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NCAB Approves Characteristics For Recognition As Comprehensive; Outlook Dim For New Division

The National Cancer Advisory Board approved seven characteristics for comprehensive cancer centers at its meeting this week, endorsing the recommendations of its Committee on

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In Brief

"WSJ" Articles Call Attention To Problems With Cancer Program; Knipmeyer To Leave NCI

MAJOR PROBLEMS faced by the National Cancer Program--NCI's severe budget situation and the increasing refusal of insurers to reimburse for cancer therapy--were described in two "Wall Street Journal" articles May 11. **Robert Young**, president of Fox Chase Cancer Center and president elect of the American Society of Clinical Oncology, wrote that the government is "dismantling the National Cancer Program" with the budget restrictions. **Lee Mortenson**, executive director of the Assn. of Community Cancer Centers, concluded that "with the wrong kind of reimbursement policies, we have the opportunity to stop research, slow innovation and even move backward". . . . **SYDNEY SALMON**, director of the Arizona Cancer Center, has been named a Regents' Professor, the highest honor the Univ. of Arizona can give a member of its faculty. . . . **HONORARY DEGREES**: Doctor of Laws to American Cancer Society President **Harold Freeman** May 28 from Niagra Univ.; Doctor of Humanities to ACS Group VP/Chief Medical Officer **Gerald Murphy** June 4 from Seattle Univ. . . . **MARY KNIPMEYER**, NCI's legislative liaison, is leaving June 18 to become director of the Div. of Legislative Policy for the Alcohol, Drug Abuse & Mental Health Administration. NCI is recruiting for Knipmeyer's replacement. Contact Iris Schneider, 301/496-5534. . . . **NEW STAFF** members in the Smoking, Tobacco & Cancer Branch: Jessie Gruman, former national director for adult education at the American Cancer Society, and Joanne Odenkirchen and Jim Colborn, both from NCI's Health Promotion Science Branch, are public health advisers; Jing Jie Yu, head of the People's Republic of China smoking prevention program, is a visiting scientist. . . . **CANCER PREVENTION** Fellowship Program, in NCI's Div. of Cancer Prevention & Control, is accepting applications for up to three years of training for 10 Fellows. Contact Douglas Weed, Cancer Prevention Fellowship Program, DCPC, NCI, Executive Plaza South T-41, Bethesda, MD 20892. Deadline for applications is Sept. 8; training begins July 1, 1990.

NCAB Approves Seven Characteristics For Comprehensive Cancer Centers

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Centers. The new characteristics will serve as principles for NCI in writing detailed guidelines for peer review of the application for comprehensive status.

The key feature of the characteristics are that recognition as an "NCI designated" comprehensive cancer center will be determined through peer review at the time the center's core grant application is being reviewed.

Centers would apply for comprehensive core grant support and would be reviewed by criteria specifically for comprehensive centers, according to the committee's report to the board.

The board's unanimous approval of the new characteristics essentially completes a process that began more than a year ago, when the Univ. of Arizona Cancer Center requested consideration for comprehensive status, a process that had not been used for 10 years. That request set off a controversy over what a comprehensive center should be and what process would be used to make that designation.

The previous system for recognition of a center as comprehensive was a less formal review by an NCAB committee, independent of core grant review.

In presenting the characteristics to the board, John Durant, chairman of the centers committee, noted the $1.2 million decrease in the President's fiscal 1989 budget for centers core grants.

"In times of financial stress, there is an inevitable urge to centralize and consolidate programs in order to improve their efficiency," Durant said. "A corollary of that urge is that this improvement of focus also tends to centralize power, and the price of increased efficiency may be diminished diversity.

"In that light, we need to remember that the heterogeneous nature of the centers is one of their enormous assets."

The centers program's budget for core grants, if measured in 1988 dollars, has dwindled from a high of nearly $120 million in 1978 to $96 million in 1989. The bypass budget for fiscal 1989 recommended $130 million for core grant support.

Core grants are not the only form of NCI support for centers, Durant said. About half of the average centers' budget comes from RO1 and PO1 grants.

In addition, Durant pointed out that of 64 cancer centers that got NCI core grants in 1977, a little more than half, 36, have been funded continuously through 1988. Twenty eight centers lost core grants and 25 centers won core grants over 11 years. "These data show that the core grant is not an entitlement program, and you can gain access as a new institution," he said.

