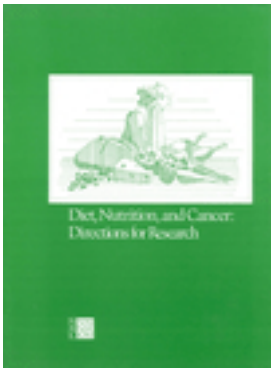

Diet, Nutrition, and Cancer: Directions for Research

Committee on Diet, Nutrition, and Cancer, National Research Council

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Committee on Diet, Nutrition, and Cancer
Commission on Life Sciences
National Research Council

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This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

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Preface

In June 1980, the National Cancer Institute (NCI) commissioned the National Research Council (NRC) to conduct a comprehensive study of the scientific literature about diet, nutrition, and cancer. The NCI requested that a study committee be constituted to carry out three tasks: (1) "review … the state of knowledge and information pertinent to diet/nutrition and the incidence of cancer"; (2) "develop a series of recommendations related to dietary components (nutrients and toxic contaminants) and nutritional factors which can be communicated to the public"; and (3) "based on the above state-of-the-art appraisals and the identification of gap areas, develop a series of research recommendations related to dietary components and nutritional factors and the incidence of cancer."

The NRC Governing Board assigned administrative responsibility for the overall project to the Executive Office of the Assembly of Life Sciences, now the Commission on Life Sciences. Subsequently, a 13-member Committee on Diet, Nutrition, and Cancer and one advisor were appointed to conduct the study. The committee's first two tasks were completed in June 1982 with the publication of a 496-page report entitled Diet, Nutrition, and Cancer. The specific boundaries of the territory surveyed under the general heading of diet, nutrition, and cancer were defined in this report, which concentrated on the relationship between the nutritive and nonnutritive components of diet and the etiology and prevention of cancer. The report also included several interim dietary guidelines for dissemination to the public.

The committee responsible for the third task, i.e., the development of recommendations for research, included 12 of the 13 original members and one advisor. The group provided a broad range of expertise in such disciplines as biochemistry, embryology, epidemiology, experimental oncology, microbial genetics, microbiology, molecular biology, molecular genetics, nutrition, nutrition education, pathology, public health, and toxicology. Institutional affiliations and major research interests of these committee members and the NRC staff are presented in Appendix A at the end of this report.

The Committee on Diet, Nutrition, and Cancer is indebted to the many scientists who contributed their ideas on directions for research and to those who participated in the miniconference on future research. Their names appear in Appendix B. It is also grateful to those who reviewed selected sections of this report at the request of the NRC. The committee particularly takes note of the excellent support received from the NRC staff headed by Dr. Sushma Palmer and consisting of Dr. Kulbir Bakshi, Mrs. Frances Peter, Mr.

Robert Hilton, Ms. Susan Barron, and Mrs. Denise Belgrave. The support and assistance of Drs. Diane Fink, Andrew Chiarodo, and William DeWys, the past and present NCI project officers for this study, are also acknowledged.

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CHAIRMAN
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Diet, Nutrition, and Cancer: Directions for Research

1

Overview and Major Recommendations

Many diseases now known to be associated with dietary imbalances or toxic contaminants in food were once thought to arise from other causes, ranging from "bad air" to disorders of the "bodily humors." Their associations with diet have tended to be worked out by the same sequence of discoveries. First, a particular human disease is linked to some aspect of diet, e.g., a lack of fresh vegetables or the fungal contamination of grain. Alteration of the diet (by crude additions or subtractions) is then shown to prevent or alleviate the disease. Subsequently, someone succeeds in producing a similar disease in an animal model (e.g., scurvy in guinea pigs or mycotoxicoses in rats and mice), which leads to the precise identification of the active components of the diet (e.g., a nutrient or a toxic ingredient). Finally, laboratory scientists discover the mechanism by which the nutrient or toxin exerts its effects, although by this stage such details have become mainly a matter of academic interest because the disease in question has already been eradicated.

A similar sequence of discoveries has taken place in some branches of cancer research. Chronic exposure to coal tar in mineral oil was observed to cause skin cancer in humans more than a century before laboratory investigators succeeded in producing cancers in rabbits by painting their skin with coal tar. Once the cancer had been produced experimentally, the active carcinogens in the tar--polycyclic aromatic hydrocarbons--could be purified and identified, and later, their mechanisms of action explained. By this time, however, skin cancer in humans resulting from such exposure had long since been effectively abolished by general improvements in working conditions in factories; however, laboratory studies of these and other carcinogens have continued and have provided important insights into the mechanisms of carcinogenesis.

These historical examples may seem too simple for predicting the the course of research to unravel interactions between a multifactorial disease like cancer and a complex mixture like diet; but they may give us some idea of what to expect. Although interest in the study of diet and carcinogenesis can be traced to laboratory experiments performed more than half a century ago, it seemed in the 1960's that we were still in the first stages of the sequence described above. At that time, despite evidence from early experiments that modification of either total food intake or some dietary components could influence carcinogenesis, the possibility that diet per se was a significant factor in human cancer was still considered remote. Then epidemiologists linked the incidence of several common cancers, e.g., breast cancer, with certain general dietary patterns. Laboratory scientists followed up these observations by developing animal models for cancers suspected of being affected by diet. Subsequently, epidemiologists observed that the high incidence of breast cancer and certain other

cancers is associated with a diet high in fat or its components, and laboratory investigators found that mammary cancers in certain species were similarly modified by changes in the amounts and types of dietary fat. Further studies may eventually permit isolation of the active dietary constituents, definition of the exact mechanism for the effect exerted by fat and other dietary components, and delineation of the precise diets capable of counteracting some of these effects.

However, research on nutrition and carcinogenesis has not invariably followed the sequence described above. Of the many hypotheses generated by the results of early experiments in animals, only some have been followed up by epidemiological studies. For example, clues about the effect of the caloric content of the diet per se on experimentally induced carcinogenesis have remained largely unexplored. Similarly, leads produced by international correlation studies of human populations have not always been followed up by more controlled epidemiological and laboratory investigations. For example, the finding in the mid-1960's that low selenium intake may be associated with increased cancer incidence or mortality has been tested in well-controlled laboratory experiments, but no controlled epidemiological studies (i.e., case-control or cohort studies) could be conducted because of a lack of knowledge about the precise intake of selenium.

It is never possible to predict exactly where major discoveries will be made, and any attempt to stipulate a particular sequence for research on diet and cancer would tend to stifle creativity. Therefore, the committee has been rather cautious in making suggestions. Nevertheless, it may be desirable to plan the research on diet and cancer in a logical but flexible conceptual framework that could encompass all the sources of data, i.e., surveys to monitor exposure, epidemiological studies, carcinogenesis bioassays in animals, short-term tests for genotoxicity, short-term in vivo bioassays to detect early biological indicators of carcinogenesis, and studies designed to elucidate metabolic pathways or pathogenic mechanisms.

After completing an assessment of the literature in 1982, the Committee on Diet, Nutrition, and Cancer concluded that “the differences in the rates at which various cancers occur in different human populations are often correlated with differences in diet. The likelihood that some of these correlations reflect causality is strengthened by laboratory evidence that similar dietary patterns and components of food also affect the incidence of certain cancers in animals.” Thus, concordance between epidemiological and laboratory data served as the principal basis for the degree of certainty allotted to conclusions and as the basis for the interim dietary guidelines proposed in the first report. The selection of this criterion reflects the committee's conviction that persistent interaction between epidemiologists and laboratory investigators is necessary to provide a framework for future research that will lead to a more definitive understanding of diet and carcinogenesis.

STRATEGIC OBJECTIVES AND PRIORITIES FOR RESEARCH

The committee has operated on the principle that research on diet and cancer should encompass the seven strategic objectives presented below. From the numerous suggestions for research made in this report, it wishes to call attention to certain general recommendations, which are listed following the strategic objective to which they apply.

1. Identification of the foods and of the dietary macro-and microconstituents that alter the risk of cancer, and elucidation of their mechanisms of action.

In the first report, the assessment of the literature resulted in the preliminary identification of four categories of dietary constituents that are likely to affect the risk of cancer. These were saturated and unsaturated fat; certain fruits, vegetables, and whole grain cereals; smoked, cured, and pickled foods; and alcoholic beverages. The committee recommends that when the epidemiological and experimental evidence associating particular dietary components with cancer risk is sufficiently convincing, studies should be undertaken to identify the specific active constituents and their mechanisms of action. For example, attempts should be made to identify the constituents of fruits and vegetables that are responsible for the observed reduction in risk associated with their frequent consumption and to define the mechanisms of action of those constituents (see Chapter 7). Similarly, studies should be pursued to elucidate the mechanism(s) by which a high fat diet increases the incidence of certain cancers (see Chapter 6). Information from such studies would be useful in refining the interim dietary guidelines recommended by the committee in its first report.

2. Improvement of the data base and the methodology for assessing human exposure to foods and dietary constituents that may alter the risk of cancer.

Better epidemiological methods should be developed to monitor and quantify dietary exposures in human populations in order to establish more clearly the relationship of dietary constituents and dietary patterns to the occurrence of cancer. For example, innovative methods are needed to measure past dietary intake. Furthermore, better techniques should be sought to validate the data produced by all these methods. Regular nutrition surveys to monitor dietary intake would augment the data base for epidemiological studies of diet and cancer (see Chapter 4).

3. Identification of markers of exposure and early indicators of the risk of cancer.

The committee recommends that attempts be made to identify early biological or biochemical changes that reflect the ability of specific

dietary constituents or dietary patterns to alter the risk of cancer in humans. For example, where neoplasia is used as the sole end point, investigations are severely limited by the long latency period between "exposure" and "expression." Therefore, one of the most pressing needs is the development of short-term tests that could identify early biological indicators of exposure to dietary constituents that affect carcinogenesis (see Chapters 4, 5, and 7).

4. Determination and quantification of the adverse or beneficial effects of the foods and of the dietary macro-and microconstituents that affect the risk of cancer.

The committee recommends that efforts be continued to evaluate the impact of potentially carcinogenic or inhibitory dietary constituents on cancer risk. These studies should include a focus on substances that can damage macromolecules, especially DNA; on those that can enhance experimentally induced carcinogenesis, i.e., promoters and cocarcinogens; and on those that can inhibit experimentally induced carcinogenesis (see Chapters 5, 6, 7, and 8).

5. Determination of the ranges of optimal intake of dietary macro-and microconstituents.

Attention should be given to determining ranges of dietary macro-and microconstituents that are optimal not merely for the prevention of deficiency diseases but also for the promotion of other aspects of health, including the reduction of the risk of cancer. For example, it would be useful to establish a dose-response curve for selenium and to define the optimal range of selenium intake, giving special attention to the levels that might be needed to achieve a reduction in the risk of certain cancers (see also Chapters 5, 6, and 7).

6. Intervention to reduce the risk of cancer.

Intervention studies should be conducted using foods or food constituents believed to be associated with a lower cancer risk, but only when a substantial body of data indicates a high likelihood of benefit without discernible risk. For example, attention might be given to reducing the consumption of fat and/or adding specific fiber components to the diet (see Chapter 6), and to the ingestion of different levels of certain microconstituents or of foods containing potential inhibitors (see Chapters 4 and 7).

7. Application of knowledge about diet and cancer to programs in public health.

To maximize the potential impact of public health programs to reduce the risk of cancer, studies should be pursued to elucidate factors that motivate people to modify their food habits. For example, it would be useful to analyze bodies of longitudinal data to learn what they reveal about factors that determine consumption patterns in different populations (see Chapter 9).

2

Approach to the Study

This report suggests useful directions for research into the relationship between diet, nutrition, and cancer. From the beginning of its study, the committee was cognizant of the widely held belief among scientists that research is most vigorous when it is the product of individual choices by investigators, rather than the result of a preconceived strategy. However, when research has an important and defined practical objective, the committee believes that there is justification for concentrating a part of the overall research effort on questions that are recognized to be central to further progress toward that objective. In approaching its task, the committee adopted the strategy described in the following paragraphs.

The assessment of the literature in the committee's first report (National Research Council, 1982) served as the primary guide to the identification of needed research. As indicated in that earlier report, the evidence associating some dietary constituents to carcinogenesis was judged to be sufficiently convincing to allow the committee not only to formulate conclusions about their carcinogenic or inhibitory effects but also to propose interim dietary guidelines toward reducing the risk of certain cancers. Among these dietary components are total dietary fat; certain fruits, vegetables, and whole grain cereals; cured, pickled, and smoked foods; and alcoholic beverages. No firm conclusions could be reached on other dietary constituents.

The committee recognized, however, that by working solely from its first report, it would be identifying only those gaps in knowledge that were implied by the already published literature. To gain assurance that it was not overlooking as yet unpublished work on new avenues of research that might have an important bearing on the relationship between diet and cancer, and to obtain insights from other researchers in the field, the committee constituted an informal panel of more than 100 distinguished scientists knowledgeable about cancer, nutrition, and related areas. These panelists were asked to contribute their suggestions for research. In addition, approximately one-third of the nearly 70 investigators who responded by sending suggestions were invited to meet with the committee at a miniconference devoted to exploring ideas for fruitful research. The resulting long lists of suggestions were consolidated and combined with the suggestions generated by the committee. Priority items were then selected.

This report contains both general and specific recommendations, reflecting the relative state of knowledge in each area. Unlike the committee's first report, which was suitable for the general scientific community, this report is directed primarily to investigators in the field and to institutions that support them.

In the chapters that follow, the committee makes three kinds of recommendations for future research. One set of recommendations derives directly from gaps in the current state of knowledge about the effects of specific dietary components. Where conclusions are uncertain, simply because information is incomplete, recommendations are directed toward supplying missing data. Where the uncertainty stems from the imprecision of the data, there are recommendations for methodological improvement. Where several causal factors seem to be operating, there are recommendations that their interactions be studied. Such recommendations only highlight what would be obvious to an experienced investigator.

A second set of recommendations arises from the fact that there are multiple etiological factors in carcinogenesis, including combinations of dietary components, complex steps in cancer progression, and a multiplicity of cancer types. This complexity has led the committee to make recommendations for long-term, multifaceted studies that are necessarily large and therefore unavoidably expensive. Such studies are likely to be most informative when they can be conducted under especially favorable circumstances. For example, high risk human populations may be studied under circumstances that permit simultaneous study of multiple risk factors. Information from such studies could be supplemented with laboratory data derived from a suitable animal model.

A third kind of recommendation calls attention to the need for behavioral and social studies. This stems from the finding in the committee's first report that most common cancers appear to be influenced by diet--suggesting that, to a certain extent, individuals may be able to influence their chances of getting cancer. However, knowledge that a certain exposure strongly influences cancer is apparently not sufficient to convince people to modify their behavior. For example, it is clear that simply demonstrating a causal connection between smoking and lung cancer has not eliminated the smoking habit. Therefore, the committee has addressed the need for social and behavioral research to supplement research in the area of physiology, pathology, cytology, nutrition, and biochemistry.

This report deals primarily with research on diet, nutrition, and cancer. The committee made no attempt to discuss other environmental or genetic factors that are known to be associated with cancer. However, Chapter 3 briefly addresses the relationship between research on the basic mechanisms of carcinogenesis and our overall understanding of the ways that diet affects cancer. Although it is the committee's judgment that research on diet and carcinogenesis can progress without waiting for further discoveries in basic mechanisms, it is aware of the need to press forward simultaneously with fundamental investigations, particularly taking advantage of new opportunities afforded by recent advances in cellular and molecular biology. Such fundamental research is likely to improve not only our understanding of the impact of diet

and nutrition on carcinogenesis but also our ability to address many aspects of the prevention and treatment of cancer.

Chapters 4 and 5 discuss methodological shortcomings regarded by the committee as major hurdles in the comparison and interpretation of data from both epidemiological and laboratory studies. Research to refine methodology as well as to reexamine certain methodological issues is recommended.

The next three chapters deal with specific dietary components. Macroconstituents (i.e., total caloric intake, fats, protein, carbohydrates, dietary fiber, and alcohol) are discussed in Chapter 6. As noted in the first report, it often is difficult to separate the effects of fat, protein, and carbohydrates. This is particularly evident in studies to determine the effect of changing the total caloric intake--which may be accomplished by changes in the levels of any or all of the three macronutrients. Compared to information that has been provided by a multitude of studies on fats, less is known about proteins and there are relatively few data on the effects of different types of carbohydrates. Therefore, there is a need to identify more clearly the effects of protein and carbohydrates, especially the individual components of dietary fiber. In its first report, the committee concluded that the evidence relating fats and certain alcoholic beverages to cancer is sufficiently convincing to justify certain interim dietary guidelines; however, further research is needed to expand the data base for both of these dietary components. It is also necessary to identify the effects of the individual components of fat as well as the mechanisms by which a high fat diet appears to increase the incidence of certain cancers.

