THE CANCER LETTER

Vol. 18 No. 5
Jan. 31, 1992

Price $215 Per Year US, Canada.
$240 Per Year Elsewhere

P.O. Box 15189 Washington, D.C. 20003 Telephone 202-543-7665

FDA Commissioner Says Swifter Drug Approvals, Enforcement Emphasis Characterize 'Today's FDA'

FDA Commissioner David Kessler, in his first appearance before the National Cancer Advisory Board, described the tremendous changes he has set in motion at the agency since being confirmed last March and addressed three key issues that have concerned oncologists recently: secondary uses for approved cancer drugs, FDA's proposal to regulate

(Continued to page 2)

In Brief

ACS Begins Narrowing List Of Job Applicants; IL-2 Gets BRM Ok; Pitot Resigns McArdle Post

NINE AMERICAN Cancer Society staff members and volunteers and approximately 450 individuals from outside the organization have expressed interest in the position of executive vice president, vacant since **William Tipping** resigned last year. The search committee, chaired by former Executive VP **Robert Gadberry**, will hold its fourth meeting Feb. 19 to narrow the list of external prospects. Staff members headed by Senior Vice President for Human Resources **Harry Linduff** are writing summaries on each of the candidates for presentation to the committee. The committee will interview the internal candidates and those selected from the external list during a three day meeting starting March 21. The committee hopes to present its recommendation to the ACS Board of Directors at its meeting in Portland, OR, in June. . . . **CHIRON'S IL-2** for treatment f metastatic renal cell carcinoma in asymptomatic patients ans ambulatory symptomatic patients was recommended for approval by FDA's Biologic Response Modifiers Advisory Committee on a 7-1 vote. Also recommended for approval was Cytogen's **OncoScint** monoclonal antibody as a diagnostic for ovarian and colorectal cancer. OncoScint was developed by **Jeffrey Schlom** of NCI. . . . **HENRY PITOT,** director of the McArdle Laboratory for Cancer Research, resigned his position to return to full-time teaching and research at the Univ. of Wisconsin Medical School, where he is professor of pathology and oncology. McArdle Associate Director **Norman Drinkwater** this month succeeded Pitot, who headed the laboratory for nearly two decades. Pitot was appointed director in 1972, succeeding the laboratory's first director, **Harold Rusch.** Drinkwater joined McArdle in 1982. . . . **ALLEN BOLTON** has been named director of community affairs for the Univ. of Alabama (Birmingham) Comprehensive Cancer Center. Bolton was former deputy director of the university's Injury Prevention Research Center. He succeeds Jeffrey Underwood.

Kessler Describes 'Today's FDA': Swifter Approvals, NCI Collaboration

(Continued from page 1)
certain continuing medical education programs, and the voluntary ban on breast implants.

The three issues represent related aspects of Kessler's emphasis on what he recently called "good, old-fashioned, straightforward enforcement" of the agency's statutes.

But before launching into a forceful discussion of "today's FDA," Kessler officially laid to rest more than a decade of acrimony between the agency and NCI on the development of cancer drugs--a problem which mostly ended about two years ago, when the agencies began discussion of several divisive issues. Kessler credited NCI Director Samuel Broder with creating much of the "turnaround" in cooperation between the agencies.

"From my perspective at the agency, I have the impression that Sam's open and generous approach to our interactions has helped close what was once a serious breach between us," Kessler said. "Of course, Sam does not work alone, and we worked hard with many others [in the Div. of Cancer Treatment]: Bruce Chabner, Mike Hawkins, Dan Longo, Mike Friedman, Mike Grever, and I am sure there are others."

FDA and NCI staff meet monthly and at other times in working groups and have a joint fellowship training program in drug regulation. In addition, NCI Deputy Director is a voting member of the Oncologic Drugs Advisory Committee, and Investigational Drug Branch Chief Michael Hawkins is a voting member of the Biologic Response Modifiers Advisory Committee.

Then Kessler arranged "the final link" between the two organizations. "A few months ago I got on a plane and flew to Kansas. I was looking for the best physician manager around, someone to be the chief operating officer for FDA." He found Jane Henney, vice chancellor for health programs and policy and Univ. of Kansas Medical Center, a former NCI deputy director. Henney came on board FDA earlier this month.

Kessler also hired a new senior investigator for science, Elkan Blout, chairman of biochemistry at Harvard Medical School and dean of the Harvard School of Public Health. Continuing as director of the Center for Drug Evaluation and Research is Robert Temple; Gregory Burke remains director of the oncology division, and John Johnson is group leader in oncology. All of the officials attended the NCAB meeting this week.

No Backlog of Oncology NDAs

"Today's FDA is not what you might think," Kessler said. "There have been major changes. Dr. Burke's oncology division is what one might call a clean-desk operation. There is virtually no backlog of new drug applications. It has no backlog of what we term efficacy supplements, requests for approval of new indications. It is a place where the work gets out on time.