The committee also recommended that NCI create a new division for the Cancer Centers Program, which would include the Research Facilities and Cancer Training Branches of the Div. of Cancer Prevention & Control, and possibly other units of NCI whose activities cut across the various divisions.

However, Durant said NCI Director Samuel Broder had suggested that the ceiling on the number of full time employees that NCI can hire probably would be a problem. It would also require approval by the Dept. of Health & Human Services.

"If staff can't be hired to implement such a recommendation, then it can't be done," Durant told the board.

The full board did not discuss the issue of the location of the centers program. Broder has said he is currently reviewing the organization of all of NCI, including the centers program.

The recent Institute of Medicine report on the centers, "A Stronger Cancer Centers Program," had recommended that the NCI director reprogram up to $6 million in funds for the current fiscal year, 1988, to try to fund as many centers as possible.

The centers committee recommended that funding not drop below 85 percent of levels recommended by peer review, and took the position that "reprogramming is not the

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answer," Durant said.

"We recognized that the centers grant controversy is a fuss about a greater issue, that the centers are only one important piece of scientific infrastructure," Durant said. "The centers program is important, but you don't accomplish anything by taking money out of one pocket and moving it to another. I call that alchemy."

Durant likened the core grant to the "core of a much bigger apple," which includes RO1 and PO1 grants and other support that centers receive. "We risk taking a bite out of the apple if we make the core bigger," he said.

According to the committee's report, "a comprehensive cancer center should be a major national source of the best new ideas in laboratory, clinical and cancer prevention and control research."

The seven "essential characteristics" of a comprehensive cancer center approved by the board are:

1. Basic laboratory research.
2. Basic/clinical research linkage (technology transfer).
3. Clinical research.
4. High priority clinical trial research.
5. Cancer prevention and control research.
6. Education, training and providing updates on current technology.
7. Information services.

(For the full text of the committee's recommendations, see **The Cancer Letter**, May 12).

Excellence in all seven areas would be required for a center to be awarded a comprehensive designation. The designation would allow a center to call itself an "NCI designated" comprehensive cancer center. Board member Helene Brown suggested that the centers be given the right to use the NCI logo on its stationery and brochures.

Board member Erwin Bettinghaus said he hoped NCI could avoid the problem it faces with a number of centers which operate information services but do not receive funds through NCI's Cancer Information Service program. Limited funds have precluded funding all the qualified services, although they do receive publications and other noncash assistance from CIS. Durant responded that the information requirement does not specify that the center have a funded CIS.

New guidelines for applicants and reviewers will be written by staff and submitted to the NCAB for approval, possibly by the next meeting in September.

Directory Of Frequently Called NCI Numbers, 1989 Edition, Enclosed

The directory of frequently called numbers at the National Cancer Institute, provided as a service to subscribers of **The Cancer Letter**, is enclosed with this issue.

The 1989 edition is in loose leaf format which may be kept in a three ring binder or with clasps. That will permit single page updates, which **The Cancer Letter** will provide as extensive changes occur among NCI staff members and their locations. Less extensive changes will be published in regular editions of the newsletter and may be noted in the directory by hand.

The long awaited moves of NCI offices from other locations to the Executive Plaza building in Rockville, MD, have almost been completed. Anticipation of those moves was one of the reasons for delaying publication of the new edition. A series of major reorganizations of the institute was another. Only a few offices of the Div. of Extramural Activities remain in the Westwood Building, and those should be relocated before the end of this year. When those moves have been completed, new pages with those locations will be sent out.

NCI Director Samuel Broder has indicated he is considering various reorganization options. When those occur, the realignments will be incorporated in revisions.

The directory was published with the assistance of a grant from Bristol-Myers Oncology Division.

Cullen Credits Staff With Success, Cites "Strong" Prevention Program

NCI's work in cancer prevention and control "has never been stronger," Joseph Cullen, deputy director of the Div. of Cancer Prevention & Control, said in a recent "farewell speech."

Cullen, who is leaving NCI to become director of the AMC Cancer Center in Denver, gave the division's Board of Scientific Counselors an update on the Smoking, Tobacco & Cancer Program, and his general thoughts about the division as he prepares to leave.

"I think some people get the impression that things are falling apart (when top NCI employees decide to leave)," Cullen said. "They are hardly falling apart; they've never been stronger in my mind.