Chapter 7 focuses on several microconstituents, i.e., vitamins, minerals, and nonnutritive constituents, and on foods rich in these substances that have been either identified in laboratory experiments as inhibitors of carcinogenesis or associated in epidemiological studies with a lower risk of cancer. We need to refine our knowledge about the effects of these components, to identify the active constituents in fruits and vegetables, and to elucidate their mechanisms of action.

Chapter 8 takes up two major subjects on which the committee did not reach firm conclusions in its first report: (1) mutagens in foods and (2) substances in foods that are naturally present (e.g., mycotoxins), that are intentionally added (e.g., additives), or that accidentally enter the food supply (e.g., pesticide residues). The contribution of such substances to overall cancer risk cannot be fully assessed for several reasons, including insufficient knowledge about the exposure of humans, the absence of carcinogenicity test data on the vast majority of these compounds, and our inability to estimate reliably the risk from exposure, even to those chemicals that are known to be carcinogenic. The committee emphasizes the need to obtain information that will enable us to understand the relevance of dietary

mutagens to human health and to determine the level of risk posed by mutagens, additives, and contaminants.

Although the committee makes no attempt in this report to focus separately on research on methods to assess risk, this theme--the need to quantify the level of risk--is encountered time and again, especially in discussing the applicability of results from laboratory studies to human health. Clearly, there is a need to develop better methods for assessing the risk to humans arising from the presence of initiators and modifiers of carcinogenesis in the diet.

Chapter 9 examines how knowledge about diet and cancer can be applied in the development of public health programs aimed at modifying behavior to reduce cancer incidence. The committee believes that studies of the factors that motivate change in consumer behavior will be necessary if knowledge on diet and cancer is to yield benefit to public health.

The first report of this committee contains extensive lists of references. Since this second report draws heavily on the same literature, the citations herein are limited to studies not previously described.

3

Diet and the Mechanisms of Carcinogenesis

Much of what we know about the causes of the most common cancers in humans has been provided by empirical studies of the epidemiology of cancer, rather than by laboratory studies of mechanisms. For example, the carcinogenicity of cigarette smoke was established for humans even though the laboratory investigator had not found a susceptible laboratory animal. But our understanding of the mechanisms of carcinogenesis has come mostly from observations of experimental animal models.

The study of experimentally induced cancers in animals, especially the production of skin cancer in mice and rabbits, has shown that carcinogenesis can be divided into early stages ("initiation") and later stages ("promotion"). With rare exception, agents that are powerful initiators have proved to be powerful mutagens (or to be capable of being metabolized into mutagens). In contrast, the most powerful promoters have proved to be agents that alter various cell properties, especially the structure of the cell surface and the pattern of gene expression. Despite these studies, the molecular biology of carcinogenesis remains obscure; it is not known whether mutagens act as initiators because they produce mutations or for some other reason, and the processes underlying promotion remain equally obscure. There is no unanimity in the scientific community on this point; however, numerous investigators believe that many, if not most, cancers in humans will eventually be shown to be the result of our exposure to the mutagenic initiators and the promoters in our environment.

It is not at all clear that the sequence of steps leading to the "spontaneous" cancers in animals can always be separated into these two stages. For example, the stages in the production of feline leukemia and bovine esophageal cancer certainly do not fit comfortably into that dichotomy. Similarly, the main risk factor for liver cancer in humans is chronic infection with hepatitis B virus, even though this virus does not appear to be a mutagen and there is no evidence that it would score as positive in any test for ability to promote the later steps of carcinogenesis.

Therefore, as we try to disentangle the effects of diet on cancer incidence by hunting through the foods we eat for mutagenic initiators and for agents that promote the later steps of carcinogenesis, we should keep in mind that the important dietary determinants of cancer rates in humans may not fall readily into one of these two classes. For example, it has not been easy to decide what mechanism is most likely to be responsible for the observed effect of a high fat diet on the incidence of cancer. The following suggestions have been made:

- Fat could enhance carcinogenesis by contributing to the formation of peroxides and other reactive forms of oxygen, which could then damage DNA.
- A high fat diet may increase excretion of sterol metabolites in the gut, which in turn may promote tumorigenesis in the colonic epithelium.
- Certain fatty acids in the diet could be incorporated into cell membranes, possibly producing changes in cell behavior that are associated with promotion.
- Certain essential fatty acids participate in the synthesis of prostaglandins, and these may influence tumorigenesis.
- A high fat diet could lead to a change in the level of certain hormones that in turn might affect the incidence of breast cancer and some other cancers.
- Lastly, fat may increase cancer rates for reasons that we cannot at present guess, simply because we do not yet know enough about the pathways that lead to cancer.

We do not know the extent to which the "initiator-promoter" model is applicable, but the answer to this question may not be critical to the design of laboratory experiments or epidemiological studies in the near future. From the evidence accumulated thus far, however, it seems clear that carcinogenesis is usually a multistep process. Furthermore, it has been observed in both epidemiological and laboratory studies that the effects of diet seem to operate more often upon the later steps than upon the earlier ones.

Up to this point, we have discussed only those agents that stimulate the production of cancer. Recent evidence has indicated that there are other agents that inhibit carcinogenesis. Therefore, as a start to the further study of the effects of diet, we would like to find out whether the critical variable is the degree of exposure to agents that stimulate the production of cancers (which otherwise would not occur) or to agents that inhibit the production of cancers (which otherwise would arise spontaneously). Even though our primary interest is in studying those agents in our environment that stimulate or inhibit the occurrence of cancer, we should remember that the action of such agents may often be modified by familial, possibly genetic, factors. For example, although the incidence of breast cancer is apparently related to fat intake and age at first pregnancy, it is well known to be strongly influenced by familial factors, which may have an environmental as well as a genetic component.

Certain technical advances are now offering us a new source of information about the mechanisms by which cancers are produced in

humans. Until recently, the process of looking for signs of DNA damage or changes in gene composition and expression was like looking for a needle in a haystack. But new methods may enable us to identify the fundamental abnormalities that determine the properties of cancer cells, i.e., which genes are changed, which show altered expression, and which cellular products are present in an abnormal form or quantity. Thus, we can see that the time may soon come when the molecular biologist will be able to give the epidemiologist some clues about factors that are likely to be critical in the production of certain cancers.

It seems generally true that the benefits derived from fundamental discoveries about mechanisms tend to arise in completely unexpected ways. For example, one of the advances that has made the study of cancer genes possible was the discovery of the restriction enzymes of bacteria--a result of studies that had no obvious connection with carcinogenesis. (Because of our knowledge of these enzymes, which are absolutely specific to certain base sequences and can be used to break up DNA molecules into short stretches, it has been possible to work out the exact sequence of whole groups of genes and to determine exactly the way in which certain cancer cells differ in sequence from their normal counterparts.) Thus, although the following chapters contain numerous recommendations for specific research areas to be pursued in the study of diet, nutrition, and cancer, the committee recognizes that important insights into the mechanisms and dietary causes of cancer may also come from research in areas that are not discussed in this report.

RESEARCH RECOMMENDATIONS.

This chapter contains no recommendations, because the general mechanisms of carcinogenesis are not within the purview of this report. Suggestions for research on the mechanism(s) of action of individual dietary components are included in the chapters that follow.

4

Epidemiological Methods

The investigation of diet and cancer in human populations has been complicated by concerns about the adequacy of the various methods of assessing exposure. The following list summarizes the approaches that have been used to measure dietary exposure in epidemiological studies:

Methods Based on Group Data	Methods Based on Individual Data
National per-capita intakes	Food intake records or diaries
Household food use	Recent (24-hour or 7-day) diet recalls
	Diet histories
	Biochemical markers of exposure
	Anthropometric measurements

These approaches and their respective strengths and limitations were described in detail in Chapter 3 of the first report by the Committee on Diet, Nutrition, and Cancer (National Research Council, 1982). The following paragraphs summarize methodological problems that characterize epidemiological studies of diet and cancer and provide suggestions for research.

Assessment of dietary intakes can be based either on group data or on data collected directly from individuals. The most frequently used method in the first category is the estimation of per-capita intakes from national food disappearance data; however, because of the rudimentary nature of such data, these estimates may not be very accurate indicators of actual consumption levels. Assessment of household food use can be based on recall histories of consumption, collected from the chief food-preparers, or on the availability of food supplies in the home, recorded by a household member or a trained nutritionist. Since this method requires contact with individual households without producing individual consumption data, it is not often used. These so-called "group" methods have proved useful for aggregate correlation analyses, which are often the basis for generating new hypotheses. Such aggregate correlations, however, do not control for confounding factors, nor do they necessarily reflect associations at the individual level.

The second type of method is based on data collected directly from individuals. These data are obtained by a variety of mechanisms, particularly through diet recalls and the contemporaneous recording of

weights or volumes of foods consumed. The collection of data from food records necessarily focuses on current intake. Because this method requires meticulous attention to detail, it is practical only in studies involving small, selected samples. Diet recalls, on the other hand, can be collected from much larger and more representative samples. In contrast to recent recalls, which are focused on specified brief periods close to the time of interview, diet histories, which are also based on recall, assess usual intakes over a longer period in the past. Thus, diet histories can be used to study intakes prior to the onset of disease in cancer cases, even allowing for relatively long induction periods. Therefore, this method has been used most frequently in investigations of the etiology of disease.

The use of biochemical markers of exposure, such as components of body fluids or tissues, represents a somewhat different approach to dietary assessment. Unfortunately, few markers that reflect long-term dietary exposures have yet been identified, since the concentrations of substances in biological fluids such as serum and urine are usually related to recent exposures or to the functioning of homeostatic control mechanisms rather than to long-term intakes and body stores. In another method, certain anthropometric measures known to be correlated with obesity (including indices based on height and weight or skinfold thickness) have sometimes been used as indirect indicators of nutritional status. Since past weight, for example, can be obtained by interview, these measures are not necessarily limited to the assessment of current nutritional status.

For studies involving large samples, the diet history is the most practical and useful method. Although many investigators have expressed reservations about approaches that rely on long-term memory, there have been few studies on the validity and reproducibility of any of the diet recall methods used in epidemiological studies. Because dietary habits do not remain constant throughout life, even diet histories must be focused on a particular period. In some instances, as in studies of putative promoters, relatively recent intakes are of interest, whereas in studies of initiators, early dietary habits are likely to be relevant.

It is important to recognize that recall errors tend to be random and apply equally to the comparison groups (e.g., cases and controls). Thus, they will contribute to a reduction in the estimate of relative risk and tend to lead to a false negative conclusion. Therefore, in the interpretation of data from studies using the diet history method, a finding of a significant association is likely to be considered valid, whereas a negative finding (i.e., lack of an association) would not be assigned as much weight.

The collection of diet histories requires consideration of a wide array of variables, since eating reflects complex social, behavioral, and cultural patterns. Thus, food preferences, the temporal pattern of

eating, portion sizes, use of condiments, and methods of food preparation (such as frying) and storage (which can affect nutrient content and provide opportunities for contamination) should all be considered, since any of these factors might have important influences on cancer risk. In few studies have investigators elected or been able to consider these many factors simultaneously. Moreover, current approaches to dietary data collection are generally based on the subjects' recollection of food items consumed, not their constituents, whereas most of the hypotheses being tested pertain to nutritive or nonnutritive food components. Since all foods are collections of such components, it has not been possible to relate the findings in epidemiological studies specifically to single constituents of foods.

Data collection is only the first step in the assessment of dietary exposure in epidemiological studies of cancer. The food intake data have to be classified in a meaningful manner and, in many instances, converted into nutrient equivalents. Useful data on food composition have been published by the U.S. Department of Agriculture (1975), and many investigators have assembled additional information from a variety of specific sources. Unfortunately, the data base is not uniform or complete, and the composition of a particular food item is not fixed and consistent; it may vary by the location and the season of its growth and by the method of its processing. Thus, the average or representative values in the food composition tables may be relatively inaccurate indicators of nutrient intakes for discrete population subgroups and may contribute to false negative conclusions, as explained above for diet histories. In addition, many nutrients and all nonnutritive components of foods (e.g., naturally occurring flavones or food additives) are not included in these tables, although they may be factors of interest in the testing of certain dietary hypotheses.

Epidemiology provides the only direct approach to the assessment of risk for human beings. However, because dietary measurements are not precise, estimates of risk or benefit tend to be less than the true effect. Furthermore, because small increments in risk might be accounted for by chance variation or by uncontrolled confounding factors, a relative risk (i.e., incidence of the disease in those exposed divided by the incidence in those not exposed) of less than 2.0 is rarely concluded to be meaningful. Other difficulties arise because of the latent period that must elapse between the initial exposure and the development of the disease--a period that could well encompass a number of decades and be affected by a multitude of modifying factors. Imprecision in measuring dose also results in imprecision in assessing the relationship between dose level and response, an important indicator for establishing causality, especially when the dose response is linear. Nonetheless, the advantages of direct measurements of risk in epidemiological studies are likely to outweigh advantages inherent in laboratory studies.

These are only a few of the methodological issues that the committee considered in relation to the needs for future epidemiological research on diet and cancer. In making research recommendations, the committee placed its major emphasis on trying to rectify the weaknesses

in methods that precluded the formulation of firm conclusions from the studies reviewed in the first report.

RESEARCH RECOMMENDATIONS

Assessment of Dietary Exposures

- New approaches to improving the quality of dietary intake data, especially in relation to long-term dietary patterns, should be explored. Research in this area should include a search for new aids to facilitate individual recalls and should enlist the participation of specialists in human behavior and psychometric measurement, who might be able to identify the best ways to elicit accurate information and to provide new insight into the factors that influence the responses of people asked to describe their diets. In addition, a search should be conducted for biochemical markers that reflect relevant dietary exposures some time in the remote past. Where direct measurements of exposure are unsuitable (e.g., in examining serum for a nutrient under homeostatic control), indirect markers, such as serum-binding proteins or enzyme levels, may be appropriate substitutes. Because rates of absorption and metabolism of nutrients may vary among subjects, however, individuals ingesting the same diet may differ in their ultimate exposure because of individual differences in metabolism and, thus, may differ in their degree of risk for cancer. These biochemical differences among individuals should be studied in relation to observed differences in cancer risk.
- More effort should be spent in evaluating the validity of dietary methods. One approach, which has not been widely used in epidemiological research, would be to compare suitable biochemical measurements with information derived concurrently from food records or diet recalls. Although this strategy is generally useful only for assessing the validity of very recent recalls, a high degree of agreement among the different forms of measurement suggests that the recall approach applied to a more remote time period may also yield relatively accurate results. This approach could be further validated if stored biological samples from the same period were available, but the limitations for the use of stored samples described on page 17 would also apply here.
- Food composition data bases should be improved with respect to information on both nutritive and nonnutritive constituents and on regional and seasonal variations in composition. The current data base lacks information on the components of fiber, essential trace elements (e.g., selenium), nonessential trace elements (e.g., cadmium), and food additives.
- In future studies, greater attention should be given to food preparation and storage. These two processes can result in the production or modification of the nature and amount of a variety of dietary components that present a potential risk for cancer (e.g., aflatoxin

contamination during storage of grain or production of mutagens during cooking).

- Better data are needed on long-term trends in the composition of average national diets. On a regular basis, cross-sectional information should be collected from representative samples of the U.S. population through surveys such as the annual Health and Nutrition Examination Surveys conducted by the National Center for Health Statistics, Department of Health and Human Services. The accumulated data can then be correlated with trends in cancer incidence. Information on such trends can also be obtained by repeated measurements of intake at well-spaced intervals among the subjects in prospective cohort studies. The resultant data will provide information not only on the changing patterns of eating during a lifetime but also on the reproducibility of the dietary assessment method used.

Types of Epidemiological Study

Each of the several epidemiological study designs offers particular advantages in certain circumstances (e.g., rare cancers can be examined in case-control studies but seldom in cohort studies). On the other hand, each of these designs has inherent limitations, as noted in the first report (National Research Council, 1982). For this reason, studies of all types, if appropriately applied, will be of value in further investigations of diet and cancer in human populations.