"In fact, during the past five years, the mean time for approval for cancer drugs and efficacy supplements has been 11 months, a remarkable improvement over the mean approval time of 40 months that was the norm for previous years. This reduced time to approval does not mean we have lowered our standards. We have maintained our standards, but we have streamlined the process.

"The number of approved cancer drugs available to cancer patients is encouraging, too. During the period from 1975 to 1985, FDA approved on the average only one new oncology drug every two years. For the last five years, the rate has gone to nearly two drugs a year and it is rising."

A recent example of improved NCI and FDA collaboration is the drug taxol, Kessler said. FDA is conducting pharmacokinetic studies of the drug in cooperation with NCI intramural scientists, and the agency is working closely with NCI and the drug sponsor, Bristol-Myers Squibb Corp., he said.

'We Never Objected' To Off-Label Use

Kessler next addressed the issue of secondary or "off-label" uses of cancer drugs that have been given market approval. According to a recent General Accounting Office survey, 56 percent of new patients receive at least one drug not labeled for that use. One third of all drugs administered in that survey were for a treatment that is not on the label (**Cancer Economics,** October 1991).

"We at FDA do not object to that practice. We have

THE CANCER LETTER

Editor: **Kirsten Boyd Goldberg**
Associate Editor: **Lisa M. O'Rourke**
Contributing Editor: Jerry D. Boyd

Editorial/Subscriptions Office
PO Box 15189, Washington, DC 20003
Tel: (202) 543-7665 Fax: (202) 543-6879

Subscription rate $215 per year North America, $240 elsewhere. ISSN 0096-3917. Published 48 times a year by The Cancer Letter Inc., also publisher of The Clinical Cancer Letter.

never objected to it," Kessler told the NCAB. "The law gives all qualified physicians a free hand at prescribing approved drugs for any use they deem appropriate. What has brought the issue to the fore is the agency's effort to regulate the promotion of drugs for nonlabeled uses. Promotion of unapproved uses of approved drugs has never been permitted under our nation's food and drug laws.

"We simply are not happy with a situation in which so much of what is done is not reflected in the labeling. For one thing, we believe our careful review can be helpful; for another, labeling can provide guidance as to the relevant studies and moderate information that is not available for unlabeled uses. Such data as dosage, monitoring and any caveat related to subsets of patients should be well established for every important indication, especially when we are dealing with drugs that are toxic."

To "stimulate submission of labeling at least the most widely prescribed secondary indications of approved drugs," Kessler said FDA will:

▶Take steps to "determine the scope of the phenomenon and identify the medically most important unlabeled uses." NCI staff have provided some recommendations, and FDA will seek help from medical specialty societies, pharmaceutical companies, and FDA advisory committees, and will look for leads in the drug compendia. [Two drugs high on NCI's list are carboplatin and etoposide, for which there are many secondary uses.]

▶"Next we will scan the available information. It is our hope that at least in some cases the medical literature on the unlabeled use may contain all of the data we need for an approval. In such instances, we might simply request the drug manufacturer to make the appropriate labeling change without any additional effort on the part of the company. In other cases, the literature will not provide enough detail and we will have to seek further data and certain case records. Sometimes more study will be needed, and we will encourage the drug sponsor to develop the necessary information."

▶When the application is submitted, FDA will use "all available resources" including outside reviewers if necessary, to process the submission. "Our safety and efficacy standards, however, will remain unchanged," Kessler said.

Kessler said FDA has already approached two companies regarding additional labeling for their products. "Just as we are taking an assertive approach to new drug development and review, we are not going to sit back and wait for efficacy supplements to arrive at our door," he said.

The actions to solicit secondary approval applications will not create a backlog within FDA's oncology group, Kessler added.

Kessler also noted that the drug label approved by FDA "should not be the basis for reimbursement" by third-party payors. "Some use our label as an excuse not to reimburse. We need to send a very strong signal to the third party community not to use our label as a benchmark. It is a real problem."

American Society for Clinical Oncology President Martin Abeloff met with Kessler last fall and in subsequent correspondence has urged that FDA place an announcement in the "Federal Register" stating its position that the label should not be used for reimbursement decisions, and that physicians may prescribe appropriate unlabeled uses of approved drugs.

CME Paper 'Only A First Draft'

NCAB Chairman Paul Calabresi asked Kessler to comment on FDA's recent draft policy paper on continuing medical education, which stated the agency's intent to impose restrictions on scientific meetings which under the agency's definition would be considered "promotional" (**The Cancer Letter,** Jan. 3).

Kessler emphasized that the paper "is only a first draft--our thinking is still open."

He said FDA's goal in drafting the policy is not to permit promotion of unapproved uses of drugs. Some drugs have been "subject to intense PR efforts" on the part of industry.

"We have not changed our policy: use is permissible, promotion is not," Kessler said. "Our first concern is to deal with promotion that is false or misleading."

He said industry and scientists have asked where to draw the line between free scientific exchange and promotion. Kessler said he saw the proposed policy as providing a "safe harbor" for scientists, since it does not take the position that "once you take money from a sponsor, it's promotion."

