REPORT OF THE N.C.A.B. AD HOC SUB-COMMITTEE ON NUTRITION AND CANCER

February 3, 1982

The N.C.A.B. Ad Hoc Sub-Committee on Nutrition and Cancer recommends that the Board advise the Director of the National Cancer Institute to give top priority to diet, nutrition and cancer research. The committee believes that an expanded effort in this field of research is necessary to increase the knowledge and understanding of such basic mechanisms as tumor promotion and anticarcinogenesis.

1. SCIENTIFIC BACKGROUND

Diet, Nutrition and Cancer Prevention

We will briefly outline four areas of this subject which seem to be important illustrations.

1. Natural mutagens and carcinogens in food. It is becoming apparent that there is an enormous variety of natural carcinogens in the human diet and that the influence of diet on cancer may outweigh the influence of man-made chemicals for all but a tiny fraction of the human population (1).

a. Plant material. Every plant in nature must synthesize toxic chemicals as a defense against the hordes of insects and animals ready to eat them (2-12). This includes all of the plants in the human diet. Toxic chemicals in our diet are being identified as mutagens, teratogens and carcinogens (2-12). The great variety of these toxic chemicals has kept organic chemists busy characterizing them for 100 years; but it is only fairly recently that toxicology is being done on many of these

compounds. Particularly in recent years with the advances in short-term tests and increased numbers of cancer tests, hundreds of natural mutagens and carcinogens are being identified. A few examples are: Quercetin and similar flavonoids, which are extremely widespread in the diet at high levels and are strong mutagens in a number of species (6,7,10); furocoumarins such as psoralen derivatives which are light-activated mutagens and carcinogens and are very widespread in plants (8,9); solanine which is a teratogen in animals and appears to be in humans as well and is present in every potato we eat (2,3). When potatoes are bruised and exposed to light, the levels of solanine in potatoes can reach lethal levels (2). (Plants respond to damage by making more toxic chemicals as a defense against insects. [12]) Plants also contain a variety of anti-carcinogens which we discuss below.

b. Rancid fat and lipid peroxidation. Epidemiological studies on the major cancers in people suggest that diet is the major factor (1). Fat intake, in particular, correlates with colon and breast cancer, which together with lung cancer (due to cigarette smoking) account for a major part of human cancer in the U.S. (1). Unsaturated fatty acids are very prone to oxidation and the lipid peroxidation chain reaction (rancidity) yields a variety of mutagens and carcinogens such as hydroperoxides, epoxides, enals, aldehydes, alkoxy and hydroperoxy radicals, and singlet oxygen, from fatty acids and cholesterol (13,13,16,19,21). Rancid fat from meat is extremely toxic and likely to be a major factor in the fat-cancer connection. Many natural compounds in our diet, such as quinones (4), are metabolized to radicals (4) which oxidize the fat in our cellular membranes by a lipid peroxidation chain reaction. Some tumor promoters appear to be effective through damage to cell membranes. Some agents producing oxygen radicals and lipid peroxidation may be effective as tumor promoters and agents inhibiting

lipid peroxidation and oxygen radical formation may be anti-promoters (19, 20,21). Age pigment (lipofuscin) has been associated with lipid peroxidation and accumulates during aging in all mammalian species (14,16). Age pigment may be formed from malondialdehyde, a major end product of rancidity, cross-linking protein and lipids (16). One attractive theory of aging at the present time is that the major cause is damage to DNA and other cell molecules by oxygen radicals and lipid peroxidation (reviewed in 13,14,16). Some of our key defenses against oxygen radicals and lipid peroxidation are anti-oxidants in the diet (section 4).

c. Mold carcinogens. A variety of mold carcinogens are present in cheeses and mold contaminated food such as nuts (5,7). Some of these, such as sterigmatocysitn and aflatoxin, are extremely potent carcinogens and mutagens (5,7).

d. Nitrite, nitrate, and nitrosamines. A number of human cancers such as stomach and esophageal cancer may be related to nitrosamines formed from nitrite in the diet (7) and endogenously from reduction of nitrate. Anti-carcinogens in the diet may be very important here as well (section 4).

2. Cooking food. The work of Sugimure and others has indicated that the burnt and browned material from cooking protein is mutagenic and carcinogenic (7,17). The amount of the burnt material in the human diet is appreciable (7). In addition to the reaction of amino acids and sugars during cooking, e.g., forming the brown color on toasted bread, produces a variety of mutagens and presumptive carcinogens (17). Cooking accelerates a rancidity reaction of cooking oils and the fat in meat (see rancidity above).

3. Alcohol. Red wine has been shown to be strongly associated with stomach cancer in France (15). This may be due to some of the toxic

mutagens in grape skins, such as quercetin, that are liberated by the yeast fermentation (10). Alcohol has long been associated with several types of cancer (1,15).