- Correlation studies, if well designed, can continue to provide useful information on the relationship between diet and cancer. Whenever possible, these studies should be based on exposure data collected directly from individuals rather than on per-capita consumption estimates. When sufficient information is available, they should also be based on morbidity rather than on mortality data, since the latter are influenced by survival patterns and can be misleading (National Research Council, 1982).
- Consideration should be given to carrying out case-control studies in populations such as those with unusual dietary habits or levels of exposure as well as those at unusual risk for specific cancers. International, collaborative case-control studies should be encouraged, but the sample size in each geographical area should be sufficiently large to permit separate analysis of the data. This would enable investigators to replicate the findings in diverse settings using a common methodology. To the greatest extent possible, the determination of sample sizes in all case-control studies should allow for meaningful examination of particular subgroups, statistical control of all important confounding factors, and the examination of interactions between separate dietary components or between dietary and nondietary factors. In estimating sample size requirements, investigators need to recognize that errors in measurement of exposure

necessitate an increase in the sample size to demonstrate statistically significant associations. Case-control studies have limited value for investigations based on biochemical indicators of exposure, since these markers may be altered by the disease in the cases. However, clues to the possible biochemical markers of exposure may be obtained from such studies.

- More cohort studies of diet and cancer are needed. This is the most suitable approach for investigations based on biochemical indicators of dietary exposures. Cohort studies are best carried out in populations at high risk for diet-associated cancers, where representative dietary data can be readily obtained and where long-term follow-up can be aided by population-based cancer registries and good vital statistics data for end points. Whenever possible in such studies, biological samples (such as serum, urine, and feces) should be collected and stored for later biochemical analysis of specimens from controls and from subjects who subsequently develop cancer. Long-term storage also enables the investigators to incorporate newer hypotheses or analytical procedures into the study at a later time. However, the utility of stored biological samples is limited because the samples reflect only one or possibly a few finite periods in the individual's life and because the samples may deteriorate during storage and handling. Because cohort studies are expensive and of very long duration, a search should continue to be made for existing cohorts for which there is relevant information on dietary exposures. In designing cohort studies, the sample size should be sufficiently large to ensure that an adequate number of cases will be identified, and their selection should be based on considerations discussed above for case-control studies.
- Intervention studies (trials) have many advantages, but they should be considered only when supporting evidence from other types of studies is strong and only after the risks involved have been carefully weighed. For ethical reasons, these studies will have to be limited to examinations of putative protective factors or of the effects from reduced exposure to risk factors. Several trials of specific microconstituents (e.g., -carotene) have recently been initiated. There is also a great need to study the effects of specific foods and food groups (e.g., dark green and deep yellow vegetables, and those of the genus Brassica--members of the cabbage family), since the biological effectiveness of a food component is probably affected by the presence of other constituents in the diet, and since the effects observed in epidemiological and experimental studies may be due to a mixture of different inhibitors of carcinogenesis. To obtain more definitive data, the randomization procedure in these studies should be based on individuals rather than on groups, whenever possible.

Analysis of Data

- Analysis of data from epidemiological studies should include examinations of specific foods and food classes, even when the hypothe

sis pertains to nutrients. Relationships involving nutrients from selected groups of foods or involving nonnutritive components of foods might be uncovered by this approach.

- Studies should be conducted to determine the limitations of the logistic regression model for the analysis of epidemiological data on diet and cancer. The extent to which the actual data in a study can deviate from the theoretical distribution and still yield meaningful results should be defined. Moreover, since many of the dietary and nondietary factors in studies on cancer are highly intercorrelated, efforts should be made to explore statistical methods that are less sensitive to collinearity than is multiple logistic regression analysis. Finally, statistical techniques need to be developed to describe more accurately the various forms of interaction among dietary variables.

5

Laboratory Methods

Laboratory data cannot be readily translated into schemes for prevention of cancer in humans. The principal shortcoming is the inability of current animal bioassays and short-term tests to identify with certainty the causes of cancer in humans and to predict the extent of risk posed by the various exposures. These limitations were discussed in the first report of the Committee on Diet, Nutrition, and Cancer (National Research Council, 1982).

In Chapter 3 of the first report, the committee explained that substances demonstrated to be carcinogenic in animals are regarded as potential carcinogens for humans. However, it also emphasized that there are major drawbacks in the standard procedure for determining carcinogenicity of compounds, i.e., the bioassay in animals fed the test substance for a major portion of their lifetime. These long-term bioassays lack sensitivity, they may produce false negative results, and, because of the high doses given to animals, extrapolation of the results to determine the response of humans exposed to lower doses cannot be accomplished with any degree of certainty (National Research Council, 1982).

There is a dearth of animal models that are both sensitive and relevant for assessing the influence of diet and nutrition on cancer in humans. For example, we do not know the extent to which these models mimic metabolism of and responses to carcinogens in humans, nor do we know all the ways in which the nutritional requirements of the animals used in these studies differ from those of humans. Furthermore, animal models need to be standardized so that studies in different laboratories can be compared. Steps should be taken to rectify these inadequacies, since animal models have to be used if we are to evaluate the influence of diet and nutrition on different stages of carcinogenesis, e.g., initiation and promotion.

The recognition that the active forms of carcinogens are electrophiles that bind to DNA has provided the impetus for studies in which short-term assays have been used to detect carcinogens. However, even though there is correspondence between mutagenicity and carcinogenicity, the short-term tests now available provide only qualitative information and cannot be used to predict cancer risk to humans.

Better methods are needed for extrapolating data from animal experiments to determine the contribution of different dietary components to the causation and prevention of cancer in humans. There is a need for laboratory methods to compare the relative contributions to human cancer made by carcinogens that initiate and carcinogens that promote the growth and development of transformed cells. If exposure

to dietary initiators is the most important variable, it would be helpful to know the detailed steps involved in their metabolism. For example, is the amount of the activated carcinogen that binds to certain sites within DNA directly correlated with the number of newly initiated cells? If so, which metabolic reactions are critical, and which are the ones most influenced by dietary constituents? How much activated carcinogen is needed to induce tumorigenesis, or is there no threshold? Is the long-term average level of critical DNA adducts more or less important than short, intense periods of adduct formation? Answers to fundamental questions such as these are needed to develop methods that can relate the in vivo response to initiators to the degree of risk.

If exposure to dietary factors that modify the course of initiation is the primary determinant of tumor development, then a different type of methodology may be required. Imaginative and sophisticated procedures will be needed to measure the effects of such modifying factors, because different mechanisms are likely to be responsible for their activity.

We need to refine our understanding of the relationship between nutrient intake (dose) and cancer risk (response). Perhaps this concept of dose response could be incorporated into the basis for defining the Recommended Dietary Allowances (RDA). These allowances were initially intended to serve as a guide to nutrient intake that would be sufficient to eliminate certain deficiency diseases in the general population. In recent years, the formulators of the RDA have attempted to define the range of adequate and safe levels of certain nutrients (National Research Council, 1980a). This concept needs to be extended so that ranges of recommended intakes also take into account potential associations between nutrients and chronic diseases such as cancer.

Finally, there are no reliable methods for the extrapolation of data from animal studies to determine the response in humans. Since current procedures are probably of little or no value for assessing the risk of nutrient-induced tumor modification, it is likely that an entirely new approach will be required (National Research Council, 1982, Chapter 18).

METHODS FOR IDENTIFYING DIETARY INITIATORS AND MODIFIERS OF CARCINOGENESIS

Methods for identifying dietary substances that initiate or modify one or more stages of carcinogenesis are inadequate. Initiators, which attack genetic material, are discussed in Chapter 8. Following the initiation of neoplasia, modifiers may either enhance (i.e., by promoting or acting as cocarcinogens) or inhibit the subsequent development of tumors by a variety of mechanisms. Therefore, methods for detecting these activities should be broad enough to detect compounds that operate by different kinds of mechanisms.

Animal models for liver and skin cancer have been used extensively to study the form of enhancement called tumor promotion. More recently, tumor promotion in the breast and colon has also been studied. Further investigation using these and other animal systems, and specific efforts to adapt such systems to detect promoters in food, would be useful. The continuing development of in vitro systems for studying promotion should also be encouraged, since they may provide insights into mechanisms of action and may serve as useful test systems for detecting promoters.

The process of neoplasia can also be affected by cocarcinogens, which enhance the tumor initiation process. Some cocarcinogens may act by increasing the binding of initiators to DNA. Others may increase cell proliferation before or during attack by carcinogens, thereby enhancing carcinogenesis. Further studies are needed to unravel the specific mechanisms of this early stage of carcinogenesis and to identify dietary constituents that act at that time.

Studies in laboratory animals have indicated that food contains many inhibitors of carcinogenesis (National Research Council, 1982, Chapter 15). It is important to identify the full spectrum of compounds in this category. Proposed research for attaining this objective is discussed in Chapter 7.

METHODS FOR ASSESSING THE EFFECTS OF NUTRIENTS ON CARCINOGENESIS.

Methods for assessing the effects of nutrients on carcinogenesis are inadequate, especially those for determining dose-response relationships and the impact of interactions of nutrients with each other and with other dietary substances.

Nutrients at certain levels of intake appear to modify rather than initiate carcinogenesis. Methods should enable investigators to define the dose-response relationship between nutrients and various cancers so that basic principles for assessing risk can be formulated. Animal models whose nutritional characteristics can be reliably related to the nutrient requirements of, and metabolism in, humans are also required. Since modification of cancer risk by individual nutrients can almost always be markedly influenced by other nutrients and other dietary components, statistical methods capable of analyzing such complexities must be used.

A lack of standardization among selected diets and experimental models often hinders the interpretation of data. It would be appropriate to consider dietary formulations such as the AIN-76 diet (Anonymous, 1977) or suitable variations thereof. Adoption of such standards should facilitate interlaboratory comparisons but should not restrict continued inquiry into varied and diverse dietary protocols that are suitable for exploring the effects of the heterogeneous diets consumed by humans.

METHODS FOR IDENTIFYING MARKERS RELATED TO NEOPLASIA IN HUMANS

One of the most pressing needs is the development of short-term tests that could identify early biological indicators of exposure to dietary constituents that affect the occurrence of neoplasia in humans. Where neoplasia is the sole end point, investigations are severely limited by the long latency period between exposure and expression of neoplasia. Accordingly, attention should be directed toward finding ways to evaluate specific dietary components for their early neoplastic or inhibitory effects in humans and to identify early markers that can be used to predict the likelihood that clinical cancer will develop in humans. For example, the early stages of neoplasia can be detected by the presence of hepatic foci with altered enzymatic activity (Pitot et al., 1980; Potter, 1981) or altered proliferative compartments in mucosal glands of the large bowel (Lipkin, 1977). Similar test systems to examine body fluids or other readily accessible tissues for such markers would be valuable if they could be used to identify the stage of carcinogenesis or to predict the occurrence of neoplasia.

There are several methods for identifying compounds suspected of damaging genetic material in humans. Of these, cytogenetic studies are the most widely used (Thilly and Liber, 1980), but their utility is limited by their lack of sensitivity. Another such method involves the identification of DNA adducts in human tissues. Studies of sister chromatid exchanges have also been reported, but further research is required to determine the implications of this phenomenon. Studies to detect genetic damage might include the "micronucleus" test (Heddle et al., 1982).

New procedures for detecting the formation of carcinogens and mutagens in humans are now being developed. For example, recent studies have shown that nitrosoproline is excreted in the urine of humans given oral doses of the precursor compounds (nitrate and proline) (Ohshima et al., 1982). This is the first test procedure for studying nitrosation in human beings. Once procedures of this type have been developed further, it should be possible to test putative inhibitors of the formation of carcinogenic nitroso compounds for their effectiveness in humans (Newmark and Mergens, 1981). Bruce et al. (1977) have found a naturally occurring mutagen in human feces, and Hirai et al. (1982) have established its chemical structure. It is not yet known whether this compound is carcinogenic. Nevertheless, the presence in the lumen of the large bowel of a compound capable of attacking DNA suggests a potential hazard. Therefore, study of dietary factors that alter the amount of this mutagen is warranted.

Short-term methods are needed to identify biological indicators of tumor promotion in humans. Possible techniques of this nature are mentioned in Chapter 7. When such systems are developed, they should be used to identify dietary compounds that have the capacity for tumor promotion.

Techniques are needed to identify identify dietary constituents that prevent carcinogens from reaching or reacting with critical target sites in human tissues. When particular constituents have been found to block carcinogenesis in animals, their effects in humans should be investigated. Because these blocking agents may affect carcinogen-metabolizing systems that are tissue enzymes, it will be necessary to select readily available as well as suitable tissues in humans. An alternative strategy is to administer noncarcinogenic prototype compounds that are metabolized in a fashion similar to that of known carcinogens and then to assess their metabolism by measuring blood and urine samples or, possibly, by quantitating volatile metabolites that are exhaled. It may be feasible to study the effects of blocking agents present in food on carcinogen-metabolizing systems in humans, but initially, considerable efforts will be required to develop appropriate techniques. Such techniques and studies on blocking agents in animals are discussed in more detail in Chapter 7.

RESEARCH RECOMMENDATIONS

Initiators and Modifiers of Carcinogenesis

- Better methods based on mechanism of action should be devised to detect carcinogens, promoters, cocarcinogens, and inhibitors in food.
- Attempts should be made to develop better methods for extrapolating to humans risk estimates derived from laboratory studies.

The Effects of Nutrients on Carcinogenesis

Methods must be developed for evaluating the effects of nutrients on carcinogenesis. Particular emphasis should be given to the following two areas.

- Methods should be developed to study the dose-response relationship between nutrients and tumorigenesis.
- Methods should be devised and used systematically to evaluate the association between carcinogenesis and the interaction of nutrients with each other and with nonnutritive dietary constituents.

Markers Related to Neoplasia in Humans

- Research should be conducted to identify biological markers of exposure to chemicals that cause cancer in humans.
- Early biological markers that can forecast the emergence of clinical cancer should be identified.

- Short-term test systems should be developed to detect the early effects of dietary initiators to which humans are exposed. Thus, techniques should be developed to identify and quantify the presence of carcinogen-DNA adducts and to detect alterations in DNA. In addition, attempts should be made to refine cytogenetic procedures.
- Short-term techniques should be devised to detect the early effects and to quantify the impact of compounds suspected of acting as promoters or cocarcinogens in humans.
- Methods should be developed for studying the in vivo formation of carcinogens and mutagens in humans.
- Methods should be developed for the detection of putative inhibitors in the diet. This should be followed by systematic evaluation of the protective effects of these inhibitors in humans.

6

Macroconstituents

The literature concerning dietary macroconstituents (i.e., fats, protein, carbohydrates, dietary fiber, alcohol, and total caloric intake) and their associations with carcinogenesis was reviewed extensively in Chapters 4 through 11 of the committee's first report (National Research Council, 1982). The paragraphs below describe the major gaps in knowledge, which are discussed in more detail in the first report, and provide recommendations for future research in those areas.

Food is a complex mixture of chemicals, and the effects of individual dietary components are dependent on many factors, including interactions among dietary constituents. However, for the sake of convenience, each macroconstituent is discussed separately.

FATS

After assessing the literature, the committee concluded that there is significant epidemiological evidence for an association between dietary fat and cancer at a number of sites, especially the breast and the large bowel. The evidence associating high fat intake with a high incidence of or mortality from these cancers was derived from both correlation and case-control studies in various populations. In most of the studies, it was not possible to identify clearly which components of fat were responsible for the observed effects. Where such a distinction was possible, however, total fat and saturated fat were implicated most frequently (National Research Council, 1982, Chapter 5).

The committee also noted that the epidemiological data are not entirely consistent, even though they point in the same direction. For example, the magnitude of the association between fat intake and breast cancer appears greater in the correlation data than in the case-control data, and some studies of large bowel cancer do not demonstrate an association with dietary fat. Possible explanations for these discrepancies were discussed in the first report.

The committee was unable to reach a definitive conclusion about the relationship between serum cholesterol and cancer in humans, because the evidence is inconsistent and not sufficiently convincing to establish a causal relationship. Data on dietary cholesterol and cancer risk are also too limited to permit any inferences to be drawn (National Research Council, 1982).