Breast Implants

Earlier this month, FDA urged physicians to discontinue use of silicone gel breast implants both in women seeking breast augmentation and in mastectomy patients (**The Cancer Letter,** Jan. 10).

The implants were on the market years before the 1976 medical device law giving FDA authority over them and under the law were allowed to remain. However, FDA began the process in 1978 of moving these devices to a higher "class" in its device approvals, thus giving it authority to decide on the safety of the devices.

Last April, FDA called for premarket approval applications from the breast implant manufacturers; seven applications were received, three were disqualified for not having any clinical data, and four proceeded through the approvals process.

"The law requires the devices to be shown to be safe," Kessler said. "The burden is on the manufacturer, not FDA."

Last November, an FDA advisory committee held a marathon three day meeting with hundreds of witnesses and concluded that the data did not show that the silicone implants were safe, but recommended that the devices should remain on the market.

Since then, Kessler said, a jury in a San Francisco court case levied $7 million in damages and $6 million in punitive damages against Dow Corning Wright, maker of one brand of silicone implant. What struck FDA, Kessler said, was the jury's finding of fraud on the part of the company.

"I was prepared to leave the devices on the market, especially for mastectomy patients, but the information we have seen in the last few weeks has given me pause," he said.

"We have been criticized for not making the documents public. I can't be party to a breach of a protective court order," Kessler said.

FDA is now urging Dow Corning Wright to make this data public, though some portions of the information have been reported in daily newspapers.

Kessler said he did not want to comment further on the issue in order not to prejudice the Feb. 18-20 meeting of the advisory committee, which will reconvene to hear additional information.

NCAB member Nancy Brinker asked Kessler what advice will be given patients who already have the implants. Kessler said that is one issue the advisory committee specifically will be asked to address.

NIH Strategic Plan: Much Ado About Cross-Cutting 'Mission'

Early next month NIH will release a strategic plan almost a year in the making that some NIH officials have likened to a de-Balkanization of biomedical research: a cross-cutting plan to bring the disparate institutes together to decide on common scientific goals and overall NIH "mission."

The blueprint outlines some leading research and policy themes for the institutes and makes clear that its activities are tied to public health goals. Drafts of the plan that have circulated over the past few months have been divided into separate reports, each prepared by panels chaired by an institute director.

NCI Director Samuel Broder chaired the panel on molecular medicine, and National Institute on Allergy & Infectious Diseases Director Anthony Fauci chaired the panel on vaccine development. The prevention panel was chaired by National Heart, Lung & Blood Institute Director Claude L'Enfant.

The final version of the strategic plan, rumored to be almost 10 inches thick, is scheduled to be "unveiled" (NIH term) at a Feb. 5 meeting at the Southwestern Foundation for Biomedical Research in San Antonio, TX. Following that will be meetings around the country through February and early March for professional organizations and individuals to comment.

Problem is, most organizations at this point might have trouble a) getting a copy of the most recent version of the plan, b) finding individuals willing to review and comment on it, and c) getting on the agenda at one of the public sessions, since spaces are filling up rapidly.

"The paperwork is voluminous," said Margaret Foti, executive director of the American Assn. for Cancer Research. "We are scheduled to present on Feb. 25 (at Farmington, CT), but we hope we can reschedule to a later date. It is a major undertaking to get a committee to review it.

"It is a very broad document, and it is difficult for any organization from the outside to even understand it," Foti said. "All you can do is question the line items."

Nevertheless, NCI Director Samuel Broder this week stressed the importance of the strategic plan. "I urge all the relevant professional societies to attend these meetings" and become involved in the strategic planning process, he told the National Cancer Advisory Board.

Broder has said that the plan "does not interfere with any categorical institute having a plan for its own mission," a reference to NCI's bypass budget request.

An early version of the molecular medicine panel's report called for NIH to provide $229 million in new funding from FY 1993-1996 for preclinical and clinical studies in gene therapy for a wide range of diseases. In addition, the panel named nine other areas that need greater research efforts.

The panel recommended new funding of $137 million on disease pathogenesis over the next four years, and new funding of $121 million for the molecular biology of inherited diseases.

Following is an executive summary of the molecular medicine panel's report:

Molecular Medicine Executive Summary. Overview: Molecular medicine cuts across all areas of basic biology and clinical investigation and epitomizes the bidirectional flow between the laboratory bench and the patient's bedside that informs the activities of virtually every institute within NIH. An understanding of the molecular interactions that determine both physiology and pathology will form the basis for rational, targeted therapeutic intervention and, ultimately, prevention and eradication of diseases that impair both the length and quality of life.

An organ system is a conglomeration of tissues which themselves are composed of diverse cells, each with specific interactive functions, melded together to yield a unique net "organ function." Normal homeostasis in every organ results from a cascade of events that begins in individual cells at the level of the genome. Net gene expression leads to the complement of products that maintain the balance between cell growth, differentiation, specific function and ultimately cell death. The cascade is modified according to cell and tissue needs through the extracellular environment (the extracellular matrix and various growth factors, for instance) and intercellular communications (adhesion molecules, cell junctions, and transmembrane receptors) that lead to intracellular signal transduction and, in turn, modulation of net gene expression.