4. Anti-carcinogens. We have many defense mechanisms to protect ourselves against mutagens and carcinogens, including shedding the outer layer of our intestines and colon every day. Understanding these mechanisms should be a major area of cancer research. In addition to dozens of defense enzymes, such as superoxidase dismutase and glutathione peroxidase, we have a variety of small molecules in our diet which are essential as anti-carcinogens (13,14,16).

a. Vitamin E (tocopherol) is one of the most important radical traps in our lipid membranes.

b. β-Carotene is another anti-carcinogen in our diet which protects our body fat and lipid membranes from oxidizing. β-carotene is a free radical trap and one of nature's most important defenses against singlet oxygen. Singlet oxygen is a very reactive form of oxygen and is a mutagen and is also particularly effective at causing lipid peroxidation. It is generated by light interacting with oxygen and dyes in our bodies. β-carotene is present in carrots and in all food containing chlorophyll as it is the plant's main defense against singlet oxygen in chloroplasts. Green vegetables and β-carotene are anti-carcinogens (1,7).

c. Selenium is another important dietary anti-carcinogen (1,7). It is a component of glutathione peroxidase, an essential enzyme for the defense against oxygen radicals, which destroys lipid hydroperoxides and endogenous hydrogen peroxide, thus helping to prevent lipid peroxidation (16).

d. Glutathione is present in food and one of the major anti-oxidants and anti-mutagens in the soluble portion of every living cell. The level of glutathione may be influenced by dietary sulfur amino acids. Glutathione, itself has been shown to be an effective anti-carcinogen when fed (18).

e. Dietary Ascorbic acid (vit C) is also important as an anti-oxidant. It has been shown to be effective as an anti-carcinogen in destroying nitrite see [(1d)]. It was recently hypothesized that ascorbic acid has been partially, but not completely, replaced in humans by uric acid during primate evolution (13).

f. Uric acid is a strong anti-oxidant present in high concentrations in the blood of humans but not rats and mice (13). It is also present in high concentrations in human saliva (13). It has been proposed (13) that it was one of the chemical inventions enabling the marked increase in life span during primate evolution. The ability to synthesize ascorbic acid was lost at about the same time in primate evolution as we gained uric acid. The level of uric acid in the blood can be increased by dietary purines, but too much causes gout.

It is likely that geographic differences in cancer rates are as much due to the absence of anti-carcinogens in the diet as to the presence of environmental mutagens, promoters, and other carcinogens.

Diet, Nutrition and Cancer Treatment

To date, the influence of the nutritional status of the patient on the outcome of treatment of malignancies has received relatively little attention. There is reason to believe, and widespread acceptance of, the likelihood that the effect of nutritional status upon specific and general physiological factors related to resistance will prove of major importance.

There is expectation that dietary interventions can be used to improve the patient's ability in general and specific ways to restrain tumor growth and to recover from the toxic side effects of radiation and of chemotherapy.

A common feature of advanced malignancy is a general loss of strength, body mass and other signs of compromised physiologic function. For many years clinical investigators and oncologists have encouraged measures that would restore physiologic function and improve the nutritional status of the patient in the hope that he/she would be generally "stronger" to fight the dual insults of the tumor and of the therapy. Total nutritional support found favor among oncologists and patients were encouraged to eat a bolstered diet to counter the general signs of debilitation. Since feeding the patients by normal procedures ran afoul of the loss of appetite, digestive, and absorptive problems, total parenteral nutrition (TPN) became, and still remains in some quarters, a direction of choice to meet the perceived nutritional needs of the patient.

The value of total parenteral nutrition to cancer patients is being seriously questioned, and has recently been reviewed and referenced by Dr. Murray F. Brennan in an article entitled, "Total Parenteral Nutrition in the Cancer Patient," in the New England Journal of Medicine, Vol. 305, pp. 375-382, 1981 (139 referenced primary articles and reviews).

Dr. Brennan presents the issues in a series of questions, "Given that TPN can save the lives of some patients with cancer who are undergoing treatment, several questions arise:

*1. Can TPN reverse the nutritional and metabolic defects accompanying malnutrition in cancer?

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*Numerals 1,2,3,4, and outline form adopted for this article without permission of author.

2. What are the practical problems in delivering all nutrients by vein to cancer patients?

3. Does TPN affect tolerance to chemotherapy, radiotherapy or surgery?

4. If so, does the effect translate into long-term survival for the cancer patient receiving TPN as adjuvant support?

To quote further from Dr. Brennan's review: "The relative degrees of nutritional injury [in humans] produced by surgery, radiation, and chemotherapy or immunotherapy have barely been examined. Isolated studies of aspects of the host's function (such as wound healing) have been performed in animals, and some attempts have been made to quantiate the effects of nutritional deficit."

The conclusion can be drawn with certainty that the questions posed by Dr. Brennan cannot be answered because of grossly inadequate attempts at clinical studies in appropriately selected patients. It appears equally clear that there has been very little attempted in animal models aimed at establishing a metabolic or physiological basis for the signs documented both for human and certain animal tumors.

Toxicity of Treatment Modalities

To discuss the kinds of efforts needed to address the possible role of diet and nutrition in the improvement of cancer treatment, some attention must be given the problem of toxicity resulting from surgery, radiotherapy and chemotherapy. From a grossly inadequate effort to survey efforts ongoing or completed in the study of toxicity in cancer patients or in tumor-bearing experimental animals, it appears that little has been reported, and the term toxicity is not generally applied to the effects of surgery or of radiation treatment. The virtue of recognizing the need

for attention to the insult in a compromised host (tumor-bearing patient or animal) lies in the possibility that the nature of insult, or the degree of exacerbation caused, may be significantly different from that of the normal host. Recovery from surgical and radiation injury in humans and in animals is a well-studied phenomenon. What of diet and nutrition and their influence upon recovery? How well investigated are these interventions in humans?