Numerous experiments on animals also indicate that dietary lipid influences tumorigenesis, especially in the breast and the colon. An

increase in total dietary fat from 5% to 20% of the weight of the diet (i.e., from approximately 10% to 40% of total calories) appears to increase tumor incidence in each of these tissues. At low intakes of total fat, polyunsaturated fat appears to be more effective than saturated fat in enhancing tumorigenesis; however, the effect of polyunsaturated fat becomes less prominent as total dietary fat is increased to 20% of the diet, suggesting that total fat intake is the more significant factor. In general, the epidemiological data and the laboratory evidence are consistent (National Research Council, 1982).

The limited data on the possible mechanisms of action by which fat exerts its effects indicate that ingested fat affects tumor promotion rather than tumor initiation; however, an effect on initiation cannot yet be ruled out. The specific mechanism involved in tumor promotion is not known, although some evidence suggests that colon cancer is associated with increased concentrations of bile acids in the feces (National Research Council, 1982).

The committee noted that of all the dietary factors that have been associated with cancers of various sites, fat has probably been studied most thoroughly and has produced the greatest frequency of direct associations (National Research Council, 1982). Nevertheless, it is clear that there is a need for more accurate data on fat intake in specific populations and on its precise effect on tumorigenesis. For example, fat intake varies widely among individuals in the United States. We are not certain that there are differences in cancer incidence between individuals at the high and low ends of the intake spectrum.

Unsaturated fat appears to exert a promoting effect on some experimentally induced tumors. Diets containing unsaturated fat may be hypocholesterolemic, and the results of some population studies suggest that individuals with low levels of serum cholesterol exhibit a greater incidence of tumors. These studies suggest that more data are needed to clarify the effects of unsaturated fat. For example, if unsaturated fat acts as a tumor promoter, what is its mechanism of action? Does it involve epoxidation, products of oxidation and degradation such as short-chain aldehydes, or effects on prostaglandin formation? There are many such unanswered questions. Therefore, the mechanism(s) by which different types of dietary fat exert their effects must be clarified. For example, effects on the immune system require further study. Heiniger (1981) demonstrated that some inhibitors of cholesterol biosynthesis suppress immune response. These findings suggest that the effects of lipids and lipoproteins (dietary fat, lipoprotein, and apolipoprotein) on the immune system require extensive investigation.

Evidence implying that males with blood cholesterol levels less than 200 mg/100 ml are at increased risk of cancer, especially colorectal cancer, was derived largely from follow-up examinations of individuals in studies directed primarily toward cardiovascular disease. Most of these were observational studies in which blood

cholesterol levels were measured and the subsequent mortality from cardiac and other diseases assessed. However, a few studies included deliberate attempts to lower blood cholesterol in subjects whose levels were high. The results from this latter type of study do not clearly indicate whether those with an increased risk of cancer were derived from the groups with initially low blood cholesterol or from groups in which blood cholesterol was lowered as a result of intervention to levels less than 200 mg/100 ml. Several investigators have suggested that the observed increase in mortality from cancer may be due to the presence of undetected cancer at the start of the study rather than to its development after blood cholesterol was measured. Thus, it is not clear whether low blood cholesterol is a consequence or possible cause of cancer (National Research Council, 1982). If causal, the responsible mechanism could be the excretion of high levels of cholesterol breakdown products in the intestine of persons with low blood cholesterol. This could occur despite the consumption of the standard North American high fat diet, which usually results in blood cholesterol levels that are higher than those in populations consuming diets with lower levels of fat. Metabolic studies are required to determine whether the excretion of cholesterol breakdown products is more active in individuals with low blood cholesterol levels.

The effect of a high cholesterol diet on the risk of colon cancer is also unclear. A Canadian case-control study of diet and colorectal cancer showed that a much weaker effect resulted from high cholesterol intake than from high saturated fat intake (Jain et al., 1980). It has been known for some time that a major dietary contributor to increased blood cholesterol is not cholesterol but, rather, high levels of fat (National Research Council, 1980b).

Thus, further epidemiological and biochemical studies are required to explain the relationship of dietary fat and cholesterol intake to serum or plasma cholesterol levels and to the excretion of cholesterol and its metabolites (i.e., neutral and acidic steroids and their microbial by-products). We need to define the level to which the current high fat intake can be lowered to achieve a maximum reduction in the risk of cancer without concomitantly increasing the risk of other disease states. In this regard, the optimum proportions of saturated, monounsaturated, and polyunsaturated fats should be delineated.

PROTEIN.

Epidemiological studies reviewed by the committee indicate possible associations between high levels of dietary protein and increased risk of cancers at a number of different sites, including the breast, colon, pancreas, prostate, and endometrium. However, the literature on protein is much more limited than that on fats. In addition, the high correlation between fat and protein intake in Western diets

and the more consistent and often stronger association of these cancers with fat intake make it seem likely that dietary fat is the more active component. Nevertheless, the committee concluded that "the evidence does not completely preclude an independent effect of protein" (National Research Council, 1982, Chapter 6).

In laboratory experiments, the relationship between dietary protein and carcinogenesis appears to depend upon the level of protein intake. In most studies, carcinogenesis was found to be suppressed by diets containing levels of protein at or below the minimum required for optimum growth. Chemically induced carcinogenesis is generally enhanced as protein intake is increased up to 2 or 3 times the normal requirement; however, higher levels of protein begin to inhibit carcinogenesis. A review of the preliminary data on possible mechanisms of action suggested that protein may affect both the initiation and the subsequent growth and development of tumors (National Research Council, 1982).

Thus, the association between dietary protein, especially different types of protein, and cancers of the breast, endometrium, prostate, colorectum, pancreas, and kidney needs further clarification. Studies should be specifically designed to determine whether the apparent effect of major dietary sources of protein, which contain a variety of other nutrients and nonnutritive components, is due to a direct association of protein with cancer at these sites or reflects the action of another constituent of protein-rich foods.

CARBOHYDRATES

The committee found only extremely limited and inconclusive epidemiological evidence concerning the role of carbohydrates (exclusive of dietary fiber) in the development of cancer in humans. The data from the few laboratory experiments on this subject could not be interpreted because of generally poor experimental designs and uncertainty about the actual carbohydrate content of the test diets (National Research Council, 1982, Chapter 7).

Thus, in contrast to lipids and protein, very little work has been directed toward the study of carbohydrate intake, especially the levels of different types of carbohydrate, and the occurrence of cancer. However, one study has suggested that rats fed sucrose are more susceptible to chemically induced tumors than are rats fed starch (Hoehn and Carroll, 1979). This area requires further investigation. A complete understanding of the effects of carbohydrates on carcinogenesis may depend on a thorough knowledge of the effects and interactions of each dietary component.

DIETARY FIBER

The association between dietary fiber and carcinogenesis, especially in the colon, has been investigated at length in epidemiological

studies. However, both correlation and case-control studies have yielded inconsistent results. Many of these studies were based on total fiber consumption estimated by grouping foods (such as fruits, vegetables, and cereals) according to their fiber content. However, in the only case-control study and the only correlation study in which the total fiber consumption was quantified rather than estimated from the fiber-rich foods in the diet, no association was found between total fiber intake and the risk of colon cancer. Thus, the committee concluded that the epidemiological evidence suggesting an inverse relationship between total fiber intake and the occurrence of colon cancer is not compelling (National Research Council, 1982).

In the only study in which the effects of individual components of fiber were assessed, there was an inverse correlation between the incidence of colon cancer and the consumption of the pentose-containing fraction of fiber. Thus, it seems likely that further epidemiological study of fiber will be productive only if the relationship of cancer to specific components of fiber can be analyzed (National Research Council, 1982, Chapter 8).

A few laboratory studies have also shown that some types of fiber (e.g., cellulose and bran) inhibit chemically induced tumorigenesis in the bowel. However, the data are somewhat inconsistent with respect to the type of fiber or specific chemical carcinogen. Moreover, the results of epidemiological and laboratory studies are difficult to equate, because most laboratory experiments have examined fiber-rich materials or their individual components, whereas most epidemiological studies have focused on fiber-containing foods whose exact composition has not been determined. Therefore, to obtain meaningful results, further information is needed on the basic chemistry and biological effects of fiber and its components (National Research Council, 1982).

Recently, more attention has been directed toward the physiological significance of dietary fiber, which generally includes indigestible carbohydrates and carbohydrate-like components of food such as cellulose, lignin, hemicelluloses, pentosans, gums, and pectins. Nevertheless, because of the complex composition of dietary fiber, the physiological functions and metabolic activity of its individual components have not yet been studied sufficiently.

Although epidemiological data concerning the role of total dietary fiber in the development of colon cancer are somewhat inconsistent, studies in animals have demonstrated that individual components of fiber, e.g., bran and cellulose, exert protective effects against the induction of cancer by chemicals, but that another type, agar, does not (Barbolt and Abraham, 1978; Freeman et al., 1978; Glauert et al., 1981). The effects of fiber should be correlated with its structural properties. It would be useful to compare the effects of adding fiber-containing foods to the diet with the effects resulting from the addition of specific dietary fibers, since current hypotheses concerning the

effects of fiber are based on dietary patterns--not on the addition of specific fibers or fiber-containing foods.

Studies are also required to separate the beneficial effects of high intakes of certain cruciferous vegetables on colon cancer from the effects, if any, of dietary fiber per se. There is little information concerning pathophysiological changes in the bowel that are associated with different types of high-fiber diets. The relationship of various types of fiber to the enterohepatic circulation of sterols, including sterol-derived hormones, is also not understood.

ALCOHOL

There have been many studies concerning the effects of alcohol consumption on cancer incidence in human populations. In some countries, including the United States, excessive beer drinking has been associated with an increased risk of colorectal cancer, especially rectal cancer. Although it is recognized that excessive alcohol consumption contributes to hepatic injury and cirrhosis, there is only limited evidence that this in turn leads to hepatocellular carcinoma. Furthermore, excessive consumption of alcoholic beverages and cigarette smoking appear to act synergistically to increase the risk for cancer of the mouth, larynx, esophagus, and the respiratory tract (National Research Council, 1982, Chapter 11).

Although some reports have suggested that alcohol consumption per se is related to cancer, others have implicated specific alcoholic beverages as risk factors for cancers at certain sites, such as the esophagus and gastrointestinal tract. This suggests that nonalcoholic components of alcoholic beverages may be the responsible agents. Furthermore, it is not yet clear what role nutrient inadequacies, imposed by excessive alcohol consumption, play in the process of carcinogenesis.

TOTAL CALORIC INTAKE

The committee found it especially difficult to separate the effect of caloric intake per se on carcinogenesis from the effects due to changes in the levels of the three macronutrients: fat, protein, and carbohydrates. It concluded that the epidemiological evidence supporting total caloric intake as a risk factor for cancer is slight and largely indirect, because much of it is based on associations between body weight or obesity and cancer rather than on direct measurements of caloric intake. Studies that have evaluated both the caloric content of the diet and the intake of fat suggest that dietary fat is the more relevant variable (National Research Council, 1982, Chapter 4).

Similarly, studies in animals to examine the effect of caloric intake on carcinogenesis have been few and are difficult to interpret.

In these experiments, animals on calorie-restricted diets developed fewer tumors and their lifespan far exceeded that of animals fed ad libitum, thereby indicating a decrease in the age-specific incidence of tumors. For example, McCay et al. (1943) and Ross and Bras (1973) showed that underfed rats lived longer and developed fewer tumors than their littermates, which were fed ad libitum. In another experiment, Lavik and Baumann (1943) found that methylcholanthrene-treated rats on restricted caloric intake developed fewer tumors than did treated rats fed ad libitum. However, because the intake of all nutrients was simultaneously depressed in these studies, the observed reduction in tumor incidence or delayed onset of tumors might have been due to the reduction of other nutrients such as fat. It is also difficult to interpret experiments in which caloric intake has been modified by varying dietary fat or fiber, both of which may by themselves exert effects on tumorigenesis (National Research Council, 1982).

Neither the epidemiological nor the experimental studies permit a clear interpretation of the specific effect of caloric intake. However, the effects of over-and under-feeding as such warrant further study, even though it may be difficult to separate caloric effects from the effects of the specific nutrients that contribute to total caloric intake.

RESEARCH RECOMMENDATIONS

A better understanding of the relationship between certain macroconstituents (e.g., fat) and cancer has enabled the committee to make some more specific recommendations in this chapter than in other chapters.

General Recommendations for Epidemiological Research

- There is probably considerable interaction among the many components of the diet. Therefore, some potentially harmful substances may be "neutralized" by other dietary ingredients. For this reason, there is a need to evaluate the interrelationships among calories, protein, and fat (and its various components) and their effect on, for example, breast and colorectal cancer.
- Simultaneously, the opportunity should be taken to evaluate the interrelationships between these nutrients and (1) the effects of hormonal status on breast cancer and (2) the effects of fiber, its components, and various micronutrients, especially vitamins and possible inhibitors in vegetables of the genus Brassica, on the etiology of colorectal cancer.
- Research on interrelationships among macroconstituents should be designed so that it is possible to determine the overall effect of different groups of foods and not just individual foods or nutrients, as discussed in Chapter 4.

- The completed dietary studies on breast and colon cancer should be extended to examine other possibly diet-associated cancers that have been correlated with breast and colon cancer. In addition to the ongoing investigations of prostate cancer, studies should be conducted on endometrial, ovarian, pancreatic, and renal cancers.
- More frequent monitoring of food intake, especially changes in intake of macronutrients in the average diet, is essential (see Chapter 4).
- Reliable data bases for food composition should be developed for the analysis of macronutrients (see Chapter 4). It is especially important that such data bases contain more information on the fiber content of each food and on the chemical composition of each type of fiber.
- It is now essential to give high priority to some long-term cohort studies that will test hypotheses about macronutrients and cancer (see Chapter 4).
- Carefully planned intervention studies, involving changes in the macronutrient content of the diet, should be conducted in humans (see discussion of intervention studies in Chapter 4). Such studies may be the only way to gain an understanding of the relative effects and the interrelationships among macronutrients. In such studies, it may be conceptually easier to plan for the addition of constituents, e.g., specific types of fiber, to the diet. However, we should not overlook the need to evaluate the effect of reducing dietary fat by consumption of foods low in fat.
- The effects of dietary macroconstituents on the later stages of carcinogenesis need to be examined in laboratory studies.

General Recommendations for Laboratory Research

- For animal experiments, the first priority is standardization of methodology. This is discussed in Chapter 5.
- The epidemiological data linking specific dietary components to cancers of the prostate, pancreas, and endometrium are limited. An expansion of the experimental data base, i.e., development of suitable animal models, is required in order to put these data into proper perspective.

Specific Recommendations.

Fat: Epidemiological Studies

- More discriminating data are needed on the effect of the level and type of fat intake by humans. For example, we need to answer the

question, "What level of fat intake is associated with the maximum reduction in cancer incidence?" Is it 30% of calories, as recently recommended by this committee? Is it 25%, 20%, or lower levels?

- More discriminating data are also needed on the effects of different types of fat. Studies should be conducted to answer the following questions: Is the finding that polyunsaturated fat increases tumor incidence in laboratory animals relevant to humans? Is this finding also relevant to the results emerging from intervention trials for cardiovascular disease? What should be the relative proportion of polyunsaturated, monounsaturated, and saturated fats in the optimal diet?
- Metabolic studies are required to evaluate the role of the breakdown products of cholesterol in individuals with low blood cholesterol levels.
- The mechanism underlying the reported association between low blood cholesterol and neoplasia should be determined. For example, it would be helpful to know whether hypocholesterolemic individuals are at high risk only if they consume a high fat diet and whether lowering fat intake in such individuals will reduce their risk. Further analysis of existing data on humans may help to answer these questions.

Fat: Laboratory Studies

- The relative roles of the level and type of fat (e.g., essential fatty acids) in all phases of tumor formation should be studied. The stage at which dietary fat exerts its effects on the induction of tumorigenesis and its effects in the prepromotional, promotional, tumor development, and metastatic stages should be systematically investigated. Other aspects of lipid nutriture and carcinogenesis also need resolution. For example, further investigation is needed to determine the effects of trans unsaturated fats, lipid pyrolysis products, and lipid peroxides and to study the effects of lipids on membrane phenomena, on prostaglandin synthesis, and on immune phenomena.
- The interplay among dietary lipids (including cholesterol), hypocholesterolemic agents, neutral and acidic fecal steroids, and gut microflora should be clarified with respect to their effects on tumorigenesis.
- Studies should be conducted in animals to determine the threshold level (percent of calories) at which dietary fat begins to exert measurable effects on carcinogenesis.
- The cholesterol vehicle (lipoprotein) should be examined for its ability to carry other substances that may affect tumor growth.