The disease state represents an imbalance in the molecular mechanisms of normal homeostasis, whether induced by external perturbations or as a consequence of intracellular genetic aberration. Some heritable diseases are the direct consequence of a point defect (loss or mutation) in a single gene locus--cystic fibrosis, retinoblastoma, ataxia-telangiectasia, inborn errors of glycoconjugate metabolism, Huntington's disease and sickle cell anemia are selected examples. More commonly for many diseases, notably the major killers such as heart disease and cancer, the pathogenesis involves multiple aberrations and reflects both a dysregulation of intrinsic controls and a loss of responsiveness to extrinsic modulation. In this regard, it is logical to speculate that several diverse diseases, especially those with multi-organ system impact, intersect through common pathogenic mechanisms. Dissection of the molecular physiology of cellular response to external stimuli (carcinogens, drugs, infectious agents) affords the ability to modulate that response in various tissues--either to block it or to induce it and use it to its greatest protective advantage. Uncovering the genetic foundations of molecular disequilibrium is essential to reversing a disease process that is already ongoing (for example, atherogenesis) and, perhaps more importantly, preventing the initiation of disease by interdicting at the most rudimentary level of susceptibility.

Magnitude of the problem: The goals of molecular medicine target four basic components: to characterize factors that modulate net gene expression and maintain homeostatic balance; to define the multiple pathogenic steps and serial interactions that culminate in disease; to use the knowledge gained about the critical determinants of disease to design rational, targeted clinical interventions (early detection, therapy, prevention); and to identify an individual's heritable risk for development (or transmission) of specific diseases, based on the predicted interactions between genetics and environment, for the ultimate purpose of disease prevention.

In its current state, the technologies of molecular medicine are very expensive to develop and implement in the clinical arena and, thus, immediate economic gains cannot be anticipated. In fact, the 10 molecular medicine initiatives described in the panel's report would require an investment of approximately $5.8 billion over five years. However, molecular medicine has the potential for impact upon virtually the whole spectrum of human diseases--their prevention, diagnosis and treatment. Cardiovascular diseases, cancer, AIDS and other infectious diseases, Duchenne's muscular dystrophy, Alzheimer's disease, sensory disorders, diabetes, sickle cell anemia, and cystic fibrosis exact a staggering economic toll, as well as causing death and suffering, and all have the potential to yield at some level to molecular medicine.

Progress and opportunities: What is learned from the study of one disease process can often be extrapolated to a seemingly disparate pathology in an apparently distinct cellular or organ system. Retinoids, acting through nuclear receptors to regulate gene expression and induce differentiation, may serve as potent chemopreventive agents against a variety of malignancies and, further, may regulate hormone production in various endocrine tissues. Regulatory growth factors, for example, transforming growth factor beta and the novel keratinocyte growth factor, promote wound healing and post-injury regeneration in various tissues. The multidrug resistance gene shares homology with the cystic fibrosis gene and their gene products are important, universal, energy dependent determinants of membrane transport, conserved from bacteria and Drosophila through humans. Calcium channel blockers, for instance the cardiac anti-arrhythmic verapamil, can effectively abrogate multidrug resistance in vitro in diverse cancers. The technology for genetic engineering applies to the correction of genetic deficiency diseases (such as the inborn errors of metabolism), to immunomodulatory therapies or vaccines against various cancers and to the blockage of viral gene expression (HIV, for example).

Special emphasis initiatives: I. Gene therapy and II. Molecular genetics of disease and disease susceptibility: The ability to introduce genetic material into human cells with successful expression of the inserted gene is a major biotechnologic advance that permits the development and clinical application of gene therapy strategies. Such strategies offer tremendous potential for the curative treatment and ultimate prevention of single gene disorders (such as cystic fibrosis, neurofibromatosis, or adenosine deaminase deficiency), complex polygenic disorders (most notably Alzheimer's, diabetes mellitus, hypertension and various forms of heart disease, various cancers, autoimmune diseases, and certain psychopathologies such as schizophrenia), and infectious diseases such as AIDS.

Increasingly, the attempt to isolate the genes underlying a particular disease, predisposition or other trait is a central feature of research on that phenomenon. Current concepts and approaches include the correction or replacement of defective genes to restore normal cellular function, the introduction of new genes into cells for the purpose of conferring new cell functions, and the development of gene targeted molecules (for example, the so called antisense constructs) to block abnormal gene expression.

III. Growth factors and signalling: Growth factors act as external modulators of cell proliferation and differentiation. They also mediate cellular response to external stimuli by triggering biochemical cascades within the cell, so-called signal transduction.