As to toxicity of agents used for chemotherapy, there is an enormous literature, concentrated, alas, almost entirely on the organ specificity and dosages of agent required to produce the tissue damage or death to the animal. Relatively little effort has been expended to investigate counteractive measures and the kinetics of blockage or reversal of stages of that damage. It is understandable that virtually no interest has been shown in exploring toxicity and its reversal in the hundreds of agents tested for anti-tumor effectiveness. It is not as clear why agents of proven efficacy in treating human malignancy have with few exceptions not been the subject of extensive anti-toxicity studies. Lacking knowledge of the molecular mechanisms of cell death does not necessarily compromise the value of studies of measures reversing or arresting toxicity in the whole animal, where a specific organ or cell type only may need to be protected. What is more, a limited number of sites of serious damage may characterize classes of anti-tumor drugs.

Compromising the Immune Mechanism

Little argument would be raised against the contention that the resistance of the host to tumor cell proliferation depends heavily upon

the immune system. It seems equally safe to assume that some patterns of malnutrition or hypoalimentation (Daly, J.M., Dudriek, S.J. and Copeland, E.M. Ann. Surg. Vol. 192, pp. 587-592, 1980) lead to anergy and can be partially corrected by dietary intervention. That being the case, the specific nutritional requirements of the immune system deserve fundamental study in experimental animals. Beyond that, the effects of treatment upon immune function of tumors in animals and in patients should be investigated with a veiw to reversing specifically, if possible, toxicity to that system. Clearly, one of the specific targets of interest in the diet and nutrition initiative should be the immune system.

Not to be ignored is the constant threat of infectious agents for the patient whose immune system is compromised by therapeutic measures. Among the potential threats to physiologic insult are the flora of the intestinal tract altered by loss of immune regulatory activity and the effects of especially chemotherapeutic agents and altered dietary intake on the balance of the flora.

Nutrition: General or Specific?

From the wealth of data accrued during decades of nutrition research, there is conclusive evidence from inadequate intake and overdosage of certain nutrients, particularly vitamins, that certain tissues such as epithelial lining tissues or certain organ systems, such as the central nervous system or bone, are far more sensitive to specific deviations in nutrients than the body generally. It is not too far fetched to propose that specific tumors may respond selectively to certain nutrients. Perhaps certain classes of tumors may have common requirements or "hypersensitivities" to nutrients, as well as to hormones such as estrogen. Given the variety of reagents now available as analogues and competitors, such studies seem warranted in animal model systems with full

recognition that they may not represent directly any human neoplasm.

The notion that nutrition is specific diseases means balance of nutrients required for optimal growth of children or maintenance of a healthy adult is a starting point in nutritional studies but should give way to explorations of imbalance as well.

Why Diet and Nutrition for the Advanced Patient Only

Give the need to identify as early as possible the nutritional deficit and/or endocrinologic dysfunction of cancer patients, should not the focus of studies in diet and nutrition include the patient immediately upon diagnosis?

Efforts to correct or reverse secondary and tertiary effects of long-term nutritional debilitation may pose problems not recognized at the current level of understanding of mechanisms. How soon does liver dysfunction lead to major distortion of the sensitive role of other organs or tissues? What kinds of feedback are operative in these complex loops?

Animal experimentation should be used to assess the efficacy of early intervention and to attempt more probing metabolic questions.

Where To Specific Nutritional Intervention and Treatment?

Anti-metabolites such as anti-folic acid compounds, puring and pyrimidine analogues depend for their effectiveness and effective dose levels upon the specific metabolism of the single patient. In the case of anti-folics, the folic metabolism of the patient should ideally be assessed in the several parameters of that metabolism before treatment, with say, methotrexate is initiated. The metabolic status of the patient may or may not be meaningfully determined at our present level of knowledge, but sufficient understanding of its metabolism should be an objective of therapists. The first and dramatic case of nutritional intervention as an integral part of the treatment protocol is "citrovorum

factor rescue" from the life-threatening toxicity of high doses of folic acid analogues.

Antioxidant countermeasures may prove of value where treatment involves the generation of free radicals, or peroxides by direct radiation or chemical action, or as a consequence of a biochemical event induced in the tissues by a treatment reagent. Thus, vitamins C and E, as well as vitamin A, β-carotene and related compounds may prove of importance to the effectiveness of certain cancer therapy measures.

2. FUNDING AND MANAGEMENT OF NUTRITION AND CANCER RESEARCH BY THE NATIONAL CANCER INSTITUTE.

Diet nutrition and cancer research projects are an integral part of N.C.I. divisional programs. The division staff do not distinguish them from other intramural or extramural projects. They are managed in the same way as any other intramural research activity, or any other grant or contract-supported extramural research project. Investigator-initiated grant proposals in the subject of nutrition and cancer are reviewed and assigned priority scores within regular D.R.G. channels and study section procedures. Funds are allocated to approved grants with "high" priority scores from divisional budgets, in competition with all other grant proposals related to the division's programs.

Nutrition and Cancer Research does however have one distinguishing organizational feature. It is co-ordinated across N.C.I. divisions by a program co-ordinator who works out of the office of the Director of the Institute. The management of Nutrition and Cancer Research is summarized in Exhibit 1.

Existing Research

The Sub-committee held three meetings in 1981 to gain an insight

into the programs, both intramural and extramural, in effect and in the planning stages. The Sub-committee focused principally upon the program of the N.C.I., but heard as well from Dr. Simopoulos, Co-ordinator for the Nutrition Committee of NIH, from Dr. Bieri conducting intramural nutrition research at NIAMDD, and from the Committee on Diet, Nutrition and Cancer of the National Research Council.