Protein: Epidemiological Studies

- The independent effects of the amount and type of protein and of their interaction with other macronutrients on the incidence of tumors in humans should be investigated.

Protein: Laboratory Studies

- The influence of the biological value of protein and the level and type of protein should be studied in different experimental systems. The effects of animal protein and vegetable protein should be compared.
- The effect of protein on different stages of carcinogenesis and the mechanism underlying this effect need further investigation.

Carbohydrates: Laboratory Studies

- Simple sugars (mono-and disaccharides) should be compared with starches from various sources for their effects on tumor formation.

Calories: Epidemiological Studies

- The relationship between total caloric intake and cancer in humans should be studied further, together with the modifying influence of energy expenditure through occupation or exercise.

Calories: Laboratory Studies

- The mechanism for the putative effect of caloric intake on carcinogenesis needs to be determined. For example, to what extent are the calories provided by fat, protein, and carbohydrate responsible for the effect on carcinogenesis? And is the effect of the caloric contribution by each of the three macronutrients equivalent?
- Effects of age at which caloric restriction is instituted should be assessed.
- Carbohydrate is usually used to replace fat or protein in the diet without considering how this may influence the outcome. However, the effect of replacing dietary fat with protein or carbohydrate in isocaloric diets has not been examined. Although this may be difficult to accomplish, it is important to attempt to study the individual effects of protein, carbohydrate, and fat in animals fed ad libitum.

Fiber: Epidemiological Studies.

- The content of fiber components in foods should be determined in order to assess dietary intake more accurately.
- The influence of fiber on cancers other than colorectal cancer should be studied.

Fiber: Laboratory Studies

- The structure-function relationships of fiber (e.g., its pentose content and its bile-acid binding capacity) in tumor formation should be studied.

- The physiological properties of different components of fiber and their effects on the absorption and availability of nutrients should be systematically evaluated in metabolic studies.
- The influence of fiber on tumors at sites other than the colon should be investigated.

Alcohol: Epidemiological Studies

- Reliable methods are needed to quantitate alcohol intake. This should be followed by investigation of the effects of different intake levels on cancer risk.
- The influence of different alcoholic beverages (e.g., wine, beer, whisky, or liqueurs) on esophageal, gastric, and other cancers should be studied.

Alcohol: Laboratory Studies

- Studies should be conducted to determine the influence of nonalcoholic components of alcoholic beverages on experimentally induced carcinogenesis.
- The association between carcinogenesis and nutrient deficiencies imposed by excessive alcohol intake should be evaluated.

7

Vitamins, Minerals, and Nonnutritive Inhibitors of Carcinogenesis

Many microconstituents of the diet have been found to have an impact on carcinogenesis. Only three groups of these substances are discussed in this chapter: vitamins A, C, and E and the carotenes; selenium and selected trace elements; and some nonnutritive compounds (i.e., indoles, phenols, aromatic isothiocyanates, methylated flavones, protease inhibitors, and plant sterols) that inhibit carcinogenesis in experimental systems. The ubiquity of these compounds is such that it is impossible for humans not to consume some of them. Evidence relating these and other microconstituents to carcinogenesis was discussed in Chapter 9, 10, and 15 of the committee's first report (National Research Council, 1982). Data relating other microconstituents (e.g., the B vitamins) to carcinogenesis are extremely limited, as explained in the first report.

A striking feature of many of the compounds in the three groups mentioned above is their capacity to prevent or retard the occurrence of neoplasia. However, there is a paucity of data concerning the conditions under which inhibition occurs, the mechanisms of inhibition, and the precise impact of these microconstituents on humans. Better data on these compounds will assist in the formulation of more definitive conclusions and recommendations to reduce the risk of cancer.

VITAMINS, CAROTENES, AND RETINOIDS

The dosages of vitamins used in experimental work and in human studies may range from levels recommended for optimal nutrition to megadoses. If research on vitamins and carcinogenesis suggests that large doses of specific vitamins or their analogs are needed to achieve effects, it should be noted that such doses are pharmacological in nature and may have deleterious consequences.

Vitamin A, Carotenes, and Retinoids

As explained in the first report, several epidemiological investigations indicate that there is an inverse relationship between estimated “vitamin A” intake and the occurrence of a variety of cancers. With few exceptions, the estimates of vitamin A intake in such studies were based on the frequency of ingestion of certain food groups, especially green and yellow vegetables that contain carotene (a provitamin that is enzymatically converted to vitamin A in vivo) and a

few foods, such as whole milk and liver, containing performed retinol (vitamin A). Thus, these studies do not clearly distinguish between the effect of vitamin A per se and that of carotene.

Experimental studies of the effects of vitamin A on carcinogenesis were also reviewed in the committee's first report (National Research Council, 1982, Chapter 9). Animal experiments indicate that increased intake of this vitamin has a protective effect against the induction of cancer by chemical carcinogens in most but not in all instances. Only a few experiments have been published on the capacity of carotenes to inhibit chemically induced carcinogenesis. In contrast, their inhibitory effect on ultraviolet light-induced neoplasia of the skin has been well documented. There is a need to gain a detailed understanding of the effects of carotenes on carcinogenesis and the conditions under which vitamin A alters responses to neoplastic agents.

In other animal experiments, certain nonnutritive compounds (i.e., indoles, phenols, aromatic isothiocyanates, methylated flavones, and plant sterols) present in fruits and vegetables were found to inhibit carcinogenesis. The specific agent(s) responsible for the lower cancer incidence observed in populations that frequently consumed fruits and carotene-containing vegetables have not been identified (National Research Council, 1982, Chapter 9). Although it is entirely appropriate to propose interim dietary guidelines on the basis of current knowledge, identification of the responsible compounds is extremely important to assist in designing better epidemiological studies and in planning more precisely focused intervention studies concerning the consumption of green and yellow vegetables and certain fruits and the occurrence of cancer.

Early studies indicating that vitamin A inhibits the occurrence of neoplasia in animals but that it can be toxic in high doses led to the synthesis of analogs of vitamin A--the retinoids. Certain retinoids are less toxic than vitamin A and can be targeted to specific organs where they exhibit inhibitory effects on carcinogenesis. Because of these properties, retinoids are an especially useful group of compounds for further investigation.

Vitamin C (Ascorbic Acid)

Epidemiological studies have suggested that frequent consumption of foods containing vitamin C may be associated with a lower risk of cancer in humans, especially in the esophagus and stomach. However, there have been no systematic studies of populations consuming pharmacological doses of vitamin C. Vitamin C has also been studied under a variety of experimental conditions for its effects on carcinogenesis. It has been well established that this vitamin can inhibit the formation of nitroso carcinogens from precursor substances. Investigations

of its effects on already-formed carcinogens have yielded less impressive results, with the possible exception of chemically induced neoplasia of the large bowel. It should be pointed out, however, that almost all studies of the inhibitory properties of vitamin C have been conducted in species that synthesize their own vitamin C, unlike humans, who require a dietary source of this vitamin. There is some indication that vitamin C has mutagenic activity. However, in-vitro studies have generally indicated that vitamin C can prevent or, under some circumstances, retard the manifestations of malignancy in cultured cells.

Vitamin E.

There are no epidemiological data concerning vitamin E and the risk of cancer in human populations. Such data may prove difficult to obtain because of the widespread occurrence of the vitamin in foods and the lack of a clear-cut deficiency syndrome in humans. For many years, efforts have been made to inhibit neoplasia by administering large amounts of vitamin E to laboratory animals, but the results of such studies have been inconclusive. However, because some of these reports indicate that vitamin E may inhibit carcinogenesis and the mounting evidence that antioxidants may play a role in inhibiting neoplasia (Wattenberg, 1981), further investigations of the effects of vitamin E are warranted.

SELENIUM AND OTHER TRACE MINERALS

Although humans require very low levels of dietary trace minerals, these micronutrients are as essential to good health as protein and energy sources. Several diseases of previously unknown etiology have been identified as trace mineral deficiencies. The prevention of goiter in the United States by supplementation of food supplies with the missing micronutrients iodine ranks among the most successful public health measures undertaken. Because minerals function in very fundamental biochemical processes, including immune reactions, detoxification, and free-radical trapping, it is reasonable to postulate that they may influence mechanisms that affect the development of cancer. On the other hand, although there is an adequate understanding of the mechanisms and sites of the physiological action of the trace elements iron, iodine, zinc, copper, chromium, and selenium, there is no precise knowledge of the mechanisms that might be involved in their effects on carcinogenesis. It is also unknown whether mechanisms for the action of pharmacological doses of trace minerals are the same as or different from those of physiological levels that are needed for normal nutrition. Furthermore, although the requirements for trace elements that are accepted as being essential for humans are well defined when protection against deficiency is used as a criterion, there is great controversy about whether higher intakes provide additional health benefits or pose the risk of adverse effects. The safety of trace

element intakes substantially exceeding the Recommended Dietary Allowances (National Research Council, 1980a) has not been established.

There is very little reliable information on the trace element composition of foods, except for their iron content. But even the reported and widely used data on this element have been recognized as erroneous and are being revised by the U.S. Department of Agriculture. Data on other important trace elements, such as selenium, are sparse. Moreover, their reliability is questionable because most have not been validated by the use of standard reference materials. In addition, since most of the analytical studies were not designed to detect regional differences, their results cannot be regarded as a reliable basis for epidemiological correlations. Finally, the rapid sequence in which trace elements with essential nutritional functions have been discovered during recent decades suggests that our present knowledge of essential trace minerals may still not be complete (National Research Council, 1982, Chapter 10).

The bioavailability of different chemical forms of trace elements can vary widely. For example, some selenium compounds have no biological activity, whereas others have pronounced physiological effects. The bioavailability of dietary iron compounds can differ by at least a factor of 10 (Bowering et al., 1976). For most micronutrients, the scientific basis for these differences has not been determined and the degree of bioavailability has not been quantified. Food processing is known to have a strong influence on the concentration and bioavailability of most trace elements, but this influence has not been adequately quantified.

Hundreds of nutrient-nutrient interactions have been described qualitatively, and many more may yet be discovered. These interactions are strong determinants of bioavailability and are involved in mechanisms that lead to the early signs of chronic toxicity. For example, large amounts of vitamin C greatly increase the bioavailability of iron compounds, while simultaneously reducing selenite to the biologically unavailable elemental selenium (Monsen et al., 1978; Newberry and Christian, 1965).

High but not excessive supplements of certain trace elements, although not necessarily toxic by themselves, can interfere with the metabolism of other elements to create secondary deficiencies (Levander and Cheng, 1980). Such effects have been clearly demonstrated for only one trace element, zinc, but they can be expected for others whenever high intakes of trace elements are maintained over prolonged periods.

Selenium

Selenium has two known biochemical modes of action: as a constituent of glutathione peroxidase, it prevents free-radical damage to

cell constituents, and it acts as a potent antagonist of chronic and acute toxicity resulting from exposure to cadmium and mercury. Although both these modes of action may be related to reduction in the risk of cancer, it is not known whether these are the mechanisms by which selenium affects carcinogenesis, nor is it known at which stage of carcinogenesis selenium might be effective.

There is only limited knowledge about the effect of different doses of selenium on the reduction of cancer incidence in animals. Much of the information on the element's inhibitory effects has been obtained with doses that are close to toxic levels. One study suggests that selenium-deficient diets increase the risk of cancer, compared to diets containing nutritionally adequate but not excessive levels (Ip and Sinha, 1981). Because of the relatively narrow range between toxic and optimum levels of selenium (National Research Council, 1980a), it is essential to define a range of selenium intake that does not result in chronic toxicity but is effective in reducing cancer risk. Experiments to establish nutrient requirements have demonstrated that the amount of selenium required for optimum nutrition is dependent on dietary levels of fat, vitamin E, and certain heavy metals. There is also evidence that at least the interaction between selenium and fat is an important determinant of the element's effect on cancer. However, these interactions have not been quantified (Levander and Cheng, 1980).

The results of a few epidemiological studies suggest a correlation between exposure to high levels of selenium and a reduction in the risk of certain cancers (National Research Council, 1982, Chapter 10). But these data are not conclusive, partly because the data base on the selenium content of foods is poor. Because selenium concentrations in food are dependent on the geochemical environment, dietary selenium levels vary widely from one region to another and cannot be calculated accurately on the basis of universal food composition data. Other reservations apply to blood concentrations of selenium as indicators of nutritional status, since there are no standard reference materials to safeguard analytical accuracy and comparability of results obtained by different laboratories. Populations in certain geographical areas of the world have substantially different levels of selenium intake, although other nutrient intakes are virtually identical. Epidemiological and/or intervention studies in such areas appear to be more promising than those in populations either with adequate selenium intakes or with relatively small differences in intake.

The metabolism of selenium depends on the chemical form of the element. These metabolic differences may affect the impact of selenium on carcinogenesis. Very little is known about the long-term consequences of elevated intakes of different forms of selenium, and there are no adequate means for diagnosing subclinical pathogenesis resulting from the accumulation of selenium in tissues.

Molybdenum, Zinc, Iron, Iodine, and Arsenic

As indicated in the committee's first report, evidence that molybdenum, zinc, iron, iodine, and arsenic play a role in carcinogenesis is limited and, in some cases, contradictory (National Research Council, 1982, Chapter 10). Molybdenum is essential for the function of certain enzymes. The next three elements are essential for human nutrition. For example, iron, zinc, and iodine have a profound influence on immune function or on hormonal status, or both, and deficiencies in these elements reported worldwide have presented major health hazards. Arsenic is considered to be essential for growth in animals. Because of their frequent occurrence in the diet of humans, basic research is necessary to formulate definitive conclusions about the role of these trace elements in carcinogenesis.

Epidemiological associations of diet with cancer rely on the adequacy with which food intake data are collected and evaluated or on the adequacy with which nutritional status is assessed by direct measurements in individuals. The data base for essential trace elements (exclusive of iron) is inadequate and, in part, erroneous. Expanded efforts to analyze trace elements in foods are essential in order to create a reliable and complete data base. Similarly, there are only a few reliable methods for the direct assessment of nutritional status for essential trace elements other than iron and iodine. Any progress in the development of such methods will significantly increase the reliability of epidemiological studies of diet and cancer.

NONNUTRITIVE INHIBITORS OF CARCINOGENESIS

An increasing number of nonnutritive substances in food have been found to inhibit carcinogenesis in laboratory animals. Included among these substances are phenols, indoles, aromatic isothiocyanates, methylated flavones, protease inhibitors, and plant sterols (National Research Council, 1982, Chapter 15). The chemical diversity of these inhibitors suggests that other compounds with inhibitory activity are likely to exist in food, but, for the most part, efforts at identifying such substances have been haphazard (Wattenberg, 1983). It is important to develop the technology to identify inhibitors of carcinogenesis in food and then to apply it systematically.

The occurrence of cancer can be inhibited at three specific stages during the succession of events leading to development of neoplasia. These stages, in sequence, are (1) inhibition of the formation of carcinogens from precursor compounds, (2) prevention of carcinogens from reaching or reacting with critical target sites, (3) inhibition of the postinitiation stages. Some procedures have been developed for identifying inhibitors that are effective at one or more of these stages, but the scope of the procedures is limited. Those that do exist have not been extensively exploited (Wattenberg, 1983).

Investigations of the inhibition of carcinogen formation have been limited largely to studies of nitroso compounds in laboratory animals. Extension of such work to investigations in humans, especially in population subgroups that appear to be at high risk from exposure to nitroso carcinogens, should be explored. Techniques of this nature are discussed in Chapter 5.

Food contains many compounds that prevent carcinogens from reaching or reacting with critical target sites. These so-called “blocking agents” have been identified by virtue of their ability to enhance the activities of enzyme systems that can detoxify chemical carcinogens. One such system is the glutathione S-transferase enzyme system (Sparnins and Wattenberg, 1981; Sparnins et al., 1982). Only limited efforts have been made to use this enzyme system to detect blocking agents in foods. Other marker systems exist as well. Research should be conducted to determine which of these systems would be effective in detecting inhibitors. Those systems should then be used for the systematic identification of inhibitors in food.