"About the cancer centers: I think (the current controversy) is a real upbeat thing,

even though we make it sound like we have problems. I think the revisiting and the revitalization of what centers mean in the U.S. is critical to cancer control and it is going to end up with a much more positive image of control in the near future."

Cullen gave his staff credit for the work that has made the smoking program a success. "Even though in a recent **Cancer Letter** (April 14) some statements were made about how on my watch all these wonderful things happened, I had nothing to do with any one of them," Cullen said. "The only thing I can take credit for is having hired first class staff."

NCI Director Samuel Broder told the board, "One of the first people I spoke to after I was appointed director was Joe Cullen. His enthusiasm for the smoking control effort was infectious. The programs on smoking are some of the most effective ever developed.

"This leaves no doubt that Denver will soon have a first rate prevention program with a major emphasis on smoking reduction," Broder continued. "We're very happy about this professional opportunity and the implications that will have in Colorado. But we're sad nevertheless that we're losing his contributions to our program."

Cullen noted three areas of prevention where he thought significant progress had been made recently: nutrition and cancer research, under the direction of Daniel Nixon, who also has announced his departure; research on cancer in minorities, through the work of Claudia Baquet; and the increased involvement of medical organizations and state health departments working with NCI on cancer control.

"Those organizations are now implementing things that should have been done 20 years ago. This is an immense movement forward."

As for the Assist and Commit programs, Cullen said communities participating in the programs have formed boards and now are developing local smoking control plans.

"The response from communities is better than anyone had anticipated," Cullen said. A presentation on the programs will be made at the next DCPC board meeting.

RFPs for four centers for Assist will be released soon, and will be funded in January, Cullen said.

STCP and a committee of the American Society for Clinical Oncology have written a document titled, "Guide to the Development of Comprehensive Statewide Tobacco Prevention and Control Plans" that gives states guidelines on carrying out smoking programs.

NCI and ACS are sending out 100,000 "Quit for Good" smoking kits to physicians on how to help patients stop smoking.

"This is beginning to blossom, physicians are coming forth through their organizations," Cullen said.

The American Dental Assn. and the National Institute of Dental Research are working with NCI to apply the same program to dentists. A contractor is developing a manual listing all of the health consequences of tobacco use, which is intended to be used by dentists.

Cullen thanked the board for supporting the smoking program and for approving every concept he had ever personally presented.

"Finally, I want to say something about my friend (DCPC Director) Peter Greenwald," Cullen said. "It's a privilege to work with the one person in the world who knows more about this than anyone else.

"I think all I see myself doing in leaving here and going to Colorado is extending the reach of Peter Greenwald further into the nation and metastasizing, in a sense. I think we could all leave and if Greenwald were still here we would still have a strong program."

DCPC Board Approves $28.5 Million Concept For Seven Year Polyp Trial

Will a low fat, high fiber, vegetable and fruit enriched diet decrease the recurrence rate of large bowel adenomatous polyps? If it does, will that have an impact on large bowel carcinogenesis?

The Board of Scientific Counselors of NCI's Div. of Cancer Prevention & Control has agreed to commit $28.5 million over seven years in a multicenter randomized controlled trial to find the answer to those questions. The board gave concept approval to the trial, scheduled to start in the 1990 fiscal year.

DCPC expects to award contracts to 12 clinical centers to recruit and follow 2,000 trial participants and another contract for a free standing data and nutrition coordinating center.

The board also approved concepts for five additional projects initiated by the Diet & Cancer Branch, at an estimated total cost over five years of $20.5 million. These would be supported through master agreements contracts for three of the projects, a contract for a fourth and an interagency agreement with FDA for the fifth.

The board tabled a sixth project for an

interagency agreement with the National Institute of Standards & Technology to develop biotechniques applications for nutritional intervention studies.

Summaries of the concept descriptions and board discussion follow:

Dietary Intervention study of the recurrence of large bowel adenomatous polyps. Thirteen contracts, seven years, total estimated cost $28.5 million.

Study participants will be randomized into either an experimental diet group for a control group (usual diet). Recruitment will take up to two years, and the followup time from randomization is four years.

Potentially eligible participants will be first identified when they are found on colonoscopy to have one or more polyps. After baseline polypectomy, subjects meeting initial age, weight and medical eligibility criteria will be invited to participate. Subsequent eligibility screening will involve dietary assessment (subjects, for example, with less than a certain minimum percentage of calories from fat would not be eligible) and pathologtic review of the resected lesion(s) (subjects with cancer or only hyperplastic polyps would be ineligible). Potential participants who remain eligible will then be enrolled in a run in phase comparising the completion of dietary records. Those who successfully complete the run in phase will be randomized into the study. It is expected that it could take up to two years to recruit the required number of subjects for this trial.