As such, growth factors are a major mechanism of host defense against environmental toxins and serve a key role in tissue regeneration and repair. Growth factors which promote stem cell regeneration of specific tissues offer the potential for repair following tissue injury (drug induced or infectious) and may protect specific tissues from damage by cytotoxic agents. On the other hand, certain growth factors and their receptors may promulgate deleterious cellular responses and, as such, are targets for blockade by specific growth factor inhibitors or agents that block signal transduction pathways.

Implementation strategies: Molecular medicine is uncovering some broad principles that govern the interplay between internal

and external factors that modulate gene expression and cellular function for many cell types.

These principles provide a unity of knowledge and cut across multiple levels of biology to inform and advance the medical practice of disparate clinical disciplines.

To maintain the momentum of progress in molecular medicine, the development of technology must continue in a way that fosters rapid translation of basic science discoveries into clinical application.

Key areas for continued and future developments in molecular technology include: animal models (including transgenic models to expand gene therapy approaches); family registries and tissue repositories for expansion of gene mapping, linkage analyses and gene probe methodologies; biomarkers to facilitate rapid screening and determine disease susceptibilities; and computer databases to correlate structure-structure and structure-function translations between DNA sequences and encoded protein structures.

Interdisciplinary collaboration and cross-communication among the various health science disciplines will speed the development of molecular technologies and clinical advances in diagnosis, therapy and prevention of disease.

Each discipline contributes a special expertise regarding the key elements responsible for the preservation of organ integrity (both structural and functional) and the mechanisms by which that integrity is disrupted. By the same token, each discipline can be enriched by perspectives derived from different angles of observation.

The effective translation of molecular discovery into practical clinical application may be addressed through the following mechanisms: establish gene transfer therapy as a major, high-priority trans-NIH initiative with targeted intramural programs and increased accessibility by the extramural community; maintain the NIH Clinical Center as a premier institution for the translation of molecular discoveries into clinical advances; develop a major intramural laboratory dedicated to molecular genetics and gene mapping that complements and augments NIH's gene transfer therapy program; enhance the role of intramural NIH in other areas of special emphasis; develop electronic "research in progress" databases to broaden information dissemination and promote rapid data exchange; hold multi-disciplinary conferences and workshops with representative expertise from multiple ICDs [institutes & centers]; and develop RFAs, RFPs and PAs that represent a joint effort among several ICDs.

Other strategies include: designate study sections that address interdisciplinary programs and incorporate multiple areas of expertise in the review process, aimed at encouraging multifaceted approaches in the extramural community; innovative use of centers mechanisms (for example, P30s, P40s and P50s) to support multi-disciplinary programs in molecular medicine; streamline the regulatory process involved in transferring molecular medicine from laboratory to clinical testing in order to facilitate the rapid approval of innovative clinical investigative protocols using novel agents (recombinant biomodulatory growth factors) and/or revolutionary modalities (gene therapy); and identification and surmounting of barriers that impede full interaction and information exchange between intramural and extramural scientific communities.

The evolving understanding of molecular mechanisms brings with it unprecedented opportunities for advances in prevention, diagnosis and therapy of disease based on detection of specific molecules or intervention at the molecular level. Increased support for molecular medicine research will result in the development and application of new technologies to a wide variety of human inherited and acquired diseases and facilitate transfer of those technologies from the laboratory to the clinic.

DCPC Advisors Approve Continuation Of Children's Diet Study For $1.6M

Advisors to NCI's Div. of Cancer Prevention & Control gave concept approval to continuation of an add-on study to a large dietary intervention trial sponsored by the National Heart, Lung & Blood Institute.

DCPC Board of Scientific Counselors committed $1.6 million for seven years to continue the NCI ancillary study to the Diet Intervention Study in Children with High LDL Cholesterol (DISC), a multi-center randomized trial supported by NHLBI through cooperative agreements.

Advisors to NHLBI will decide next month whether to continue DISC at a cost of $10 million. The NCI study cannot continue if NHLBI decides not to proceed.

The DCPC board also voted unanimously to table a concept for a new RFA that would have set aside $8 million over four years to fund grants in psychosocial interventions for cancer patients. Board members said the concept should be more clearly focused on patients at high risk or newly diagnosed with cancer.

Following is the concept statement for the DISC study:

Evaluation of the Effects of a Fat-Modified Diet on Hormones During Adolescence (DISC Hormone Study). Continuation of cooperative agreements for six clinical centers and one coordinating center, and contract for a hormone laboratory. Total $1.6 million over seven years.

This concept requests support for continuation of the NCI Ancillary Study to the Diet Intervention Study in Children with High LDL-Cholesterol (DISC), a multi-center randomized clinical trial supported by NHLBI under the cooperative agreement mechanism. The objective of DISC is to evaluate the feasibility, safety, and efficacy of a fat-modified diet to lower LDL cholesterol in children ages 8 through 13. DISC was initially approved and funded by NHLBI for a total project period from FY 86 through FY 93. Continuation of DISC trial for an additional seven years is currently under consideration by NHLBI and a concept will be presented to NHLBI's Advisory Council in February. The NCI Ancillary Study on Hormones was initially approved and funded for the period of FY 91 through FY 93.