Current technology makes it feasible to identify dietary compounds that can inhibit neoplasia during the promotion phase. For example, there are three biochemical events that are associated with some facets of tumor promotion in laboratory animals. The induction of ornithine decarboxylase activity occurs in some tumor promotion systems (Boutwell, 1977), and inhibition of the induction of this enzyme's activity could be used as a parameter for identifying putative inhibitors of tumor promotion. The inhibition of free radicals that are formed during tumor promotion could be used as another method for identifying such inhibitors (Troll et al., 1982). Finally, inhibition of the stages in the arachidonic acid metabolism cascade has also been used to study inhibition of promotion (Verma et al., 1980). Accordingly, the development of appropriate methodology offers promise that putative dietary inhibitors of promotion can be identified.

The identification of compounds that can inhibit carcinogenesis after exposure to neoplastic agents would be very important. The prototype compound in this category is vitamin A. The mechanism by which vitamin A and its synthetic analogs, the retinoids, bring about inhibition has not been established. Pending the emergence of definitive data on the mechanism of action, it may be possible to apply some of the existing technology to detect other dietary constituents that inhibit by the same means. Inhibitors of arachidonic acid metabolism have been found to inhibit carcinogenesis when administered during the postinitiation stages. Detection of dietary constituents that inhibit components of this cascade might aid in the identification of compounds that can inhibit carcinogenesis after exposure to carcinogenic agents.

GENERAL RESEARCH RECOMMENDATIONS

Because the data accumulated thus far suggest that further study of dietary inhibitors may be fruitful, the recommendations in this chapter are more detailed than in some other chapters.

- Research should be conducted to determine the laboratory conditions under which the occurrence of neoplasia can be prevented by the microconstituents discussed in this chapter, i.e., vitamins A, C, and E and the carotenes; selenium and possibly some other trace minerals; and nonnutritive inhibitors of carcinogenesis.
- The mechanisms by which these microconstituents prevent carcinogenesis should be determined.
- Efforts should be made to establish dose-response curves for microconstituents (e.g., vitamin A, carotenes, and selenium) that inhibit carcinogenesis.
- The metabolism of vitamins A, C, E, carotenes, and possibly some trace elements should be fully elucidated.
- Studies should be undertaken to determine if there are biochemical markers that are indicative of long-term nutritional status of humans with regard to these microconstituents.
- Investigations should be expanded to include a determination of the amounts of these microconstituents in various foods. These should be followed by analytical epidemiological studies (case-control or cohort studies) to determine the effects exerted by various levels of microconstituent intake on the occurrence of cancers in humans.
- Consideration should be given to studying the incidence of specific cancers in populations consuming large doses of vitamin supplements.
- When justified by sufficiently definitive data from experimental and/or epidemiological investigations, intervention studies with these microconstituents or with foods rich in these substances should be considered (see Chapter 4).
- Techniques should be developed for detecting dietary compounds that have the capacity to inhibit carcinogenesis. These should be applied systematically to identify such inhibitors, and when new ones are discovered, they should be subjected to each of the recommendations mentioned above.
- Experiments should be conducted in animals to evaluate the effects of dietary microconstituents on later stages of carcinogenesis.

SPECIFIC RESEARCH RECOMMENDATIONS

Chapters 4 and 5 contain general suggestions for improving both epidemiological and laboratory methods. Recommendations pertaining specifically to microconstituents and inhibitors are presented below.

Vitamin A and Carotenes

- Case-control or cohort studies are needed to distinguish between the effects of retinol and those of -carotene as they pertain to cancer risk, since the dietary sources of these two nutrients are different.
- Studies to examine the potential risk-reducing effect of "vitamin A" and the retinoids would be worthwhile. For example, studies could be conducted on certain high-risk groups, such as asbestos workers who smoke. Intervention trials on this subject may be productive.
- Experiments in several different animal models should be conducted to determine the inhibitory effect of different doses of vitamin A.
- Studies to determine the mechanism(s) of inhibition for vitamin A and the retinoids should be pursued.
- Additional experiments should be conducted in animals to determine if -carotene and other carotenes have the capacity to inhibit carcinogenesis and, if so, to identify the conditions under which such inhibition occurs and the mechanism by which it occurs.
- Improved techniques for evaluating vitamin A and carotene levels in human tissues would be helpful, as would be studies of the metabolism of vitamin A and carotenes.

Vitamin C (Ascorbic Acid).

- The effects of vitamin C on chemically induced neoplasia of the large bowel should be studied further in laboratory animals, especially in the guinea pig.
- Further studies should be pursued to determine if vitamin C has broadly applicable inhibitory effects on neoplastic manifestations of cells in culture.
- Epidemiological studies should be conducted to assess more directly the possible inhibitory effects of vitamin C on the induction of gastric cancer and possibly cancer of other sites in the gastrointestinal tract, e.g., the colorectum.

Vitamin E

- Studies should be conducted in laboratory animals to determine the effects of vitamin E on chemically induced neoplasia of the large bowel and the breast.

- Epidemiological studies should be conducted to examine the relationship of vitamin E to cancer risk in humans.

Selenium and Other Trace Elements

Selenium

- Basic studies should be conducted to determine the effect of selenium on immune reactions, its interactions with DNA, its interactions with heavy metals, and the mechanisms by which it protects tissues against attack by free radicals.
- The stage of carcinogenesis at which selenium is most effective should be determined.
- A complete dose-response curve for the protective effect of selenium against chemical and viral carcinogens should be established, and the influence of dietary fats, heavy metals, and vitamin E on such curves should be quantified.
- Better methods to analyze the selenium content of foods should be developed, and the results of the subsequent analyses should be consolidated into a data bank and validated. This effort must be undertaken for each different geochemical region.
- Valid methods should be developed to assess the nutritional status of humans with regard to selenium. This would require that standard reference materials (e.g., foods, blood, and urine) be developed for selenium.
- Cohort studies based on biochemical assays of selenium are needed to corroborate observations from correlation studies. Epidemiological studies of selenium and cancer will need to take into account the interactions of selenium with other dietary constituents (e.g., vitamin C, copper, and zinc), since these interactions can affect the bioavailability of selenium.
- Studies in humans should be conducted under close medical supervision to monitor the metabolic effects of different forms of selenium supplements used in moderate amounts.
- Ultimately, consideration should be given to intervention studies in countries known to have inadequate selenium intakes, e.g., China, New Zealand, and Finland.

Molybdenum, Zinc, Iron, Iodine, and Arsenic

- Initially, research on molybdenum, zinc, iron, and iodine should be directed toward confirming or disproving their carcinogenicity when administered orally.

- If justified by findings from the initial research, basic research should be pursued to elucidate the mechanisms by which molybdenum, iron, iodine, and zinc might affect carcinogenesis.
- Analytical methods should be developed to determine more accurately the molybdenum, iron, iodine, and zinc content of foods.
- Valid methods should be developed to assess the nutritional status of individuals in regard to molybdenum, zinc, iron, iodine, and arsenic.
- Analytical epidemiological studies should be conducted to examine the possible carcinogenic effects of exposure to the low levels of zinc, iodine, and arsenic that are present in the average diet. The relationship between exposure to iodine and thyroid cancer should be examined in case-control studies that clearly separate the follicular and papillary histological types of tumors.

Nonnutritive Inhibitors of Carcinogenesis

- Studies should be conducted to detect dietary constituents that have the capacity to prevent the occurrence of neoplasia.
- Studies should be conducted in animals to determine the conditions under which these compounds will inhibit carcinogenesis and to identify characteristics that are related to their potential for preventing neoplasia. Their mechanisms of inhibition and their adverse effects, if any, also need to be identified.
- Short-term studies should be conducted in humans to identify the protective responses elicited by these compounds.
- Epidemiological studies, including intervention trials when appropriate, should be conducted to determine if consumption of foods containing high concentrations of these compounds results in a lower incidence of cancer (see also Chapter 4).

8

Food Additives, Contaminants, Carcinogens, and Mutagens

More than 2,500 chemical substances are intentionally added to foods to modify flavor, color, stability, texture, or cost. In addition, an estimated 12,000 substances are used in such a way that they may unintentionally enter the food supply. These substances include components of food-packaging materials, processing aids, pesticide residues, and drugs given to animals. An unknown number of naturally occurring chemical contaminants also find their way into food. The most notable of these are the products of mold growth called mycotoxins, which include the aflatoxins. The association of these substances with carcinogenesis is described in Chapters 12, 13, and 14 of the committee's first report (National Research Council, 1982).

The introduction of a new food additive requires the prior approval of the Food and Drug Administration (FDA). This approval can be granted only when the FDA concludes that the manufacturer has submitted sufficient toxicological data to demonstrate the safety of the additive. Long-term studies to evaluate the carcinogenicity of "direct" additives, i.e., those intentionally added to food, may be required when the intended level of usage is high or when possible carcinogenicity is suspected because of the structure or known biological activity of the additive. This same policy applies to "indirect additives," which are used in food packaging and as food processing aids. However, these substances are generally present in foods at such low levels that a carcinogenicity test requirement would be imposed only if the indirect additive were suspected of being a carcinogen because of its chemical structure or biological activity.

There has been no requirement to perform tests to determine carcinogenicity for most substances added to food. Substances in this category include those "generally recognized as safe" (GRAS), hundreds of flavoring agents, most additives approved before the 1958 Food Additives Amendment (P.L. 85–929) to the Food, Drug, and Cosmetic Act (U.S. Congress, 1958), and additives used at levels considered low by the FDA, except for suspected carcinogens. Furthermore, very little is known about the tumor-promoting activity of the few food ingredients that have been tested for carcinogenicity (National Research Council, 1982).

Of the additives that have been tested, those shown to be carcinogenic when administered orally to laboratory animals are generally prohibited from use. However, there are some exceptions. For example, Congress has passed special legislation (P.L. 95–203) preventing the FDA from restricting the use of the artificial sweetener saccharin, even

thought it has been shown to induce tumors in test animals (U.S. Congress, 1977). In addition to saccharin, two other known carcinogens--vinyl chloride and acrylonitrile--may appear at very low levels in food as a result of their application in the manufacture of plastics used in food-packaging materials. According to a recently adopted policy, such chemicals as vinyl chloride and acrylonitrile are considered by the FDA to be "constituents" of food-packaging material rather than additives. Thus, the FDA believes that these chemicals may be exempted from the absolute legal prohibition that applies to carcinogenic additives (U.S. Food and Drug Administration, 1982a, b).

Residues of pesticides that can induce tumors may contaminate foods through their application directly on crops or from other sources of environmental contamination. Chemicals that are intrinsic constituents of foods, such as hydrazines in mushrooms, may also be carcinogenic. Certain unavoidable contaminants in foods, such as aflatoxin B_1 and polychlorinated biphenyls, have been found to be carcinogenic in long-term toxicological studies. Such contaminants are generally permitted in foods only up to levels that the FDA considers the lowest level generally attainable without resulting in severe economic losses or adverse effects on the food supply.

In addition to known carcinogens that may appear in food as natural constituents, contaminants, or additives, there are a number of chemicals in food whose carcinogenic potential has not been adequately assessed but which are suspected carcinogens because of their known mutagenic activity, i.e., they can cause heritable alterations in the genetic material of cells. Systems for determining the mutagenicity of chemicals include tests in bacteria, fungi, mammalian cells in culture, and laboratory animals. Positive results from any of these test systems may be of toxicological significance, because the genetic material, DNA, is similar in all organisms and the mutagenicity of chemicals, even to bacteria, has been correlated with carcinogenicity in animals (National Research Council, 1983).

Most of the studies that have been conducted to identify mutagens in foods have utilized bacteria (Salmonella typhimurium) as the target organism in the initial screening. Positive results in the bacterial assay generally lead to further testing in other systems. Substances that are negative upon initial screening are only rarely investigated further. Since different mutagenicity test systems may give different results with a given test chemical, the use of the Salmonella assay alone in screening for mutagenicity could lead to a failure to identify mutagens or carcinogens in foods. Therefore, it is important to use other genetic tests in addition to the Salmonella assay in the initial screening of foods and food components for mutagenic activity. Mutagens in foods identified by any one test system should be assessed for mutagenic activity in a variety of in vitro and in vivo mutagenicity test systems, in vitro transformation assays, and carcinogenicity tests

in vivo. It would be ideal to supplement laboratory tests for mutagenicity with systems that could be used to assess mutagenic damage to human cells in vivo. The detection of chromosome aberrations in peripheral lymphocytes is the most widely used of such methods, but its apparent insensitivity limits its usefulness. Other tests, both for chromosome damage and for more subtle chemical changes in the DNA (i.e., gene mutations), are in various stages of development and may become suitable for application to populations consuming different diets. The development of such methods for detecting mutagenic effects in human cells in vivo is an important area for continued research.

There are several different sources of dietary mutagens. For example, intrinsic components of certain foods may be mutagenic. Into this category fall caffeine, other methylxanthines, and methylglyoxal (Kasai et al., 1982) in coffee as well as flavonoids in a wide variety of plants used for food. Other mutagens may be present in foods as naturally occurring contaminants such as aflatoxin B_1, as unintentional contaminants such as industrial chemicals or pesticides, or as intentionally used additives such as nitrites. In addition, mutagens may enter food during various food-processing techniques. For example, the smoking or charcoal-broiling of meat will result in the deposition of mutagenic polynuclear aromatic hydrocarbons such as benzo [a] pyrene; the cooking of some foods can result in the formation of potent mutagens, some of which are the products of the pyrolysis of amino acids; and nitrosamines can be formed during the frying of bacon that contains nitrite (National Research Council, 1982).

The significance of the presence of mutagens in food with respect to cancer risk is largely unknown. Some of the mutagens, such as aflatoxin B_1 and certain polynuclear aromatic hydrocarbons, are known to be carcinogenic. For others, such as nitrite and caffeine, long-term feeding studies in laboratory animals have failed to demonstrate carcinogenic activity, although endogenous reactions of nitrite with amines in the gastrointestinal tract can produce carcinogenic nitrosamines. The results of animal studies on the widely distributed flavonol quercetin are conflicting. Most mutagens in foods have not been adequately assessed for carcinogenic activity in animals. Only further research will enable us to decide whether significant health benefits might be derived from reducing the levels of mutagens that naturally occur in foods or of those that appear during cooking or processing of foods.

Dietary components may be converted to mutagenic (potentially carcinogenic) chemicals in vivo. The reaction between nitrite and amines to form nitrosamines is an example of such a reaction, as mentioned in Chapter 7.

Regulatory agencies regard chronic feeding studies in whole animals as the only definitive method for establishing the carcinogenicity of a chemical in foods. Thus, positive mutagenicity data are regarded only as an indication of the need for additional testing for carcinogenicity. When carcinogenicity in laboratory animals is established, a chemical

is generally regarded and treated as if it were known to be carcinogenic in humans. However, there are no satisfactory methods for establishing, or even estimating, the magnitude of the cancer risk that may be associated with a given level of human exposure to a substance known to be carcinogenic in animals. Furthermore, the cancer risk associated with particular food additives cannot generally be determined through epidemiological studies, because the use of these additives is so widespread that the reliable identification of unexposed controls would not be feasible. Therefore, federal regulatory agencies have generally adopted the prudent policy of attempting to restrict the presence of known carcinogens in food to the lowest feasible levels, including outright banning of most carcinogenic food additives. The actual health benefit of this policy cannot be determined, however, since satisfactory methods of quantitative risk estimation for carcinogens do not currently exist.

RESEARCH RECOMMENDATIONS

- Identify compounds responsible for most of the mutagenic activity in normally prepared foods and beverages. Food chemicals that are mutagenic in vitro should be assessed for stability in the gastrointestinal tract. In some cases, efforts to identify DNA adducts formed in vivo may be useful.
- Assess the effects of cooking, other processing, and storage conditions on the presence of mutagens in foods. Such mutagens might result, for example, from the pyrolysis of proteins or amino acids, from browning reactions involving sugar and amines, or from the oxidation of fats.
- Obtain better measurements of the levels of food additives consumed and the distribution of their intake among different population subgroups. In addition, use existing food intake data, if possible, to determine the relationship between the levels of food additives produced and the amounts consumed. Such studies are needed in order to assess levels of exposure to both direct and indirect additives. Once populations with different levels of exposure to food additives are identified, conduct epidemiological studies to evaluate the effect of these additives on cancer risk.
- Obtain better measurements of consumption levels and the distribution of intake among different population subgroups for carcinogens and mutagens in foods, such as hydrazines in mushrooms, aflatoxins, other mycotoxins, mutagenic flavonoids, and mutagens resulting from cooking. This effort would have to include a study of the patterns and frequencies of household and commercial cooking practices, including the cooking temperature and the duration of cooking for various types of food in which mutagens or carcinogens are produced during heating.