The dietary intervention group will be provided a nutrition education and counseling approach aimed at providing skills necessary to make a permanent lifestyle change to a low fat, high fiber, vegetable and fruit enriched eating plan. The target goal is 25% calories from fat, 35 grams of dietary fiber daily, and seven medium servings of vegetable and fruits daily. The general strategy will incorporate teaching nutrition skills, self monitoring techniques, behavior modification techniques, and social support systems. Common protocols, data forms, educational materials, and participants manual will be developed and training workshops for nutritionists will be conducted to establish uniformity in methods and procedures for the intervention group.

The major approach to dietary intervention will be a step by step approach to dietary change based on the needs and abilities of the individual participant. A low fat, high fiber, vegetable and fruit enriched eating plan will be developed based on information obtained from a food frequency questionnaire collected at baseline.

The intervention will begin with six weekly individual sessions (phase 1), followed by three biweekly sessions (phase 2\0, and then nine monthly sessions (phase 3). Phase 4 (maintenance) will then follow with yearly meetings. It may be possible in later phases to incorporate group counseling. Self monitoring tools (for example, a fat and fiber counter) will be used as educational and monitoring aids. These self monitoring tools will help the participant learn (1) the fat and fiber content of typical foods; (2) how to balance the fat, fiber and vegetable and fruit content of typical foods; (3) to record progress. Phases 1 and 2 rely on transfer of information, setting short term goals, collecting recipes and meal plans that fit into the low fat/high fiber/vegetable enriched eating style. Phase 3 emphasizes behavioral strategies associated with lifestyle change, such as coping skills, identifying problem areas and developing solutions, self direction, social support and dealing with compliance in challenging situations. This phase encourages the participants to accept responsibility for their lifestyle changes.

Previous intervention studies have provided indirect evidence that the experimental diet can be successfully adopted. The Women's Health Trial has shown that free living women can reduce their fat intake from nearly 40% of calories derived from fat to less than 25%. A subgroup of men participating in a large coronary risk factor intervention study (the Oslo study) reduced their fat intake from 44% to 28% of total calories after intensive dietary counseling. A similar subgroup of men from the Multiple Risk Factor Intervention Trial reduced their fat intake from approximately 40% to 25% of calories. NCI's previous controlled feeding studies at the U.S. Dept. of Agriculture have shown that men could readily tolerate a diet (20% calories from fat and over 40 grams of dietary fiber daily), more extreme than the proposed intervention diet.

The control group will not be offered a nutrition intervention program since the general strategy adopted for this group will be minimum interference with customary diets while collecting nutritional data considered necessary for appropriate comparison with the nutrition intervention group. If needed, control group subjects will be provided counseling and educational materials on basic nutrition principles for maintaining nutritionally adequate diets with no emphasis placed on modification of fat, fiber, or vegetable intake. Subjects in the control group are expected to maintain their usual diet (approximately 38-40% of calories from fat, nine to 15 grams of fiber per day, and three and a half servings of vegetables and fruit daily.

Food frequency questionnaires and/or four day diet records will be administered periodically to assess dietary intake. In addition, unannounced 24 hour recalls will be administered by phone. It is anticipated that each center will have two research dietitians participating in the study, so that different dietitians will be involved in the counseling and assessment aspects of the dietary intervention. Blood specimens will be collected, since it is likely that serum cholesterol and serum beta carotene, for example, will be altered on the experimental diet.

After the baseline colonoscopy and polypectomy, participants will have a repeat colonoscopy one year later and three years after that. All resected lesions will be sent for pathology review.

Although the primary endpoint of this study is recurrence of any polyps, possible endpoints also include the number, size and histotype of recurrent polyps. Although data on polyp recurrent will be available from baseline onward, the principal analysis will be from repeat colonscopy at one and four years. The reason for this is that it is expected that some polyps will be missed at the first (baseline) procedure; it is reasonably certain that the bowel is clean after the first repeat colonoscopy. In addition, such a design allows for a possible one year lag in the effect of the intervention.

A reduction in recurrence rate of 20-25% is realistic in view of quantitative findings from laboratory and epidemiologic studies.