The primary objective for this continuation is to extend the NCI Ancillary Study on the effect of a fat-modified diet on serum sex hormones in boys and girls through ages 17-18. Secondary objectives are: To assess the associations of age, Tanner stage, anthropometric measures, physical activity, food patterns, and nutrient intake with levels of serum sex hormones; to assess the associations of diet, anthropometric measures, and physical activity with sexual maturation and, in girls, age at menarche; to assess the associations of diet, anthropometric measures, and physical activity with menstrual cycle length and the frequency of anovulatory menstrual cycles in post-menarcheal girls.

Diet has been purported to play a role in breast and prostate cancers. Because of problems with recall, few case-control studies have attempted to assess the association of adolescent

diet with cancer risk. Early age at menarche is a well known risk factor for breast cancer. Girls whose menses begin at a younger age are taller and heavier compared to other girls. Diets high in fat and fiber have been reported to be associated with later age at menarche. However, the role of diet in determining age at menarche remains unclear.

Sex hormones may be intermediaries in the development of breast and prostate cancers. Metabolic feeding studies in adult women and men have shown that serum levels of sex hormones respond to dietary fat. Little is known, however, about the effect of diet on endogenous sex hormone levels during adolescence. One observational study reported an inverse association between dietary fiber and plasma estradiol levels in adolescent girls. No intervention studies have been reported.

DISC is a randomized clinical trial of a fat-modified diet in children ages 8 through 13 years. Participants, therefore, currently are followed from pre-puberty into the early stages of puberty. If the proposed continuation is approved, the effect of diet on serum sex hormones would be evaluated in children ages 8 through 18 years or from pre-puberty through completion of puberty. Associations of physical activity and body size with hormone levels throughout puberty also would be assessed. Approximately 35% of girls will reach menarche in the present study. If DISC is continued all girls will go through menarche, providing the opportunity to evaluate associations of diet, physical activity, and body size characteristics that may be related to breast cancer risk.

Randomization and Follow-Up: A total of 663 children (363 boys and 300 girls), which represented 110% of the recruitment goal, were randomized into DISC between April 1988 and July 1990. Eligibility criteria specified that children be 8-10 years old at randomization, have LDL-cholesterol levels between the 80th and 98th percentiles but otherwise be healthy, be within the 5th and 90th percentiles of weight for height, be pre-pubescent, not have any behavior problems that could interfere with participation in the intervention, and not already be following a low fat diet. Follow-up visits are conducted at 12, 24, and 36 months for all intervention and control group children randomized, and additional 48 month visits are conducted with those cohorts randomized early in the trial.

Dietary Goals: DISC dietary goals for the intervention group are to reduce total fat intake to 28% of calories, saturated fat to 8% of calories, and cholesterol to 75 mg/1000 calories. The control group children continue their usual diets.

Intervention: DISC intervention is implemented through a series of group sessions augmented by individual family sessions. The initial six months is an intense phase consisting of twelve group sessions and four individual family sessions. This is followed by long term maintenance consisting of a minimum of two group and two individual contacts per year. Monthly phone calls and newsletters are also employed to maintain compliance to the study diet. Attendance at the intervention sessions has been excellent with a 95% attendance rate for each child and at least one parent for the intensive intervention sessions and a 90% attendance rate for maintenance sessions.

Preliminary Results: A total of 593 children (93%) completed 12-month follow-up visits. Based on three 24-hour recalls, diets of intervention group children at the 12-month visit were significantly lower in calories, percent of calories from fat, and percent of calories from saturated fat, compared to control group children. Heights and weights of intervention and control group children were not significantly different at 12 months. Intervention group children, however, had a significantly lower mean body mass index.

Thirty-six month follow-up visits have been completed for the first 146 children (22%) randomized into the trial. Preliminary results from the 36-month visit are similar to those at 12-months.

Continuation Activities: This concept is to continue the seven DISC cooperative agreements and hormone laboratory contract for seven additional years. NCI funded continuation activities would include: a. Collection of serum biannually at follow-up visits up to age 18 on both the intervention and control groups; b. collection of data on age at menarche; c. collection of weekly menstrual cycle calendars by mail for six weeks preceding and six weeks following each biannual blood drawing to allow determination of the day of the menstrual cycle when blood was drawn; d. re-training and re-certifying data collection staff for collection of data on menarche and menstrual cycles biannually; e. analysis of serum estradiol, estrone sulfate, testosterone, sex hormone binding globulin (SHBG), albumin, progesterone (girls only), dihydrotestosterone (boys only), and estimation of free, SHBG-bound and albumin-bound estradiol and testosterone.

