacks, and serum cholesterol levels. In the Framingham population, as an example, dietary studies failed to reveal a relationship between diet and serum cholesterol level. Various people have concluded that the diet can have little to do with the level of serum cholesterol or heart attacks. Such conclusions ignore the universal experience that in any group of men fed a constant diet on a metabolic ward, differences in serum cholesterol levels persist; yet when one modifies the diet the cholesterol level will go up or down as predicted. The differences between individuals, presumably representing genetic differences, are large. Approximately 10% of American men have serum cholesterol levels of 200 mg/100 ml or less and are at little risk of heart attacks more or less regardless of the diet they eat. Thus, when the genetic variable is large, relative to the dietary variable, one should not be surprised if case studies do not show the expected correlation with dietary patterns, and certainly one cannot conclude from such studies that diet is not a variable of importance. Since incidence rates for cancers are low within relatively homogeneous populations, it seems certain that inherent susceptibility is an important, probably the most important, factor.

Studies on dietary relationships to heart disease have an advantage over similar studies with regard to cancer. In the former the risk factor is apparently serum cholesterol, not diet *per se*, and one can measure serum cholesterol. To this degree the mechanism is understood and the effectiveness or expected effectiveness of dietary modification can be estimated. We have no such short-term indicators of cancer susceptibility.

One must also consider the cancer rates. For many we are talking about rates of 5, 10, or 100 per 100,000 of the population. A doubling of the rate from 5 to 10 or even from 100 to 200 would be a very large change. Yet during the year there are 99,000 or so in the population who do not develop the disease. Unless the dietary differences are large, these differences in rates must be well within the error term of dietary data.

It is true, of course, that over a lifetime a very large number of people develop cancer. Thus, in an extended study the probability of determining differences is improved. However, it still calls for a degree of accuracy in dietary data that may be well beyond that which can be achieved.

The situation is quite different when one is comparing population groups. Mean differences in intake can be rather easily demonstrated, although substantial improvements in the design and analysis of survey data can be made (2).

Some distinction has been made in this symposium between nutrition and diet. Nutritional status, which is ordinarily thought to mean the assessment of the adequacy of the intake of essential nutrients, may well be an important factor and must be considered when evaluating population differences. Yet I believe it is more important to stress that we are entering a new era of nutrition, which may or may not have much to do with essential nutrients. Heart disease is again the prime example, at least as far as we know, of a major disease in which there is a strong dietary component but which has little or nothing to do with essential nutrients. There has been a long and continuing argument over whether fluoride is an essential nutrient, *i.e.*, essential for life. This is a rather unproductive argument since the effect of fluoride on dental decay is obvious and its use in public health has nothing to do with our usual definition of essentiality. The fact is that it is essential for the maintenance of good dental health even though dental cavities might be avoided on low-fluoride diets if we could be nourished by by-passing the mouth. In all probability the matter of cancer of the colon, whether it be related to fat or meat or dietary fiber, will have little to do with essential nutrients.

It is now becoming clear that the adequacy of a diet with regard to iron cannot be assessed by a knowledge of the iron content. The availability of dietary iron is affected by several factors, including the kind of iron in the diet and the foods that are eaten with the dietary iron and that promote or retard absorption. Thus, although an adequate diet must supply iron, other factors are more important than the iron content itself.

It will obviously be difficult to evaluate dietary data if one does not know what one is looking for. I call to your attention the apparent inverse relationship between milk consumption and gastric cancer presented by Dr. Hirayama. It seems unlikely to me that if this is a causal relationship it is related to essential nutrients in milk. We should note Dr. Wattenberg's paper in which stimulation of the mixed oxidase resulted from the consumption of materials in the vegetables of *Brassica* family and that various phenolic antioxidases also have an effect. Clearly, conventional dietary histories will not evaluate such variables.

The role of dietary fiber is and, I think, will remain in limbo until we decide what dietary fiber is and until we are capable of measuring it. If we mean by dietary fiber those materials that affect fecal bulk, it is clear that the conventional "crude fiber" reported in food tables is not what we are talking about. This has long been evident (3, 8). Anyone who has examined the feces of rats fed a crude diet and a purified diet containing cellulose will recognize this also. Furthermore, the more elaborate methods of determining "unavailable carbohydrate" (6, 7) are simply empirical methods and it is uncertain which, if any, of the fractions measured are of physiological importance. I am distrustful of the attempts to correlate "fiber" intake with disease whether these show positive or negative correlations. Yet there is no doubt that there are materials in food that cause the changes generally ascribed to "fiber" or "bulk."

I see no way out of this dilemma other than hard, painstaking studies in the laboratory, with both patients and animal species. We must begin to dissect food again with regard to those factors that may play a role in carcinogenesis. It would seem certain that this will call for increased use of animal models, and I have already pointed out that we have been relatively unimaginative in the use of the animals available. Rather, we have been more or less content to utilize the laboratory rat, whose nutritional needs are better defined than any other species. We have also failed to utilize the potential that genetics has for developing more useful strains within species. We should also be aware that, although we can use purified diets with rats, and these have great advantages in many experimental situations, the use of such diets may eliminate from consideration materials that may be exactly those of prime importance. Thus, the whole process of developing the most appropriate diets for experimental animals should be continually evaluated.

I would also comment on the matter of caloric restriction. At the moment this is the one agreed way in which one can modify susceptibility to cancer and also clearly influence aging and longevity (4, 5). This has great implications and may be relevant to much of the epidemiological information presented at this symposium. However, the energy needs of humans are a relatively unexplored field. In spite of the great advances in enzymology and our current understanding of the systems for the production of useful energy within the body tissues, these have contributed little to our understanding of the energy needs of humans. We calculated energy needs by measuring the basal metabolic rate and adding the amount of energy required for physical work. According to these estimates much of the world's population is deficient in calories and should not be able to survive. Obviously, they adapt to low energy intakes, but we do not understand what this means or how it is accomplished (1). This is a fundamental problem to much of biology and, in view of the problems of the world food supply, is crying for investigation.

I would also note that our experimental models may not be very appropriate. Ordinarily, when we restrict animals, we feed them 1 meal a day, which they consume in a very short time. Feeding 1 meal a day produces a number of metabolic changes, and it is not the way that underfed populations consume their food.

Finally, I would support Dr. Wynder's position that one does not need to know all of the answers before one can make practical recommendations. Indeed, if we take that position we will never make recommendations. Rather, we must consider the problem in terms of our best knowledge and the degree of risk involved. We known what the risks are in our current life-style, dietary and otherwise. We should ask ourselves what the risks are of recommending more "prudent diets." Such diets mean consuming less fat, less meat, less cholesterol, and less food and more fruits, vegetables, and cereals, especially crude cereals. I believe that the only risk one can identify is to the well-being of the industries involved. These industries deserve some consideration, but their interests cannot supersede the health interest of the population they must feed. We, of course, must use proper caution in how we present our case. Excessive claims or changing recommendations disillusion the public. We can anticipate a long and continuing debate since the case for similar changes with regard to heart disease has a stronger base and has been continually made but with only modest progress.

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