Noncompliance with the intervention and drop in to the intervention by the control group will certainly dilute any effect of the intervention diet. For this reason we have chosen the large sample size of 2,000 so as to detect the small percentage reductions in recurrence. The sample size calculations do not formally include compliance rates. Since the healthy diet is multifaceted, any measures of compliance are multidimensional and cannot be related to sample size in the absence of a reliable model relating each facet of the intervention to the level of reduction in the polyp recurrence rate.

It is proposed that the Board of Scientific Counselors appoint an ongoing advisory group of BSC members and other experts to serve as one of the oversight committees involved in this trial. This advisory

group will formulate quantitative recruitment and compliance goals for the trial, and will establish criteria for terminating the trial in the event these goals are not met.

Board member Edward Bresnick asked for an explanation of the differences between this study and the Women's Health Trial, which was discontinued before it went into the major implementation phase because of various objections.

Arthur Schatzkin, coproject officer with Elaine Lanza, said that the polyp trial has a series of endpoints compared to one for the Women's Health Trial, it is shorter by several years and less expensive.

DCPC Director Peter Greenwald added that an issue in WHT was whether "people will follow a diet. We now have data that they will. This has clear, specific endpoints."

Board member Robert McKenna pointed out that "there are people who are at higher risk for colon cancer. I'm not sure they should be entered in this trial." Schatzkin agreed that that issue needs to be considered. "It is not our intention to recruit people with familial polyposis or colitis."

Board member Lloyd Everson asked if CCOPs (Community Clinical Oncology Program) could be involved in the trial. Greenwald said that NCI contracts staff had determined it would not be appropriate to support the trial through the CCOP mechanism but that "people involved in CCOPs" could compete for the contract awards.

Board member Mary-Claire King offered the only serious opposition to the proposed trial. "Your fundamental hypothesis is that diet is related to polyps which are related to cancer," she said. "All the epidemiological evidence you presented could lead to another hypothesis. There is real naivite vis a vis genetics. There is new evidence that genetic susceptibility is likely to be a real modifier. It should be possible to build that into this trial."

"I anticipated you would bring that up, so I read everything there is on genetic factors," Schatzkin said. "There is overwhelming evidence that diet plays a major role. We feel that the genetic evidence is not strong enough not to test the clear evidence on diet. It was felt that genetics can be taken care of in the randomization."

King was not convinced and continued to argue for addition of genetic factors to the study. As proposed, "if you get a negative study, all you've shown is that diet is not related to polyp recurrence, but it will be seen as showing that diet is not related to colon cancer."

Board member Frank Meyskens agreed that "genetic makeup may put a person at higher risk for progression or recurrence. We haven't sorted out all those factors, but that is no reason not to start this trial. Genetic variations can be accounted for."

Board member James Holland objected to the cost, but Schatzkin and Greenwald noted that the need for dietitians, counselors and other personnel accounted for the cost estimate.

Board member Rumaldo Juarez asked if an effort would be made to recruit minorities into the study. Schatzkin said that no one would be excluded but that no special effort would be made.

"The intent is not to randomize or stratify by race or ethnic factors," Board Chairman Paul Engstrom said.

Juarez argued for positive action to include minorities; "if there is not, you will have the possibility that you will not be getting information that means anything to those populations."

The concept was approved, with King voting against it and Juarez abstaining.

Methods development for phytochemical compliance markers in designer foods. Master agreement contracts over a five year period, with an estimated three to five awards annually, at an estimated $200,000 per award. Total for the project, $900,000 per year.

Diet and cancer intervention studies would greatly benefit from valid and accurate measures of compliance. Hundreds of safe and naturally occuring compounds found in edible plants, i.e., phytochemicals, might be suitable for development as compliance markers in experimental foods destined for cancer research on free living study participants.

The phytochemicals in edible fruits and vegetables can be grouped into two general categories for relevance to cancer prevention studies applied to humans. The first is comprised of those substances that are present in limited quantities, exhibit chemical uniqueness in their structures, and are found only in specific fruits and vegetables. By virtue of their uniqueness these substances could rationally be incorporated into experimental foods as compliance markers. Substances in this category might include rare tocopherols, isomeric isoprenoids, unusual methoxylated flavenoids, and uncommon heterocyclic and hydrocarbon based plant pigments.