Within N.C.I. presentations were made by Dr. Sporn, Dr. Ziegler, Dr. Poirier, Dr. Morrison, Dr. Kidwell, Dr. DeWys, Dr. Diane Fink, Dr. Portel, Dr. Terry, Dr. Leuky, and Dr. Chiarodo. Dr. Murray Brennan presented his testimony in the form of a letter to Dr. Chiarodo.
Dr. Stephen Carter presented a report on DRCCA chemoprevention activities. Reports from several meetings of the Chemoprevention Workshops of DRCCA were made available to the Nutrition Sub-committee.

The Sub-committee asked itself if the current amount of research in the field is (a) sufficient, (b) of adequate quality, and (c) appropriately focused in terms of subject matter and disciplines.

The Sub-committee came easily to the firm conclusion that the current N.C.I. research emphasis in diet, nutrition and cancer is not sufficient.

It felt that an appropriately constituted and charged scientific review group should look at the quality of research work being supported. Further, it came to the strong conclusion that the state of the art of research in nutrition and cancer had to be given serious consideration. Specific nutrition and cancer grants (R01) from the extramural grants program have been reviewed twice within the past two years by the N.C.A.B. Sub-committee on Special Actions as part of its systematic review of summary sheets and program objectives with the staff of each N.C.I. program.

The findings of the Special Actions and Ad Hoc Nutrition Sub-committees were in agreement about the difference between the state of the art of

research in nutrition and cancer, and that of cancer research in other disciplines. Research in nutrition and cancer is at an evolutionary stage in its development. It needs to bring new sciences and scientists into the field and persuade them to apply their technologies to cancer research. It has to conceive and implement multidisciplinary research approaches and to prepare the way for community-based trials of cancer prevention.

The overall focus of current research was hard to evaluate by the process chosen by the Sub-committee, although it was perfectly clear that there is little or no overall direction in the intramural or extramural programs, with the exception of Epidemiology and Chemoprevention. The latter (at its present level of knowledge) was seen by the Sub-committee to be in every way a legitimate subsection of diet, nutrition and cancer research.

The intramural program as such is a paper program comprised of whatever could be considered nutrition research already under way in laboratories of N.C.I.: Dr. Sporn on vitamin A and retinoic acids; Dr. Morrison on feeding habits, weight loss and tumor growth; Dr. DeLuca on biochemical glycosylation and vitamin A; Dr. Kidwell on lipids and carcinogenesis. There are good reasons to reconsider the intramural program with a view to bringing diet and nutrition into focus with two or three distinguished young investigators.

The approach of the epidemiology group under Dr. Fraumeni seems particularly encouraging, having established a plan that includes:

1. Those studies designed to test in human populations hypotheses generated by animal experiments or by other epidemiological studies
2. Those studies that seek to explain the unusual geographic patterns

in cancer risk revealed by the U.S. Cancer Maps

3. Those studies that develop and utilize national data resources

4. Those studies that focus on migrants and their gradual changes in lifestyle and cancer patterns.

The Extramural Program of Diet and Nutrition has been subdivided into eight areas (see Program Summary for FY 81, attached, for more detailed consideration):

I. Epidemiologic studies

II. Dietary Manipulation and Tumor Inhibition

III. Fats, Proteins and Carcinogenesis

IV. Minerals and Vitamins

V. Naturally Occurring Carcinogens

VI. Inhibitors of Chemical Carcinogenesis

VII. Mutagens in Foods and Body Fluids

VIII. Miscellaneous

For fiscal 1981 a total of forty-four R01 grants ($4.772 millions), three P01 grants ($2.007 millions) and one R13 grant ($.033 millions), for a grand total of forty-eight grants for $6,812,000 are in force. No further detail could be developed for fiscal year 1981 projects at the time this report was prepared. It was however assumed that a picture of fiscal year 1980 research projects would provide the same insight into areas of research emphasis.

Exhibit 2 shows funding for nutrition-related grant research in fiscal year 1980 according to N.C.I. program and research thrust. $7.4 million were spent on grants that included some nutrition-related research activity. When these research projects were examined by cancer site and dollar amounts budgeted for their nutrition components, total budgeted expenditures dropped to $4.7 (Exhibit 3). About one quarter was spent in the context of

breast cancer, and about twenty percent each within the contexts of colon and liver cancer research.

About $7.1 was provided in contract funds to support research with a nutritional component. $4.6 were budgeted in direct support of the specific nutritional research activities. Research supported by these contracts give most support to nutritional research associated with colon, breast and stomach cancers (Exhibit 4). The majority of research contracts were let by the epidemiology program of the Division of Cause and Prevention. They were essential to organization and management of population based etiologic studies (Exhibit 5). Current interest in chemoprevention and anti-carcinogenesis would be reflected in expenditures to support research into vitamins and cancer. The same funding information is retabulated to show funding vitamin research by methods of providing funds and by vitamins of interest. Three-quarters of all the vitamin research dollars were spent on vitamin A research. Investigator-initiated research projects on vitamins qualified for about $2 million. $2.5 were spent in contractual support of vitamin research. The total amounts of money awarded by each funding mechanism were almost identical for research on food-borne carcinogens. Nitrosamine was the research focus of the greatest single largest expenditure--about one-quarter of the total.

Although there does appear to be an organ site emphasis in grant and contract expenditures in support of nutrition-related research, further analysis of the subject matter does not support this first impression. The epidemiological research has been tabulated in detail because this body of research was one holding greatest promise of providing en masse a more or less coherent research program (Exhibits 6 and 7).