- Assess the feasibility of conducting epidemiological studies to evaluate the effect of cooking, processing, and storage on the carcinogenic potential of the diet.
- Continue to evaluate the carcinogenic potential of suspect compounds in common foods. These compounds include certain mycotoxins, polycyclic aromatic hydrocarbons, and naturally occurring constituents such as flavonoids and methylglyoxal.
- Determine the effects of diet on the endogenous formation of mutagens, such as nitrosamines and fecal and urinary mutagens, and assess the carcinogenicity of such mutagens. Chemical identification of nitrosatable precursors and endogenously produced mutagens should be pursued.
- Develop techniques for assessing the mutagenic effects of chemicals on human cells in vivo. As such techniques become available, they should be applied to test populations known to be consuming diets that are believed to present a high or a low risk for cancer.
- Investigate the possibility that comutagens and inhibitors of mutagenesis may work through mechanisms that are relevant in vivo. At present, such effects observed in in vitro mutagenicity assays may simply be artifacts related to conditions in the assay systems being used.
- The search for possible tumor-promoting activity of food additives and contaminants should be pursued. For example, studies should be conducted to examine the tumor-promoting effects of butylated hydroxytoluene (BHT) and the tumor-inhibiting effects of both BHT and butylated hydroxyanisole (BHA) to determine their relevance to humans. These are such widely used additives with known effects in experimental systems that intensive investigation is warranted. An effort should be made to determine the feasibility of epidemiological studies on these widely distributed substances.

9

Consumer Behavior

Although it is clear that people do markedly alter their diets during the course of their lives, we know very little about either the environmental factors that are responsible for such changes or the temporal pattern, if any, of their occurrence. There has been essentially no long-term research on patterns of food selection by humans and the factors that affect them. Thus, even when knowledge about diet and disease relationships is certain enough to make interventions prudent and appropriate, there are no proven measures that either educators or policymakers can take to help the public modify its long-term food intake.

Because we lack knowledge about the causes and patterns of long-term dietary behavior, it is difficult to reach even post hoc conclusions about their possible relationships to various (often desirable) effects. It is now clear, for example, that the rates of death from coronary heart disease are declining in the United States and that they have been doing so for at least 14 years (Stamler, 1982; Walker, 1977). It is also clear from marketing research, from public opinion surveys, and from other research that several other changes have taken place over this same period: (1) some unknown portion of the population has adopted a low-meat or essentially vegetarian lifestyle; (2) other persons have modified their diets in different ways for some specific health-related reason; and (3) a certain segment of the population has taken up some form of regular exercise, begun treatment for high blood pressure, and given up smoking (Jones and Weimer, 1981; Louis Harris and Associates, Inc., 1978, 1979; Mark Clements Research, Inc., 1980; Rowland and Roberts, 1982; Stamler, 1978; Yankelovich, Skelly and White, Inc., 1978, 1979, 1980). The extent to which any of these changes is related to the reduction in cardiovascular disease and--more to the point here--to intentionally undertaken educational programs or other interventions is unclear.

Indeed, as elucidated in a recent report on the Multiple Risk Factor Intervention Trial (MR0FIT), “spontaneous”--that is, unexplained--behavior change can reduce the observed differences between experimental and control groups in even carefully designed prospective studies. Enrolled in this 7-year trial were almost 13,000 men at high risk of heart attack, one-half of whom were given “special intervention” to help them stop smoking, reduce their blood pressure, and modify their diets to lower their serum cholesterol. As it turned out, the control group (which only had physician contact) also modified its risk factors and had lower mortality from cardiovascular disease over the period of the trial, as did the entire U.S. population (Multiple Risk Factor Intervention Trial Research Group, 1982). As yet, there

are no parallel data from "cancer reduction trials." The MRFIT data make it clear that failure to study "spontaneous" dietary change, even as we are mounting intervention trials, may entirely becloud the results of those trials.

The results from other intervention programs, even very intensive and expensive ones, would not have encouraged one to predict a widespread effect as great as that implied by a 30% "spontaneous" drop in mortality from coronary heart disease (Farquhar et al., 1977; Maccoby et al., 1977; Ringen, 1983; Smith et al., 1982; Stamler, 1982). The results from several such studies are especially instructive in that they involve the use of media and of governmental intervention. These are often regarded as potentially highly effective channels through which desirable dietary change can be promoted in the United States, even though they are often also regarded as economically and politically unfeasible.

In the Stanford Three Community Study, a sophisticated media campaign used in conjunction with intensive face-to-face instruction had relatively modest, although statistically significant, effects on dietary behaviors associated with heart disease (Cohen and Cohen, 1978; Farquhar et al., 1977; Fortmann et al., 1981; Leventhal et al., 1980; Maccoby et al., 1977; Meyer et al., 1980a, b; Stern et al., 1976). More recently, Smith et al. (1982) conducted a pilot intervention study using mass media plus school, store, community, and parent involvement. They attempted to increase children's consumption of snack foods that were low in caloric content or high in nutrient density and to decrease their consumption of snack foods containing high levels of sugar and fat. Despite the fact that the campaign materials placed a major emphasis on increasing the use of fruits as snacks, the only measurable effect of the intervention was a modest reduction in the consumption of soft drinks and other sweets not specifically promoted. There was no increase in the consumption of heavily promoted snacks.

Schucker and his colleagues (1982) studied the effects of the saccharin warning label on sales of diet soft drinks. Although there was a drop in the growth rate of sales for these products following extensive publicity about the finding that saccharin caused cancer in animals, the investigators found it difficult to disentangle the effects of the warning label from the effects of price increases and advertising decreases during the same period. In summer 1980, when advertising returned to its prepublicity level, sales of diet sodas reached an all-time high.

In Norway, an entire nation committed itself to a policy intended to modify its agricultural, marketing, and educational efforts in a manner that would encourage the consumption of a healthier and more "responsible" diet (Ringen, 1983; Royal Norwegian Ministry of Agriculture, 1975). Although there were some changes in food intake in the

desired direction, it was concluded after 5 years that "where consumption patterns so far have agreed with the goals of the nutrition policy, the credit should be given to chance more than to conscious decision making" (Ringen, 1983).

Extensive data have also been published from two other kinds of studies whose relevance to directed long-term dietary change is unclear: (1) successful programs that result in the modification of behaviors other than eating and (2) short-term interventions involving populations who volunteer to be educated nutritionally (or who have no choice, e.g., schoolchildren). In regard to the first of these, it is obvious that those concerned with long-term modification of food habits need to become acquainted with the extensive body of research into the psychological factors affecting participation in such health-related behaviors as smoking cessation, compliance with a medical regimen, or participation in immunization or health screening programs (Enelow and Henderson, 1975; Olson and Gillespie, 1981). However, the extent to which the findings from these studies are transferable to "spontaneous" dietary modification is not clear. The kind of lifetime dietary change that is usually prescribed for risk reduction--and implied by the ~30% decline in heart disease--involves a complex series of choices made 3 or more times a day from an ever-changing mix of many thousands of food products of increasingly unfamiliar composition. Therefore, where food is concerned, the desired behaviors are more complex, i.e., determining how to modify one's diet meal by meal every day is a much more complex activity than simply remembering to take a pill or to go to the doctor. Moreover, monitoring compliance is also considerably more complicated, involving at the least the elicitation of several dietary reports from the subject.

Most studies of the effects of nutrition education on food intake may also not be directly relevant to the question at hand, since they involve measuring short-term changes in the behavior of specific captive populations exposed to a carefully organized series of lessons for a relatively short period. It is not clear how much light such experiments can shed on the changes that actually occur over time in free-living populations exposed to the multimedia message stream in the United States.

Moreover, the results from such studies are quite unimpressive where actual behavior change is concerned--when such change is one of the outcome measures. The data are best, perhaps, for weight loss programs, simply because there are so many of them and the outcome is so readily measurable. A number of studies have now documented the fact that educational programs to encourage weight loss have a generally dismal record (Brightwell and Sloan, 1977; Stunkard and McLaren-Hume, 1959; Wing and Jeffery, 1979).

Thus, there is evidence that people have changed their food habits, but there is little evidence that they have done so in large numbers on the basis of nutrition education programs aimed at producing such

change. A recent study by Schacter (1982) suggests one possible explanation for this apparent inconsistency. Noting that most studies on the effects of weight-loss regimens show a very low rate of success, especially over the longer term, Schacter undertook a study of weight histories and weight-loss attempts in two arbitrarily selected samples, one consisting of all persons associated with a university psychology department and the other consisting of persons working in establishments that are open all year in a resort community. Contrary to expectation, he found that 62.5% of all those with a history of obesity who had attempted to lose weight had succeeded and had kept the weight off. Schacter's suggested explanation of this phenomenon is that weight-loss programs, like those aimed at smoking or narcotic addiction, measure only one attempt of any one person to cure himself. Successful dieters, he speculates, probably try many times, finally succeeding on the nth try.

Whether or not Schacter's data are confirmed by subsequent studies, they illuminate the reality that dietary change need not be--indeed, probably rarely is--a single dramatic change, but, rather, it may be accomplished through a series of modifications that take place over time in response to a variety of stimuli (Kolasa, 1981). Meanwhile, intentional educational interventions cannot be shown to have had a substantial measurable effect, even though health statistics (including those on general life expectancy) suggest that substantial positive changes are taking place. It is possible, of course, to speculate that food choices are being beneficially altered by public awareness of a growing professional consensus that lifestyles associated with affluence are related to a whole spectrum of diseases. However, there is no assurance that a consensus on dietary change is being communicated clearly, if at all (Skelly, 1982). And it is also not at all clear what people actually do--as opposed to what they say they will do--when they are informed. A survey taken shortly after the release of this committee's first report showed that 53% of those contacted were aware of the report (Anonymous, 1982). However, 36% of the surveyed population said they would make practically no change in their diets, 16% said they would make a moderate change, and 2% indicated they would make a major change as a consequence of knowing about the report.

All dietary change, whether “directed” or “spontaneous,” may have a major impact on one or another sector of the food industry, with the result that there is often conflict between the private sector's interest in maximizing production and what public health officials regard as the public's interest, where health is concerned. The food industry has already made changes in response to recommendations from various groups in the past, for example, lowering the sodium content or modifying the fat content of foods. Attention should continue to be directed toward finding ways in which recommended changes can be phased into the food supply to minimize the damage to the industry without compromising on matters that affect public health.

Taking all these factors into account, what research directions would be most useful? We need to know considerably more about the motives that lead people to change their food habits. How could this be studied? An example from another field might be illuminating. In the more than 20 years since the relationship between economic and social "disadvantage" and high rates of school failure was brought to public attention, researchers have looked valiantly for the factors in poverty that might account for its association with failure in school and in subsequent employment. Only recently has it been recognized that a more interesting question is not why so many individuals from disadvantaged environments fail, but why some individuals succeed. Research on consumer education in relation to diet might well profit from a similar emphasis on success, since there is evidence that many people have, in fact, changed what they eat in a direction that most health professionals would consider potentially beneficial.

The public is anxious to be given dietary guidelines to avoid cancer, but scientists are anxious not to make promises prematurely. In considering this dilemma, one must recognize that (1) the public must make dietary choices every day; (2) these choices are being made from a food supply that is changing rapidly; and (3) the best judgment of scientists at any point is certainly as good as--and very likely to be better than--what the public can get anywhere else. To do nothing in the way of helping the public translate the present state of knowledge into behavior is to do something, namely, to imply that nothing has been learned from several decades of research.

Although the issues raised above are pertinent to many other areas of nutrition education research, the committee has limited its specific recommendations to those that seem especially relevant to its charge to disseminate the findings resulting from this study. Within the past few years, several major conferences and workshops have addressed the topic of nutrition education and needed research in the field. Interested readers are advised to consult the publications reporting the work of those conferences for a fuller understanding of overall research issues (Brun, 1980; Dwyer, 1980; Olson and Gillespie, 1981; Sims and Light, 1982). The following areas show particular promise as subjects for fruitful research. Many of them have also been recommended by other groups in other reports.

RESEARCH RECOMMENDATIONS

- We urgently need research that would begin to examine the behaviors and motivations of persons who have already changed their diets--for example, in the directions suggested in the Dietary Guidelines for Americans (U.S. Department of Agriculture and U.S. Department of Health, Education, and Welfare, 1980) or in this committee's first report. If we simultaneously study those who have not changed their diets, we may begin to understand the obstacles to change. Although

individuals who undertake "spontaneous" change may differ from the population as a whole, finding out who they are, and when, why, how, and during what periods in their lives they changed their eating patterns, would help us begin to understand the factors that lead to long-term dietary change (Kasl, 1980).

- Research is needed to learn the "natural history" of diets consumed by humans. We know essentially nothing about which sorts of life occurrences--leaving home, getting married, having children, getting a new job, or losing a job--lead to substantial and lasting dietary change in the presence of a rapidly changing food supply and the proliferation of information in the media. Over the life spans of most individuals, are there periods of vulnerability to change in food consumption when dietary education might be most effective? Moore et al. (1982) have recently suggested one potentially useful technique for such an investigation.
- Suggestions are made in Chapter 4 of this report that more (and more frequent) monitoring of food intake and of patterns of food consumption in different groups will add to our understanding of the effects of different diets and of long-term dietary change. We need to collect data on a national basis about what people eat and how this varies in relation to such factors as geographical location, lifestyle, social affiliation, and other social factors as well as such conventionally considered variables as ethnic and socioeconomic groups. The data should be collected in such a manner that they can also be analyzed for information about the history of an individual's lifetime food habits, including changes in those habits.
- Existing bodies of longitudinal dietary data, such as those from the Harvard (Burke et al., 1959) and Colorado (Beal, 1967) growth studies, should be examined for what they might reveal about patterns of food consumption over time and points at which diets change. Some longitudinal data have been examined in terms of nutrient intake (e.g., Valadian et al., 1981) but not, as far as the committee has been able to determine, in terms of food intake patterns.
- Almost nothing is known regarding the acquisition of food habits by children, with the exception of the findings from one 50-year-old study (Davis, 1928, 1934, 1939). Consideration should be given to supporting additional long-term studies by researchers and/or observers to learn the factors affecting the acquisition of childhood eating patterns (see, e.g., Thomas et al., 1963).

References

Anonymous. 1977. Report of the American Institute of Nutrition Ad Hoc Committee on Standards for Nutritional Studies. J. Nutr. 107:1340–1348 .

Anonymous. 1982. Roper poll shows high public awareness of NAS diet-cancer report. Food Chem. News 24(27):14 .

Barbolt, T. A., and R. Abraham. 1978. The effect of bran on dimethyl-hydrazine-induced colon carcinogenesis in the rat. Proc. Soc. Exp. Biol. Med. 157:656–659 .

Beal, V. A. 1967. The nutritional history in longitudinal research. J. Am. Diet. Assoc. 51:426–432 .

Boutwell, R. K. 1977. The role of the induction of ornithine decarboxylase in tumor promotion. Pp. 773–783 in H. H. Hiatt, J. D. Watson, and J. A. Winsten, eds. Origins of Human Cancer, Book B: Mechanisms of Carcinogenesis. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.

Bowering, J., A. M. Sanchez, and M. I. Irwin. 1976. A conspectus of research on iron requirements of man. J. Nutr. 106:985–1074 .

Brightwell, D. R., and C. L. Sloan. 1977. Long-term results of behavior therapy for obesity. Behav. Ther. 8:898–905 .

Bruce, W. R., A. J. Varghese, R. Furrer, and P. C. Land. 1977. A mutagen in the feces of normal humans. Pp. 1641–1646 in H. H. Hiatt, J. D. Watson, and J. A. Winsten, eds. Origins of Human Cancer, Book C: Human Risk Assessment. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.

Brun, J. K., ed. 1980. Nutrition Education Research: Directions for the Future. Conference Proceedings. National Dairy Council, Rosemont, Ill. 77 pp.

Burke, B. S., R. B. Reed, A. S. van den Berg, and H. C. Stuart. 1959. Caloric and protein intakes of children between 1 and 18 years of age. Pediatrics 24:922–940 .