The second category of phytochemicals are those that are found in higher quantities, occur in several edible species, and may be ingested by humans daily in gram quantities. This second group exhibit a potential for modulating human metabolism in a manner favorable for cancer prevention. Examples of these phytochemicals include classes of indoles, sulfides, terpenes, isothiocyanates, phenolic glycosides, bioflavanoids, coumarins and other lactones, lignans, carotenoids, sterols, naphthoquinones, saponins, tetrapyrroles and polyacetylenes.

It is the major objective of this project to develop analytical methodology for detecting and quantifying the first category of phytochemicals in experimental food fortifications where they are purposely introduced, and in the blood of humans consuming these experimental foods. The major goal of this project is to validate rare or unusual fruit or vegetable phytochemicals as complance markers so that they may be added to dietary substances for more detailed nutritional modulation trials. In order to do this it is necessary to establish a pool of interdisciplinary investigators to apply existing analytical methodology for phytochemical analyses and refine it for measuring compliance markers in foods and in fluids of humans.

This project will be the first quantitative evaluation on the absorption and blood levels of GRAS phytochemicals puposely formulated into the experimental foods as compliance markers. In addition, this project will be the first industrial link with NCI for continuous and consistent supplies of designer foods for cancer prevention studies.

There are two general questions about dietary phytochemical food fortifications that impede development of human applications:

--How do you measure phytochemicals in a variety of experimental foods given the large number of potentially interfering molecules present in the food?

--How do you measure classes of phytochemical compliance markers in the blood, urine, saliva, tears, etc. of humans?

The existing technology must be applied and modified according to NCI requirements in order to answer these questions. This project focuses on developing the analytical technology required to measure marker phytochemicals in designer foods formulated by industry and in human fluids after consumption of these foods. In order to do this, contractors are required who can incorporate the areaas of phytochemistry, food technology, and clinical chemistry into an interdisciplinary research group.

NCI will provide the experimental food through

agreement with the food industry. Master agreement holders will bid on tasks specifying the analysis of phytochemical compliance markers in the experimental foods and/or in human fluids.

"This is absolutely step one for all of these studies," Bresnick said. It was approved without opposition.

Herbert Pierson is the program director.

Clinical evaluation of fruit and vegetable based experimental food supplements. Estimated three project area awards per year, through master agreements over five years, $100,000 per award, $900,000 per year.

Although there is much epidemiological evidence suggesting that the consumption of fruits and vegetables is extremely important for human cancer resistance, little research has focused on identification of epidemiologically important phytochemicals and their nutritional pharmacological impact on potential cancer preventive pathways in healthy humans.

The major objective of this project is to apply and refine analytical methodologies for:

--Measurement of selected phytochemicals in foods purposely fortified with them.

--Measurement of the above phytochemicals in the blood of healthy humans ingesting these foods.

--Measurement of the manner in which the circulating phytochemicals may influence clinical parameters in humans.

In order to do this it is necessary to establish a pool of interdisciplinary investigators with expertise in specific clinical nutritional measurements of human metabolism. Targeted for this purpose is the dietary modulation in humans of certain physiological and biochemical processes by foods containing the above fortified phytochemicals. For example, these parameters may include modulation of estrogen hydroxylation patterns and steroid excretion; influences on circulating dehydroepiandrosterone levels; influences on circulating arachidonic acid metabolites; and modulation of pharmacokinetic parameters known to facilitate the elimination of harmful substances from the body.

This project focuses on short term studies designed to assess the modulatory influences of fruit and vegetable based food supplements on both endogenous and exogenous human metabolism. Master agreements will be sought for three project areas:

Task 1. Dietary modulation of human drug metabolism by phytochemical constituents in fruits and vegetables.

Task 2. Dietary modulation of human arachidonic acid metabolism by phytochemical constituents for fruit and vegetables.

Task 3. Dietary modulation of human steroid metabolism by phytochemical constituents in fruit and vegetables.

"I believe designer foods are inevitable and will become a major part of our diet," Greenwald said. "It is our hope that this will be done for health reasons, not for economic or geographic reasons. The food industry is willing to work with us."

Holland asked if GRAS (FDA's recognition of a substance as "generally recognized as safe") is valid at 10 times the normal dose.

"That is a good question," program director Herbert Pierson said. "FDA says you can combine as many GRAS compounds as you want and it will still be safe."

"Water is safe but you can still get into trouble with too much," Holland said.