The analysis shows that the subjects of inquiry are scattered over

sites, possible carcinogens and possible anti-carcinogens, and that much of the grant-supported research has the appearance of preliminary, exploratory inquiries. A more formal research plan is needed to capitalize on existing research and add to it.

The Sub-committee asked itself whether chemoprevention research within the program of D.R.C.C.A. would be "sufficient" in terms of research related at least to anti-oxidants and vitamins. Information provided by the division's ad hoc committee on chemoprevention led the committee to make an assessment that the resources available to the division at this time permit narrowly focused research which is not sufficient to serve as the major N.C.I. thrust in this area. The committee therefore includes more general research into specific vitamins and other chemopreventives within the framework of its conclusions and recommendations. A tabulation of chemoprevention trial research is included as Exhibit 8 only to illustrate the research focus. The point must be made that some of this research has terminated and much of it has not been funded by N.C.I.

In September, 1979 a postdoctoral program in Diet, Nutrition and Cancer sought candidates for individual fellowships in 1) Nutritional Biochemistry, 2) Nutritional Physiology, 3) Nutritional Microbiology, 4) Nutritional Immunology, 5) Nutritional Epidemiology, and 6) Nutritional Endocrinology.

The Sub-committee members received pink sheets following review of responses to these proposals, as well as routine proposals for nutrition and cancer training programs. The members concluded that the state of the art of nutrition research and the evolution of scientific disciplines of interest and application to this field of research were having an adverse effect on these proposals and their review, in the same way as they are affecting the preparation of nutrition and cancer research grant proposals.

3. SUBCOMMITTEE CONCLUSIONS AND RECOMMENDATIONS

Conclusions

The N.C.A.B. Ad Hoc Sub-committee on Diet, Nutrition and Cancer Research reached the following conclusions:

1. Diet and nutrition are being increasingly recognized as major factors in cancer.

2. The presence and absence of anti-carcinogens in the diet is an important new area of research.

3. The mechanisms by which diet acts as a promoting agent is also an important area for research.

4. Dietary and nutritional balance is as important a subject of research as the specific effect of dietary carcinogens and anti-carcinogens.

5. Scientists from other disciplines must be recruited into cancer research to expand the study of the mechanisms of dietary carcinogens and anti-carcinogens.

6. Chemoprevention trials are an important but limited component of nutrition research directed at cancer prevention.

7. Biochemical epidemiology will be an important research resource.

8. Attention must be given to the development of animal models in all aspects of nutrition research, e.g., to gain insight into diet and treatment research and to understand the specific nutritional requirements of the immune system.

9. There is no body of information from clinical studies carried out in representative samples of patients. The body of information assembled from clinical studies in appropriately selected patients is inadequate to answer some questions that are fundamental to further research.

10. There is need for research in nutrition and cancer which takes a much more comprehensive view of toxicity.

11. The current N.C.I. nutrition and cancer research effort is insufficient.

12. There is a need for expert review of the quality of current research in the field.

13. There is need for a definite diet, nutrition and cancer research program with its outline and goals known to the scientific community so that individual research projects and additional research needs can be designed and identified in relation to the goals of the program.

14. There must be input from all N.C.I. divisions into the goals, design and specification of the overall program.

15. There must be continued, and probably increased, coordination between intramural and extramural research activities, at least until the nutrition and cancer research effort is adequate in amount, quality and focus.

16. The state of the art of current diet, nutrition and cancer research must be considered within the review process of both research and training proposals.

17. The N.C.I. should make judicious use of its choices of operating mechanisms to recruit appropriate highly-qualified scientists from other research fields into cancer research.

18. Because the National Academy of Sciences committee will not review ongoing research, it will not be in a position to prepare a research agenda for operating purposes.

Recommendations

The N.C.A.B. Ad Hoc Sub-committee on Diet, Nutrition and Cancer Research should advise:

1. The Director of the National Cancer Insitute to earmark

additional funds specifically for diet and nutrition research related to cancer. The special allocation should be provided for only a limited time, with careful review of the ongoing amount, quality and focus of diet and cancer research before it is renewed for any additional period of time. The specific recommendation is therefore for a time limited budgetary allocation to implement and stablize an N.C.I.-wide research thrust in diet, nutrition and cancer. This allocation should be in addition to, and not instead of, funds now spent on nutrition and cancer research within intra- and extramural divisional programs.

2. The Director of the National Cancer Institute should establish a time limited special administrative arrangement to plan and implement an N.C.I.-wide research program and recruit new scientific investigation into this field of research. This arrangement should be administered within the N.C.I. and should be interdivisional. The Sub-committee believes that it is necessary to have a special administrative arrangement to: plan a comprehensive interdisciplinary research plan; prepare a research agenda; inform the scientific community of the plan and the agenda; provide sheltered peer review until the state of the art of nutrition research stablizes and the necessary new sciences have become familiar with the cancer field. This review must be arranged to be consonant with the research agenda, but free from any opportunities for conflict of interest among scientists.

The Sub-committee is proposing a "Nutrition-Cancer Task Force" to the N.C.A.B. and to the Director of the Institute as one way of addressing its recommendations. The recommended Nutrition-Cancer Task Force would include at least the following elements:

A. Composition

1) The Task Force would be composed of members from various disciplines judged to be essential to the nutrition-cancer area.

2) There should be a representative from each of the four Boards of Scientific Counselors to provide liaison with the divisional programs.