NHLBI funded continuation activities would include: a. yearly follow-up visits to age 18 on both the intervention and usual care groups, consisting of a fasting venous blood sample for lipids, three 24-hour recalls, anthropometry, blood pressure, Tanner staging, and psychosocial and cognitive measurements; b. continued maintenance intervention on the intervention children and their families, consisting of two group and two individual sessions each year, monthly contacts through telephone calls or newsletters, yearly analyses of food records or recalls for monitoring dietary changes, and semi-annual case conferences for each intervention family by the intervention staff; c. re-training and re-certification of data collection staff for measurement of end-point data every two years; d. genetic analysis for apolipoprotein E, the LDL (B,E) receptor, and Lp(a); e. measurement of insulin in frozen sera stored since the beginning of DISC and in sera at the completion of the trial; and f. semi-annual meetings of the DISC Steering Committee.

Eight Centers Chosen To Host Regional Breast Cancer Meetings

Eight cancer centers have been chosen by NCI and the Susan Komen Foundation to host regional Breast Cancer Summits this year.

The meetings will be hosted by NCI designated comprehensive cancer centers and modeled on the two national Women's Leadership Summits the Komen Foundation held in Washington in the past two years.

"We see this effort to promote regional breast cancer outreach programs as a logical next step," said Nancy Brinker, founder of the Komen Foundation and member of the President's Cancer Panel.

Each summit is supported by a grant from NCI of up to $25,000. The centers chosen for the summits are: Arizona Cancer Center, Tucson, AZ; Sylvester Comprehensive Cancer Center, Miami, FL; Meyer Prentis Comprehensive Cancer Center, Detroit, MI; Roswell Park Cancer Institute, Buffalo, NY; Kaplan Comprehensive Cancer Center and Memorial Sloan-Kettering Cancer Center, New York, NY; Duke Comprehensive Cancer Center, Durham, NC; Fox Chase Cancer Center, Philadelphia, PA; M.D. Anderson Cancer Center, Houston, TX.

NCI Advisory Group, Other Cancer Meetings For Feb., March, Future

Cutaneous Malignancies: 1992 Skin Cancer Update--Jan. 31-Feb. 2, La Jolla, CA. Contact Susan Buntjer, Conference Coordinator, Scripps Clinic & Research Fdn., phone 619/554-8556.

Imaging in the Health Sciences--Jan. 31-Feb. 2, Houston, TX. Contact Jeff Rasco, Conference Services, M.D. Anderson Cancer Center, phone 713/792-2222.

American Assn. for the Advancement of Science--Feb. 6-11, Chicago, IL. Contact Nan Broadbent, AAAS, 202/326-6431.

Radiation Therapy Oncology Group Semi-Annual Meeting--Feb. 7-9, Philadelphia. Contact Nancy Smith, RTOG, 1101 Market St., Suite 1400, Philadelphia, PA 19107, phone 215/574-3205.

Aging: The Quality of Life--Feb. 10-12, Washington, D.C. Contact Suzanne Kuntz, 202/639-4524.

Molecular Oncology as a Basis for New Strategies in Cancer Therapy--Feb. 10-14, Honolulu, HI. Contact American Assn. for Cancer Research, Public Ledger Bldg., 620 Chestnut St. Suite 816, Philadelphia, PA 19106, phone 215/440-9300.

Oncology Nursing Conference--Feb. 11-14, Houston, TX. Contact M.D. Anderson Cancer Center, Jeff Rasco, phone 713/792-2222.

Current Concepts in Cancer Management: Symposium for Primary Care Physicians & Cancer Care Providers--Feb. 13-15, Newport Beach, CA, Hoag Cancer Center. Contact Meeting Management, 5665 Oberlin Dr., Suite 110, San Diego, CA 92121, phone 619/453-6222.

ACS National Conference on Prostate Cancer--Feb. 13-15, San Francisco. Contact Andy Cannon, American Cancer Society, 1599 Clifton Rd. NE, Atlanta, GA 30329, phone 404/329-7604.

Cancer Management Course--Feb. 17-18, San Juan, Puerto Rico. Contact Dr. Reynold Lopez, American College of Surgeons, 55 East Erie St., Chicago, IL 60611, phone 312/664-4050.

Clinical Hematology & Oncology--Feb. 17-19, La Jolla, CA. Contact Susan Buntjer, Scripps Clinic & Research Foundation, phone 619/554-8556.

President's Cancer Panel--Feb. 21, San Francisco, CA. Cole Hall, Univ. of California San Francisco, Medical Sciences Bldg., 513 Parnassus Ave. Open 8:30 a.m.

Society of Toxicology--Feb. 23-27, Seattle, WA. Contact Society of Toxicology, 1101 14th St. NW, Suite 1100, Washington, D.C. 20005, phone 202/371-1393.

NCI Div. of Cancer Treatment Board of Scientific Counselors--Feb. 24-25, NIH Bldg. 31 Conf. Rm. 6, open 8:30 a.m.

Cancer Education Review Committee--Feb. 24-25, Holiday Inn, Chevy Chase, MD. Open Feb. 24 8:30-9 a.m.

Cancer Research Manpower Review Committee--Feb. 25-28, St. James Hotel, 950 24th St. NW., Washington, DC. Open Feb. 25 7:30-8 p.m.