"Designer food is inevitable," Meyskens said. "Industry has been designing foods for a long time to give us things we like. Now we are asking for them to give us somethjing we like and is also healthy."

Holland observed that "this is a highly leveraged contract. A little bit of NCI money will go a long way in Battle Creek." The concept was approved without opposition, although there were four abstentions.

Special studies facilitating the flow of preclinical research leads into clinical practice. Master agreement contracts for five years, with two to three tasks anticipated for award each year, estimated $200,000 per award, total $900,000 per year.

Progress in applied human diet and cancer research requires new perspectives on experimentation focused on bridging the information gaps between numerous preclinical mechanistic studies and clinical-epidemiological observations worldwide. This project proposes a rational new approach to laboratory studies in diet and cancer.

The major goals of this project are:

* Obtain information from animal studies that bridges the research gaps between the preclinical and clinical areas thereby facilitating conduct of human studies.

* Provide NCI with new research leads supporting new trial development.

Reports on the effect of phytochemicals on animals and in some cases humans indicate the potential importance of the consumption of fruits and vegetables for human resistance to chronic diseases like cancer. Examples of potential cancer preventive endpoints include garlic induced reduction of blood lipids and modulation of prostaglandins, antiestrogenic effects of soybean constituents, anti-inflammatory activity of edible plant pigments, hepatoprotective activity of volatile compounds in spices and medicinal foods, modulation of many key regulatory enzymes by phenolic compounds, and enhanced metabolism and excretion of harmful foreign compounds.

The major objective of this project is to methodically and systematically understand the magnitude of the modulatory value of fruit and vegetable phytochemicals on biological processes thought to be important for human resistance to cancer. This is an important objective since humans consume gram quantities of mixtures of phytochemicals daily. Very little research has focused on specifically understanding the magnitude of the influence of naturally occurring mixtures and ratios of dietary phytochemicals on biological pathways potentially important for human benefit. Knowledge of the magnitude of the modulatory influence of dietary components on such biological processes would be extremely useful for targeting such diets in indicated populations.

The Diet & Cancer Branch has identified over 1,400 food additives in the human diet considered to be generally regarded as safe by FDA. The majority of these substances are phytochemicals of edible plant origin and include colors and color control agents, pH control agents, sanitizing agents, encapsulating agents, antioxidants, antimicrobial agents, flavoring agents, sequestrants, sweeteners, firming agents, texturizers, stabilizers, and thickeners. These classes are chemically represented by alcohols, ketones, esters, aliphatic acetals, alicyclic carbohydrates, aliphatic hydrocarbons, amines, thiols, phycols, lactones, carboxylic acids, amino acids, sulfides, pyrazines, salicylates, terpenes, phenols, acetophenones, epoxides, aromatic aldehydes, ethers, dithioles, pyrroles, furans, thiophenes, thiazoles, rosins, oleoresins, and sterols. Since these substances are permitted in foods and during food processing, research emphasis has been in the past directed toward final food product development and human acceptability. Other biological activities of these substances are now being reported and many of these are thought to be highly relevant to cancer prevention.

One manner in which to expedite the application of research leads to humans is to target designer foods enriched with phytochemicals of known activity to

human populations that would best benefit from specific food supplementation. One way to target designer foods to indicated populations is to identify valid biological processes that would potentially be modulated in directions favorable for human cancer prevention. This project will be the first step forward to develop a program for validating the biological processes in laboratory animals. In order to rationally accomplish the goal of targeting designer food supplements to best benefited populations, a biological matrix composed of key pathways to be modulated by specifically designed mixtures of phytochemicals in designer foods should be implemented. The biological matrix might be composed of the following modulatable endpoints:

--Serum lipids, antiestrogenic activity, prostaglandin biosynthesis, anti-inflammatory responses, viral enzyme activity, cyclic nucleotides, ornthine decarboxylase induction, glucose-6-phosphate dehydrogenase activity, steroid hormone hyroxylation patterns, xanthine oxidase activity, glucuronidase activity, and glutathione conjugation.

It is likely that some single fruit and vegetable phytochemicals if consumed on a regular basis are already for this targeting. It is also likely, however, that two or more GRAS substances need to be combined specifically in the diet in order to modulate different preventive pathways and express synergistic or potentiative responses beneficial for cancer prevention. This project therefore addresses short term laboratory studies on animals for clarifying the potential clinical significance of cancer preventive designer foods.