Cohen, C. I., and E. J. Cohen. 1978. Health education: Panacea, pernicious or pointless? N. Engl. J. Med. 299:718–720 .

Davis, C. M. 1928. Self selection of diet by newly weaned infants. An experimental study. Am. J. Dis. Child. 36:651–679 .

Davis, C. M. 1934. Studies in the self-selection of diet by young children. J. Am. Dent. Assoc. 21:636–640 .

Davis, C. M. 1939. Results of the self-selection of diets by young children. Can. Med. Assoc. J. 41:257–261 .

Dwyer, J., ed. 1980. National Conference on Nutrition Education: Directions for the 1980s. J. Nutr. Educ. 12:79–137 .

Enelow, A. J., and J. B. Henderson, eds. 1975. Applying Behavioral Science to Cardiovascular Risk: Proceedings of a Conference. American Heart Association, New York. 215 pp.

Farquhar, J. W., N. Maccoby, P. D. Wood, J. K. Alexander, H. Breitrose, B. W. Brown, Jr., W. L. Haskell, A. L. McAlister, A. J. Meyer, J. D. Nash, and M. P. Stern. 1977. Community education for cardiovascular health. Lancet 1:1192–1195 .

Fortmann, S. P., P. T. Williams, S. B. Hulley, W. L. Haskell, and J. W. Farquhar. 1981. Effect of health education on dietary behavior: The Stanford Three Community Study. Am. J. Clin. Nutr. 34:2030–2038 .

Freeman, H. J., G. A. Spiller, and Y. S. Kim. 1978. A double-blind study on the effect of purified cellulose dietary fiber on 1,2-dimethylhydrazine-induced rat colonic neoplasia. Cancer Res. 38:2912–2917 .

Glauert, H. P., M. R. Bennink, and C. H. Sander. 1981. Enhancement of 1,2-dimethylhydrazine-induced colon carcinogenesis in mice by dietary agar. Food Cosmet. Toxicol. 19:281–286 .

Heddle, J. A., D. H. Blakey, A. M. V. Duncan, M. T. Goldberg, H. Newmark, M. J. Wargovich, and W. R. Bruce. 1982. Micronuclei and related nuclear anomalies as a short-term assay for colon carcinogens. Pp. 367–375 in B. A. Bridges, B. E. Butterworth, and I. B. Weinstein, eds. Indicators of Genotoxic Exposure. Banbury Report 13. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.

Heiniger, H. J. 1981. Cholesterol and its biosynthesis in normal and malignant lymphocytes. Cancer Res. 41:3792–3794 .

Hirai, N., D. G. I. Kingston, R. L. Van Tassell, and T. D. Wilkins. 1982. Structure elucidation of a potent mutagen from human feces. J. Am. Chem. Soc. 104:6149–6150 .

Hoehn, S. K., and K. K. Carroll. 1979. Effects of dietary carbohydrate on the incidence of mammary tumors induced in rats by 7,12-dimethylbenz( )anthracene. Nutr. Cancer 1(3):27–30 .

Ip, C., and D. K. Sinha. 1981. Enhancement of mammary tumorigenesis by dietary selenium deficiency in rats with a high polyunsaturated fat intake. Cancer Res. 41:31–34 .

Jain, M., G. M. Cook, F. G. Davis, M. G. Grace, G. R. Howe, and A. B. Miller. 1980. A case-control study of diet and colorectal cancer. Int. J. Cancer 26:757–768 .

Jones, J. L., and J. Weimer. 1981. Health-related food choices. Fam. Econ. Rev. Summer 1981, pp. 16–19 .

Kasai, H., K. Kumeno, Z. Yamaizumi, S. Nishimura, M. Nagao, Y. Fujita, T. Sugimura, H. Nukaya, and T. Kosuge. 1982. Mutagenicity of methylglyoxal in coffee. Gann 73:681–683 .

Kasl, S. V. 1980. Cardiovascular risk reduction in a community setting: Some comments. J. Consult. Clin. Psychol. 48:143–149 .

Kolasa, K. M. 1981. Nutrition education and changing behavior. Prog. Clin. Biol. Res. 67:415–422 .

Lavik, P. S., and C. A. Baumann. 1943. Further studies on the tumor promoting action of fat. Cancer Res. 3:749–756 .

Levander, O. A., and L. Cheng, eds. 1980. Micronutrient interactions: Vitamins, minerals, and hazardous elements. Ann. N.Y. Acad. Sci. 355:1–372 .

Leventhal, H., M. A. Safer, P. D. Cleary, and M. Gutmann. 1980. Cardiovascular risk modification by community-based programs for life-style change: Comments on the Stanford study. J. Consult. Clin. Psychol. 48:150–158 .

Lipkin, M. 1977. Growth kinetics of normal and premalignant gastrointestinal epithelium. Pp. 569–589 in B. Drewinko and R. M. Humphrey, eds. Growth Kinetics and Biochemical Regulation of Normal and Malignant Cells. Williams and Wilkins Co., Baltimore, Md.

Louis Harris and Associates, Inc. 1978. Health Maintenance. Available from Pacific Mutual Life Insurance Company, Newport Beach, Calif.

Louis Harris and Associates, Inc. 1979. The Perrier Study: Fitness in America. Great Waters of France, Inc., New York.

Maccoby, N., J. W. Farquhar, P. D. Wood, and J. Alexander. 1977. Reducing the risk of cardiovascular disease: Effects of a community-based campaign on knowledge and behavior. J. Community Health 3:100–114 .

Mark Clements Research, Inc. 1980. Highlights from a Study of Trends in Nutrition. The Benchmark Survey. February, 1980 . Conducted for Self Magazine. Available from Self Magazine, New York.

McCay, C. M., G. Sperling, and L. L. Barnes. 1943. Growth, ageing, chronic diseases, and life span in rats. Arch. Biochem. 2:469–479 .

Meyer, A. J., J. D. Nash, A. L. McAlister, N. Maccoby, and J. W. Farquhar. 1980a. Skills training in a cardiovascular health education campaign. J. Consult. Clin. Psychol. 48:129–142 .

Meyer, A. J., N. Maccoby, and J. W. Farquhar. 1980b. Reply to Kasl and Leventhal et al. J. Consult. Clin. Psychol. 48:159–163 .

Monsen, E. R., L. Hallberg, M. Layrisse, D. M. Hegsted, J. D. Cook, W. Mertz, and C. A. Finch. 1978. Estimation of available dietary iron. Am. J. Clin. Nutr. 31:134–141 .

Moore, J. V., L. L. Prestridge, and G. R. Newell. 1982. Research technique for epidemiologic investigation of nutrition and cancer. Nutr. Cancer 3:249–256 .

Multiple Risk Factor Intervention Trial Research Group. 1982. Multiple risk factor intervention trial. Risk factor changes and mortality results. J. Am. Med. Assoc. 248:1465–1477 .

National Research Council. 1980a. Recommended Dietary Allowances. Ninth Revised Edition. Committee on Dietary Allowances, Food and Nutrition Board, Division of Biological Sciences, Assembly of Life Sciences, National Research Council. National Academy of Sciences, Washington, D.C. 185 pp.

National Research Council. 1980b. Toward Healthful Diets. Food and Nutrition Board, Division of Biological Sciences, Assembly of Life Sciences, National Research Council. National Academy of Sciences, Washington, D.C. 24 pp.

National Research Council. 1982. Diet, Nutrition, and Cancer. Committee on Diet, Nutrition, and Cancer, Assembly of Life Sciences, National Research Council . National Academy Press, Washington, D.C. 496 pp.

National Research Council. 1983. Identifying and Estimating the Genetic Impact of Chemical Mutagens. Report of the Committee on Chemical Environmental Mutagens, Board on Toxicology and Environmental Health Hazards, Commission on Life Sciences, National Research Council. National Academy Press, Washington, D.C. 295 pp.

Newberry, C. L., and G. D. Christian. 1965. Rapid colorimetric determination of microgram amounts of selenium in soils and biological samples, using millipore filters. J. Assoc. Off. Anal. Chem. 48:322–326 .

Newmark, H. L., and W. J. Mergens. 1981. Blocking nitrosamine formation using ascorbic acid and -tocopherol. Pp. 285–298 in W. R. Bruce, P. Correa, M. Lipkin, S. R. Tannenbaum, and T. D. Wilkins, eds. Gastrointestinal Cancer: Endogenous Factors. Banbury Report 7. Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.

Ohshima, H., J.-C. Bereziat, and H. Bartsch. 1982. Monitoring N-nitrosamino acids excreted in the urine and feces of rats as an index for endogenous nitrosation. Carcinogenesis 3:115–120 .

Olson, C. M., and A. H. Gillespie, eds. 1981. Proceedings of the Workshop on Nutrition Education Research: Applying Principles from the Behavioral Sciences . J. Nutr. Educ. 13:S1–S118 .

Pitot, H. C., T. Goldsworthy, H. A. Campbell, and A. Poland. 1980. Quantitative evaluation of the promotion by 2,3,7,8-tetrachlorodibenzop-dioxin of hepatocarcinogenesis from diethylnitrosamine. Cancer Res. 40:3616–3620 .

Potter, V. R. 1981. A new protocol and its rationale for the study of initiation and promotion of carcinogenesis in rat liver. Carcinogenesis 2:1375–1379 .

Ringen, K. 1983. Norway's nutrition and food policy: Overview, results and future directions. Pp. 163–181 in D. S. McLaren, ed. Nutrition in the Community: A Critical Look at Nutrition Policy, Planning, and Programmes. Second Edition. John Wiley and Sons, New York and London.

Ross, M. H., and G. Bras. 1973. Influence of protein under-and over-nutrition on spontaneous tumor prevalence in the rat. J. Nutr. 103:944–963 .

Rowland, M., and J. Roberts. 1982. Blood pressure levels and hypertension in persons ages 6–74: United States, 1976–80. Advance Data from Vital and Health Statistics 84:1–11 . U.S. Public Health Service, Hyattsville, Md.

Royal Norwegian Ministry of Agriculture. 1975. On Norwegian Food and Nutrition Policy. Report No. 32 (1975–76) to the Storting, December, 1975 . Royal Norwegian Ministry of Agriculture, Oslo. 80 pp.

Schacter, S. 1982. Recidivism and self-cure of smoking and obesity. Am. Psychol. 37:436–444 .

Schucker, R. E., R. C. Stokes, M. L. Stewart, and D. P. Henderson. 1982. Impact of the Saccharin Warning Label on Sales of Diet Soft Drinks in Supermarkets. Food and Drug Administration, Washington, D.C. [27] pp.

Sims, L. S., and L. Light, eds. 1982. Directions for Nutrition Education Research--The Penn State Conferences--A Proceedings. College of Human Development, The Pennsylvania State University, University Park, Penn. 108 pp. Available from the Society for Nutrition Education, Oakland, Calif.

Skelly, F. R. 1982. The attitudes of the consumer. Nutr. Rev. 40 (Suppl.):35–39 .

Smith, K. W., S. K. Nelson, and J. J. O'Hara. 1982. Final Report, Food for Thought Project. Submitted to: Office of Policy, Planning and Evaluation, Food and Nutrition Service, U.S. Department of Agriculture, Alexandria, Va. Contract No. 58-3198-9-15. American Institutes for Research in the Behavioral Sciences, Cambridge, Mass.

Sparnins, V. L., and L. W. Wattenberg. 1981. Enhancement of glutathione S-transferase activity of the mouse forestomach by inhibitors of benzo[a]pyrene-induced neoplasia of the forestomach. J. Natl. Cancer Inst. 66:769–771 .

Sparnins, V. L., P. L. Venegas, and L. W. Wattenberg. 1982. Glutathione S-transferase activity: Enhancement by compounds inhibiting chemical carcinogenesis and by dietary constituents. J. Natl. Cancer Inst. 68:493–496 .

Stamler, J. 1978. Lifestyles, major risk factors, proof and public policy. Circulation 58:3–19 .

Stamler, J. 1982. Diet and coronary heart disease. Biometrics 37 (Suppl.):95–114 .

Stern, M. P., J. W. Farquhar, N. Maccoby, and S. H. Russell. 1976. Results of a two-year health education campaign on dietary behavior: The Stanford Three Community Study. Circulation 54:826–833 .

Stunkard, A., and M. McLaren-Hume. 1959. The results of treatment for obesity. Arch. Intern. Med. 103:79–85 .

Thilly, W. G., and H. L. Liber. 1980. Genetic toxicology. Pp. 139–157 in J. Doull, C. D. Klaassen, and M. O. Amdur, eds. Casarett and Doull's Toxicology: The Basic Science of Poisons, Second Edition. Macmillan Publishing Co., New York, Toronto, and London.

Thomas, A., S. Chess, H. G. Birch, M. E. Hertzig, and S. Korn. 1963. Behavioral Individuality in Early Childhood. New York University Press, New York. 135 pp.

Troll, W., G. Witz, B. Goldstein, D. Stone, and T. Sugimura. 1982. The role of free oxygen radicals in tumor promotion and carcinogenesis. Pp. 593–599 in E. Hecker, N. E. Fusenig, W. Kunz, F. Marks, and H. Thielmann, eds. Carcinogenesis--A Comprehensive Survey. Volume 7: Cocarcinogenesis and Biological Effects of Tumor Promoters. Raven Press, New York.

U.S. Congress. 1958. Food Additives Amendment of 1958, Public Law 85–929, September 6, 1958. 85th Congress, 72 Stat. 1784–1789 , Washington, D.C.

U.S. Congress. 1977. Saccharin Study and Labelling Act, Public Law 95–203, November 23, 1977. 95th Congress, 91 Stat. 1451–1454 , Washington, D.C.

U.S. Department of Agriculture. 1975. Nutritive Value of American Foods in Common Units. Agriculture Handbook No. 456. Agricultural Research Service, U.S. Department of Agriculture, Washington, D.C. 291 pp.

U.S. Department of Agriculture and U.S. Department of Health, Education, and Welfare. 1980. Nutrition and Your Health. Dietary Guidelines for Americans. Home and Garden Bulletin No. 232. U.S. Department of Agriculture and U.S. Department of Health, Education, and Welfare, Washington, D.C. 20 pp.

U.S. Food and Drug Administration. 1982a. D&C Green No. 6; Listing as a color additive in externally applied drugs and cosmetics. Fed. Regist. 47:14138–14147 .

U.S. Food and Drug Administration. 1982b. Policy for regulating carcinogenic chemicals in food and color additives; Advance notice of proposed rulemaking. Fed. Regist. 47:14464–14470 .

Valadian, I., C. Berkey, and R. B. Reed. 1981. Adolescent nutrition as it relates to cardiovascular disease and reproductive capacity later in life . Nutr. Rev. 39:107–111 .

Verma, A. K., C. L. Ashendel, and R. K. Boutwell. 1980. Inhibition by prostaglandin synthesis inhibitors of the induction of epidermal ornithine decarboxylase activity, the accumulation of prostaglandins, and tumor promotion caused by 12-0-tetradecanoylphorbol-13-acetate. Cancer Res. 40:308–315 .

Walker, W. J. 1977. Editorial: Changing United States life-style and declining vascular mortality: Cause or coincidence? N. Engl. J. Med. 297:163–165 .

Wattenberg, L. W. 1981. Inhibitors of chemical carcinogens. Pp. 517–539 in J. H. Burchenal and H. F. Oettgen, eds. Cancer: Achievements, Challenges, and Prospects for the 1980's, Volume 1 . Grune and Stratton, New York, London, Sydney, and San Francisco.

Wattenberg, L. W. 1983. Inhibitors of neoplasia by minor dietary constituents. Cancer Res. 43:2448s–2453s .

Wing, R. R., and R. W. Jeffery. 1979. Outpatient treatments of obesity: A comparison of methodology and clinical results. Int. J. Obes. 3:261–279 .

Yankelovich, Skelly and White, Inc. 1978. Nutrition--A Study of Consumers' Attitudes and Behavior Towards Eating at Home and Out of Home. 1st Woman's Day Family Food Study. Available from Woman's Day, New York.

Yankelovich, Skelly and White, Inc. 1979. Family Health in an Era of Stress. The General Mills American Family Report 1978–79. Available from General Mills, Inc., Minneapolis, Minn.

Yankelovich, Skelly and White, Inc. 1980. Nutrition vs. Inflation: The Battle of the Eighties. 2nd Woman's Day/FMI Family Food Study. Available from Food Marketing Institute, Washington, D.C.

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