Frontiers in Cancer Care: Grief--Feb. 28, Cleveland, OH. Contact Education Coordinator, Ireland Cancer Center/Case Western Reserve Univ., phone 216/844-7858.

Generating Designer Ligands for Biological Targets--March 1-2, Holiday Inn Crowne Plaza, Rockville, MD. Contact Dr. Roy Wu, NCI, Cancer Therapy Evaluation Program, 301/496-8866.

International Conference on Monoclonal Antibody Immunoconjugates for Cancer--March 5-7, San Diego, CA. Contact Cass Jones, Professional Conference Management, 619/565-9921.

Cancer Nursing: AIDS-Related Lymphomas--March 6, Cleveland, OH. Contact Education Coordinator, Ireland Cancer Center/Case Western Reserve Univ., phone 216/844-7858.

Controversies in the Management of Breast Cancer--March 6-7, New York City. Contact Ann Boehme, Long Island Jewish Medical Center, 718/470-8650, fax 516/352-4081.

American Society of Preventive Oncology Annual Meeting--March 14-16, Bethesda, MD. Contact Dr. Richard Love, ASPO, 1300 University Ave., Madison, WI 53706, phone 608/263-6919.

Society of Gynecologic Oncology Annual Meeting--March 15-18, San Antonio, TX. Contact SCO, 312/644-6610, fax 312/527-6640.

Society of Surgical Oncology Annual Meeting--March 15-18, New York City. Contact SSO, 508/526-8830.

NCI Div. of Cancer Biology, Diagnosis & Centers Board of Scientific Counselors--March 16, NIH Bldg. 31 Conf. Rm 6, open 8:30 a.m.

German Cancer Congress--March 16-22, Berlin, Germany. Contact Deutsche Krebsgesellschaft, Paul Ehrlich Str. 41, 6000, Frankfurt am Main 70, Germany.

NCI-EORTC Symposium on New Drugs in Cancer Therapy--March 17-20, Amsterdam, The Netherlands. Contact EORTC New Drug Development Office, Free University Hospital, De Boelelaan 1117, NL-1081 HV Amsterdam, The Netherlands, phone 31-(0)20-5487881, fax 31-(0)20-5486101.

Advances in Cancer Treatment Research & Autologous Bone Marrow Transplantation Symposium--March 18-20, New York City. Contact Office of Continuing Medical Education, Montefiore Medical, 212/920-6674.

Current Perspectives in Cancer Therapy: The Multimodal Approach--March 18, Cleveland, OH. Contact Education Coordinator, Ireland Cancer Center/Case Western Reserve Univ., 216/844-7858.

Cancer & AIDS: Integrating Science, Medical Practice & Health Policy--March 23-25, Paris, France. Contact International Society for Global Health Policy, 74 Ave., Kleber, 75016 Paris, France, phone 47.27.01.39.

NCI Div. of Cancer Etiology Board of Scientific Counselors--March 26-27, NIH Bldg. 31 Conference Room. Open 1 p.m.-adjournment March 26 and 9 a.m.-noon March 27.

Cancer Centers Support Grant Review Committee--March 26-27, Hyatt Regency, Bethesda. Open 8-8:30 a.m. March 26.

Future Meetings

Illinois Cancer Center Conference--April 8, Chicago, IL. Contact Carole Johnson, ICC, 312/986-7033, fax 312/986-0404.

J. Donald Woodruff Symposium on Gynecologic Oncology--April 9-11, Baltimore, MD. Contact Johns Hopkins Office of Continuing Education, 410/955-2959.

Transcriptional Control of Cell Growth & Oncogenesis--April 23-24, Chapel Hill, NC. Contact Dianne Shaw, Public Information, UNC Lineberger Comprehensive Cancer Center, 919/966-3036.

Molecular Basis for Cancer Prevention--April 24, Memphis, TN. Contact Dr. James Hamner, Univ. of Tennessee, 901/528-6354.

Advances in Internal Medicine--April 27-May 1, Ann Arbor, MI. Contact Angela Stewart, Univ. of Michigan, 313/763-1400.

Innovations in Oncology Social Work--April 29-May 2, Detroit, MI. Contact Andrea Andrlik, Social Work Service, VA Hospital, 708/216-2100, fax 708/832-6945.

Stem Cell Factor & Cytokines in Congenital Bone Marrow Dysplasias--May 1-2, Bologna, Italy. Contact Dr. Ann Murphy, Hipple Cancer Research Center, 513/293-8508, fax 513/293-7652.

Advances in Pain Management--May 28-31, Cleveland, OH. Contact Cleveland Clinic Educational Foundation, 800/762-8173, fax 216/445-9406.

Challenges and Controversies in Cancer Research--Sept. 9-12, Columbus, OH. Contact Nancy Jones, Arthur James Cancer Hospital, 300 W.10th Ave., Columbus, OH 43210.

Chemotherapy Foundation Symposium: Innovative Cancer Chemotherapy--Nov. 11-13, New York City. Contact Jaclyn Silverman, Mount Sinai School of Medicine, 212/241-6772.