This is a master agreement contract activity that focuses on understanding the potential synergism and enhancement of phytochemical mixtures on biological processes in laboratory animals that are known to be important for resistance to chemical carcinogens and therefore highly relevant to healthy humans. Projects will be initiated to determine the dietary modulation of similar classes of phytochemicals on different preventive biological responses. A research matrix utilizing different preventive endpoints titrated against systematic combinations of dietary phytochemicals will be developed by interdisciplinary teams of research scientists possessing this expertise. There will be four task areas to this master agreement:

Task 1. Evaluation of phytochemical mixtures in designer food supplements for modulation of circulating lipids and lipoproteins.

Task 2. Evaluation of phytochemical mixtures in designer food supplements for antiestrogenic activity, hormone receptor function and modulation of steroid hormone levels and metabolism.

Task 3. Evaluation of phytochemical mixtures in designer food supplements for modulation of arachidonic acid metabolism and chronic inflammatory responses.

Task 4. Evaluation of phytochemical mixtures in designer food supplements on key regulatory enzymes, antioxidative defense, and cyclic nucleotide levels.

The concept was approved without opposition, although three board members abstained.

Technical support for the experimental food program. One five year contract, with an estimated cost of $900,000 per year.

Diet and cancer studies focused on clinical evaluation of discrete experimental foods specifically designed by NCI as cancer research materials must be separately housed independently of drugs and chemicals, properly stored, shipped, tracked, protected, and managed in accord with federal regulations governing investigational substances.

The major objective of this project is to possess the technical capability of receiving, storing, shipping, inventorying, reordering, tracking, and evaluating experimental foods so that these cumbersome, costly, and time consuming responsibilities do not interfere with the conduct of studies by principal investigators supported by the Diet & Cancer Branch. The major goal is to provide essential technical support for diet and cancer studies.

The branch has and will continue to enter into agreements with the food industry to develop research materials for human studies. With minimal exception, food companies have agreed to formulate the research foods designed by NCI; assay the experimental formula on a sensory panel; provide continuous and consistent supplies of these materials for evaluation; provide limited packaging and labeling of these materials; provide limited storage capability; provide limited chemical analyses of experimental food ingredients; conduct limited shelf life stability tests on experimental foods; and make single large shipments to a single site.

Although the food industry is cooperating with NCI to make experimental foods, at minimal or no cost to the government, the firms tend to have limited research budgets for storing experimental products destined for new markets and uses, and practically no funds to support special animal studies, regulatory studies, clinical evaluations, detailed analytical chemical analyses, multiple shipments to study sites, or archiving and inventorying activities required by research programs.

The contractor shall assist the branch in many unique capacities by:

--Identifying manufacturers and sources of food materials.

--Establishing production milestone schedules.

--Ensuring on time receipt of foods.

--Operating designer food warehousing required under federal law.

--Ensuring delivery to study sites.

--Delivering samples for detailed analyses.

--Obtaining, processing, and maintaining management information.

Maintaining a food warehouse with the appropriate technical capabilities is required for handling the types, volumes and stable time periods of experimental foods. Types of foods include those packaged in sashes, bottles, cans, cartons, freeze dried pouches, boxes, and bags. Volumes may range from small kilogram lots of single production runs to many barrels of bulk materials for controlled feeding studies. The time periods for shelf life determinations may range from several days for experimental breads to several months for experimental juices to possibly a year or more for breakfast bars.

Board member Johanna Dwyer objected to the prospect that industry might use joint efforts with NCI to give the NCI "imprimatur" to some of its products. "Why should NCI have to pick up the costs?" Dwyer asked. "If industry benefits, why should NCI pay?"

Other board members disagreed. Philip Cole said "this is extremely critical" to the Diet, Nutrition & Cancer Program. Meyskens added, "If we had had this capability 10 years ago, chemoprevention could have been speeded up by three to five years."

The concept was approved, with Dwyer casting the only vote against it. There were three abstentions.

The concept for an interagency agreement with FDA will provide up to $500,000 a year for five years. FDA will provide essential information on new food safety and will conduct special studies required for program planning by NCI and outside investigators.

The proposed interagency agreement with NIST would support, at an estimated cost of $500,000 a year for five years, biotechniques applications for nutritional intervention studies. It was tabled on a 6-5 vote after Meyskens called it "a fishing expedition. I'm not sure it would produce useful information."