3) There should be a representative from the National Academy of Sciences group which is now preparing the N.C.I.-sponsored nutrition-cancer report. Since the final report is not due until 1983, it would be important for each group to know of the other's activities and plans.

4) N.C.I. staff would consist of an Executive Secretary from the Division of Extramural Affairs, and a liaison person such as the Coordinator, Diet and Nutrition Cancer Program.

5) The Task Force would also be divided into various sub-committees as needed to focus on more specialized areas such as training, research areas, and clinical problems.

B. Functions

1) Planning - The Task Force should produce comprehensive documentation and set priorities for a National Agenda on nutrition and cancer. The Agenda should specify the major goals and problems in the nutrition-cancer area, and critically define the research and manpower needs. The Task Force should also address how it plans to target, recruit, and utilize the following potential populations of scientists: those currently active and funded for nutrition and cancer research; those in the nutrition area but not working on cancer problems, and the converse group; scientists who have not yet specialized and scientists seeking a mid-career change.

The Task Force should identify critical research areas that need to be urgently explored. The Task Force would then formally solicit grant applications targeted at these research problems.

The Task Force should consider whether it wants to exercise a screening function prior to review to determine if an application is appropriately addressing the identified targeted goals of the program or is an obvious deviation of already supported nutrition-cancer research. This screening function could have several advantages: the review process and use of funds would be more efficient; a more rapid feedback could be provided for desirable applications which need to be strengthened; and the Task Force could monitor the effectiveness of its methods and quickly identify needed modifications.

2) Review - The Task Force would review new applications using the same criteria as regular study sections with the added element of program relevance and need.

N.C.A.B. concurrence would be obtained as usual.

Successful applications would be managed and administered by the appropriate program officials from the operating N.C.I. divisions.

C. Limitations

1) The Task Force would have a limited lifespan of two to four years (to be determined in advance). Upo to one year would be devoted to planning, with subsequent years devoted to review.

2) Task Force members would not submit applications in direct response to this committee's solicitations. They could continue to seek support through the previously available NIH mechanisms.

3) The Task Force would not review any Type 2 renewal applications. All such applications would go through the regular NIH review mechanisms.

In summary, it is the view of the Nutrition Sub-committee that the N.C.I. should define and focus an extramural program in diet, nutrition and cancer with objectives that offer new approaches to nutrition and its physiologic implications for human disease. The redefinition should be formulated by a workshop and planning committee approach with significant input from scientists from a number of disciplines not now designated as nutrition oriented. The program when conceived will require new leadership, hopefully with strong biochemical competence.

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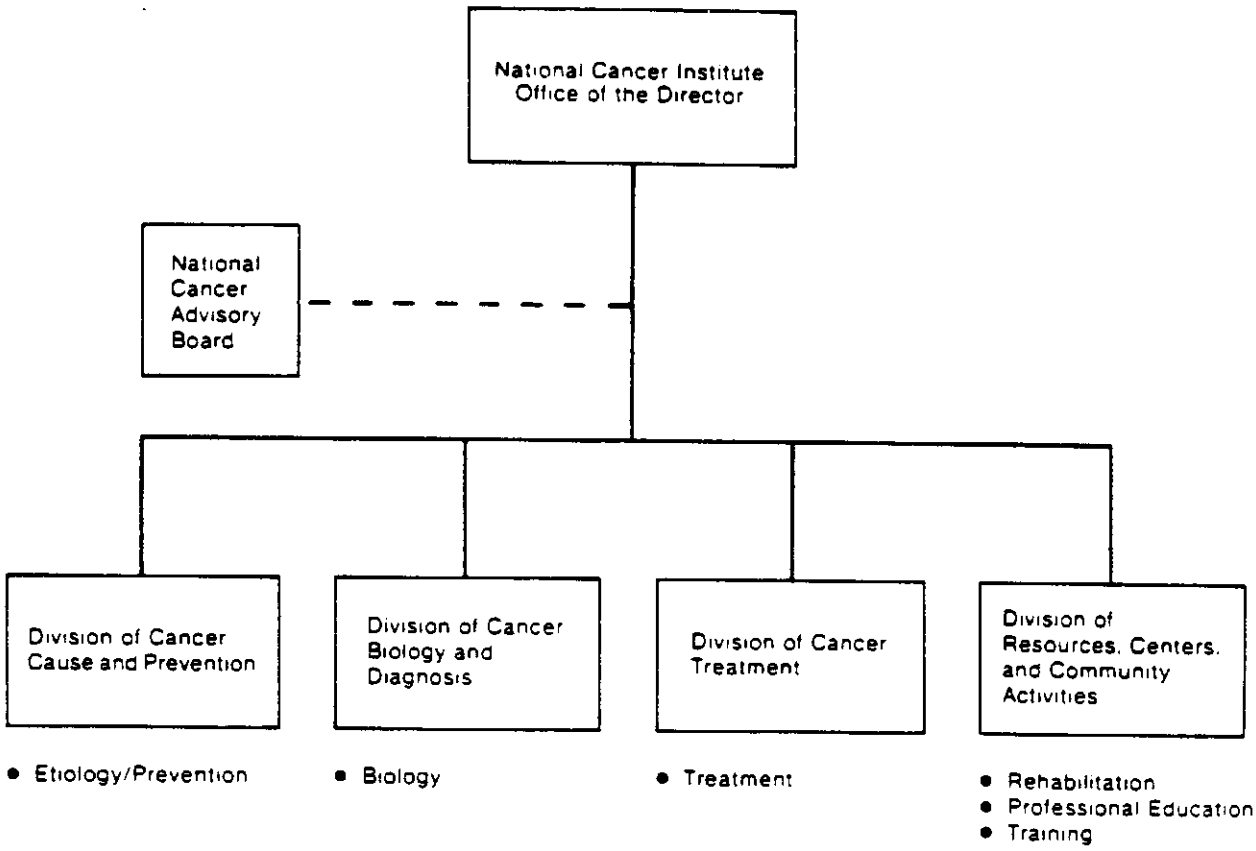
Exhibit 1
National Cancer Institute
Framework of Nutrition Research



FUNDING FOR NUTRITION-RELATED GRANT RESEARCH, FY 1980 BY NCI PROGRAM AND THRUST*

NCI PROGRAM	RESEARCH THRUST: CAUSE AND PREVENTION	DETECTION & DIAGNOSIS	TREATMENT RESEARCH	CANCER BIOLOGY	TOTAL BY PROGRAM
CHEMICAL AND PHYSICAL CARCINOGENESIS	$3,767,844	$ --	$ --	$ --	$3,767,844
CLINICAL TREATMENT	--	--	815,119	--	815,119
EPIDEMIOLOGY	900,832	--	--	--	900,832
IMMUNOLOGY	--	46,469	116,618	--	163,087
NUTRITION	5,058,501		1,103,456	1,205,148	7,367,105
PRECLINICAL TREATMENT	--	--	383,347	--	383,347
REHABILITATION RESEARCH	--	--	348,613	--	348,613
TUMOR BIOLOGY	--	--	--	789,620	789,620
VIRAL ONCOLOGY	5,166	--	--	--	5,166
SUBTOTAL	9,732,343	46,469	2,767,153	1,994,768	14,540,733
CANCER CENTERS (P30)					1,703,428
CANCER CONTROL (R18)					442,601
TRAINING AND EDUCATION GRANTS (K04, K06, K07, T32, F32, R25)					477,810
TOTAL NUTRITION GRANT FUNDING					$17,164,572

*Program and thrust designations are given to grants within the following NIH mechanism categories: R01, R10, R12, R26, and P01. Some, but not all R18 grants have program and thrust designations.

EXHIBIT 3

GRANTS
(R01's)

Organ Site	Total FY 80 Funding	Nutrition Funding
Breast	$1,415,844	$1,244,719
Bladder	222,291	175,071
Brain	102,926	10,293
Colon	1,108,016	861,035
Esophagus	94,781	94,781
Gastrointestinal	276,569	235,979
Kidney	50,703	46,188
Liver	1,022,105	813,470
Lung	548,631	438,212
Pancreas	286,227	286,227
Prostate	82,778	12,416
Skin	356,048	64,425
Thyroid	124,946	6,247
Oral	93,876	93,876
Uterine	103,116	103,116
Various	167,657	167,657
TOTAL	$6,056,514	$4,653,712

EXHIBIT 4

CONTRACTS
(NO1's)

Organ Site	Total FY 80 Funding	Nutrition Funding
Bladder	$1,316,122	442,855
Breast	1,166.059	908,418
Colon	1,302,698	1,035,355
Gastrointestinal	624,132	243,039
Pancreas	275,215	33,672
Skin	466,697	466,697
Stomach	837,147	787,947
Lung	824,930	521,446
Liver	109,040	109,040
Esophagus	98,390	24,598
Testicle	5,500	5,500
Various	50,692	12,693
TOTAL	$7,076,622	$4,591,260

EXHIBIT 5

Contracts for FY '80 by Divisions

	Total funding	Nutrition #
Division of Cancer Biology & Diagnosis	537,566	465,880
Division of Cancer Treatment	1,139,247	679,487
DRCCA	214,808	2,148
Office of the Director	32,393,884	356,356
Division of Cancer Cause & Prevention	10,736,624	6,434,863
Total	45,022,129	7,938,734

Vitamin Research for FY '80

a) by mechanism

No 1	2,490,750	2,490,750
Po 1	1,293,601	1,156,374
Ro 1	2,208,336	1,635,077
R 26	69,617	20,885
Yo 1	162,030	162,030
Zo 1	76,500	25,875
	6,300,834	5,490,991

b) by vitamin

retinoids, Vit. A & Carotine	4,304,085	4,053,853
Solate & B_{12}	355,879	275,017
B_6	192,459	192,459
Ascorbic Acid	145,534	145,534
Vit. E & Selenium	224,440	191,496
Miscellaneous	1,078,437	632,632
	6,300,834	5,490,991

EXHIBIT 5
(continued)

Food borne carcinogens		
a) by mechanism		
No 1	37,708,274	2,499,287
Po 1	1,536,899	618,608
Ro 1	2,057,676	1,104,536
R 26	182,851	111,196
	41,485,700	4,333,627
b) by carcinogen		
Nitrosamines	3,948,567	1,120,069
Aflatoxin B1	561,274	342,242
Alcohol	89,237	66,314
Miscellaneous (including saccharine)	36,886,622	2,805,002
	41,485,700	4,333,627

EXHIBIT 6

CONTRACT SUPPORTED EPIDEMIOLOGICAL RESEARCH IN NUTRITION AND CANCER, FY 1980.

	SITE	AGENT
(E)	Bladder	Saccharin, Coffee, Source of drinking water
(I)	All Sites (Columbia)	
(E)	Stomach	Nitrate, Nitrite, Vits A, C, E
(D)	All Sites (Utah)	All diet
(D)	Colon (Louisiana & S. America)	Polyps, Atherosclerosis, Fecal mutagens
(E)	Stomach, Large Bowel (Japan Hawaii Migrants)	Salted and Dried Foods, meats, and legumes
(E)	Breast	Lipids
(E)	Lung, Pancreas, Stomach	Food, Source of drinking water, calories
(E)	All Sites (Alaska)	Dietary Carcinogens
(E)	Bladder	Trihalomethane in drinking water
(E)	Colon, Stomach (China)	Diet
(E)	Colon	Diet, Genetic/familial factors, occupation
(E)	Colon, rectum, breast, esophagus, lung	Fat, meat, food group, Vits. A, C, food additives, ethnic foods, cooking
(E)	Oesophagus, breast, bladder	Food, beverages, coffee, sweeteners, bracken fern, sources of drinking water
(E)	Liver	Alcohol

(E) = Etiology

(I) = Incidence

(D) = Description

GRANT SUPPORTED EPIDEMIOLOGICAL RESEARCH IN NUTRITION AND CANCER, FY 1980

	Site	Agent
(E)	Oesophagus	Diet, Alcohol
(I)	Major Sites	Diet
(E)	Lung	Vit. A.
(E)	Melanoma	Diet
(Pr)	All Sites	Diet
(P)	Lung	Vit. A.
(E)	Breast, Large Bowel	Fat, Protein Fiber, Vit. A, Trans Fatty Acids
(Ex)	Lung	Mutagens in urine
(E)	Colon	Fecal Cholesterol Products
(E)	Breast	Diet
(E)	Colon	Metabolites of dietary components and intestinal microflora
(E)	Pancreas	Diet, Alcohol
(E)	Lower Urinary Tract	Coffee, Sweeteners, Analgesics, Bracken Fern
(E)	Bladder	Coffee, Sweeteners, Analgesics
(D)	Large Bowel	Beef, Fat, Fiber, Beer
(E)	Lower Urinary Tract	Coffee, Sweeteners, Mutagens in urine
(E)	Colon	S. Bovis x standard, or vegetarian diet
(E)	Bladder (Utah)	Coffee
(E)	Prostate	Fat trace elements, Vit. A.
(E)	Bladder, Pancreas	Coffee, Sweeteners, Alcohol
(P)	Breast	Fat related hormones
(E)	Buccal Cavity, Larynx, Oesophagus, Stomach	Diet, Alcohol
(E,P)	Breast	Dietary Carcinogens

(E) = Etiology; (Ex) = Exposure; (I) = Incidence; (D) = Description; (P) = Pathogenesis
(Pr)= Prediction.

CHEMOPREVENTION TRIALS

Population	Number	Design	Intervention	End Point
Healthy U.S. Males, 50-75	21,900	Double Blind Randomized Placebo Trial (2x2)	325mg Aspirin, 30mg Beta Carotene	Cardiovascular mortality; Cancer Incidence
Albino Children (Tanzania)	50	Phase I: All participate	Canthoxanthen	Skin Cancer
Patients with Cervical Dysplasia (Mild or mod.)	50	Double Blind Randomized Phase I: Bioassay	Topical Retinyl Acetate Gel	Cytology, Pathology, Blood Levels
Patients with Colon Polyps Removed	200	Double Blind Randomized Placebo Trials	100mg Ascorbic Acid, 100mg dl-a-tocopherol	Polyp Recurrence
Patients 40+ with Oral Leukoplakia	24	Phase I-II: Bioassay	13 Cis-Retinoic Acid	Complete Remission
Post-Colectomy Patients with Active Polyp formation	60	Double Blind Randomized Placebo trials	Ascorbic Acid 4mg Daily, Alpha Tocopherol 400mg Daily	Decrease in Number and Area of Polyps
Adult Patients with preleukemia	21	Phase I: Bioassay	13-cis-Retinoic Acid	Hematological Response
Patients with Mammary Dysplasia	100	Double Blind Randomized Bioassay	dl-a-tocopherol	Comparisons of before and after examinations
Treated Patients free from Bladder Cancer	64	All Patients, 2 doses	13-cis-Retinoic Acid	Rate of Non-recurrence
Patients with Cervical Dysplasia (Mild and Mod.)	36+	Development of topical applicator and dose	B-trans-Retinoic Acid	Permanent suppression of pre-neoplasia

EXHIBIT 8

CHEMOPREVENTION TRIALS CONT.

Population	Number	Design	Intervention	End Point
Post-Colectomy Patients with active Polyp formation	60	Double Blind Randomized Placebo Trial	Ascorbic Acid 4mg daily, Alpha Tocopherol 400mg	Decrease in number and area of polyps
Adult Patients with pre-leukemia	21	Phase I: Bioassay	13-cis-Retinoic Acid	Hematological Response
Patients with Mammary Dysplasia	100	Double Blind Randomized Bioassay	dl-a-Tocopherol	Comparisons of before and after examinations
Treated Patients free from bladder cancer	64	All Patients, 2 doses	13-cis-Retinoic Acid	Rate of non-recurrence
Patients with Cervical Dysplasia (Mild or Moderate)	36+	Development of topical applicator and dose	b-trans Retinoic Acid	Permanent suppression of pre-neoplasia

EXHIBIT 8 - Continued