THE CANCER LETTER

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Epstein Alleges Conflict Of Interest Of Former Panel Chairmen And Sloan-Kettering Directors

Invited to the inner sanctum of what he calls "the cancer establishment," Samuel Epstein intensified his offensive by alleging conflict of interest on the part of two former chairmen of the President's Cancer Panel.

Speaking before the National Cancer Advisory Board last week, Epstein said Benno Schmidt, the first Panel chairman, "has deep and

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In Brief

ACS Committee Picks Seffrin For Executive VP; Charles Wilson Named To NCAB; 5 Leave Board

JOHN SEFFRIN has been selected for the position of executive vice president of the American Cancer Society, to succeed William Tipping, **The Cancer Letter** has learned. A search committee chaired by former national executive VP Robert Gadberry chose Seffrin last week from a list of 10 candidates. Seffrin served as chairman of the ACS Board of Directors from 1989-91. The committee will present its recommendation to the Board of Directors at its meeting June 2-6 in Portland, OR. . . . **CHARLES WILSON**, director of the Brain Tumor Research Center at the Univ. of California (San Francisco), has been appointed to the National Cancer Advisory Board, the White House announced last week. Wilson takes the seat vacated by Kenneth Olden, who as director of the National Institute of Environmental Health Sciences, is now an ex-officio member of the Board. . . . **FIVE NCAB** members have served out their terms: **John Durant, Bernard Fisher, Phil Frost, Irene Pollin**, and **Zora Brown.** They may continue to serve until the White House names their replacements. Brown, who took **Nancy Brinker's** seat when Brinker was named to the President's Cancer Panel, is expected to be reappointed to the Board for a full term. . . . **PRESIDENT'S CANCER** Panel is scheduled to meet June 8, 9:30 a.m.-1 p.m. at the American Health Foundation, 320 E. 43rd St., New York, to discuss "Cancer In Minority Populations: Opportunities and Obstacles." . . . **DONALD (Skip) TRUMP**, director of experimental therapeutics at Duke Univ. Comprehensive Cancer Center, was named deputy director for clinical investigations at Pittsburgh Cancer Institute. Trump will assume the newly created position on July 1. At Univ. of Pittsburgh Medical Center, Trump will serve as professor of medicine and surgery and co-director of urologic oncology. . . . **MARY JOY JAMESON** was named vice president, public affairs, of Memorial Sloan-Kettering Cancer Center.

Epstein Intensifies Offensive Against 'Establishment,' Alleges Conflicts

(Continued from page 1)

close personal ties with drug industries." The late Armand Hammer, Epstein said, "was chairman of Occidental Petroleum, one of the nation's leading producers of carcinogenic chemicals."

Further, Epstein said, the Board of Overseers of one of the nation's leading cancer centers, Memorial Sloan-Kettering, is dominated by representatives of the pharmaceutical and chemical industries. MSK directors also serve as directors of drug, oil, steel, automotive, and other companies and the center owns stock in several drug companies, Epstein said.

"This is an important concept because the Sloan-Kettering clearly represents a very substantial segment of the scientific community which constitutes a powerful national lobbying and pressure group," Epstein said. "The Memorial Sloan-Kettering is an excellent example of how the major decision making body in the prototype national cancer center is dominated by industrial and drug company interests."

Schmidt, who chaired the committee whose recommendations led to the National Cancer Act of 1971, was traveling and unavailable for comment early this week.

"We will decline the opportunity to comment," a spokesman for Memorial Sloan-Kettering told **The Cancer Letter.**

A Two-By-Four

"For the last 20 years, I have been attempting, and others have been attempting, to influence NCI more and more in the direction of primary cancer prevention," said Epstein at the May 5 presentation. "The first time we got your attention was when you were hit over the head with a two-by-four. And I'm delighted we have your attention now."

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The proverbial piece of lumber Epstein was referring to was the publicity he received as a result of a Feb. 4 press conference in Washington, paid for by Food & Water Inc., an environmental group that has received funding from a tobacco family foundation (see story, page 5). The publicity figured heavily into the decision to invite Epstein to the NCAB, NCI sources said.

Epstein, professor of occupational and environmental medicine at Illinois Univ., repeated the arguments he made in a statement signed by more than 60 supporters: NCI has misled the public and Congress by overstating gains in treatment of cancer while ignoring the role of industrial carcinogens. The statement was inserted in the April 2 "Congressional Record" by Rep. John Conyers (D-MI), chairman of the House Government Operations Committee.

"Let me assure you that we welcome criticism and any discussion on a high scientific plane," NCAB Chairman Paul Calabresi said to Epstein.

Basic Research Not Relevant?

Much of Epstein's presentation echoed the claims he made at the February press conference and in newspaper opinion pieces (**The Cancer Letter,** Feb. 14 and May 1). New allegations included:

▶Basic research, particularly molecular biology, is not relevant to cancer "in general." Epstein quoted a remark attributed to David Baltimore to that effect, and called research on mechanisms "a game."

▶Cancer survival rates are "near static" and treatment results are based mainly on tumor response. Epstein quoted, among others, NCI Div. of Cancer Treatment Director Bruce Chabner.

▶Epstein said NCI's estimates on lifestyle risk factors are based on an "obsolete analysis" by Richard Doll and Richard Peto. NCI calculates that 35% of cancer is related to diet, 30% tobacco, 7% reproductive/sexual behavior, 4% occupational, 3% alcohol, 3% geophysical factors, 2% pollution, 1% industrial products, and 1% medicine and medical procedures.

▶NCI's definition of primary cancer prevention is too broad. "Chemoprevention is important but irrelevant to primary prevention," Epstein said.

▶NCI's response to his criticism amounted to "scientific McCarthyism," he said.

He recommended that NCI conduct a national campaign to inform the public "that much cancer is avoidable and due to past exposures to chemical and physical carcinogens" and "provide scientific expertise to Congress on primary cancer prevention."

In particular, Epstein said, NCI should tell Congress about, "the validity of extrapolation to humans of data

from valid animal carcinogenicity tests; the invalidity of using insensitive or otherwise questionable epidemiological data to negate the significance of valid animal carcinogenicity tests; and the scientific invalidity of efforts to set safe levels or thresholds for exposure to chemical and physical carcinogens. NCI should stress that the key to cancer prevention is reducing or avoiding exposure to carcinogens, rather than accepting and attempting to manage such risk."

Further, Epstein called for the expansion of the NCI program for occupational and environmental cancer studies.

"Do You Have Any Data?"

"I think the bottom line is, are we a perfect institute? No. Do we try to do what is right? I think we do. Can we learn from dialogue? I think the answer is yes," NCI Director Samuel Broder said.

"There are important issues related to environmental carcinogenesis and prevention, and they are important enough, and they are complicated enough that they will require our full time attention on a scholarly basis," Broder said. "I would hope that one need not invoke on either side of the debate some additional non-scientific agenda or some issue related to motivation or conflicts."

President's Cancer Panel member Geza Jako, who has been critical of NCI in the past, asked Epstein about the NCI estimate of 4% incidence of occupational cancers: "Do you have any scientific data that would show that it is greatly different than 4%?"

"There is no evidence whatsoever to support this 4%," Epstein said. "These estimates of Doll and Peto are based on data from 1933 to 1977, times at which occupational exposures were very low. Doll, Peto and [former NCI staff member Marvin] Schneiderman, who examined these issues in great detail, have agreed that the estimates would account for up to 20-40%, as opposed to 4.6%."

The latter statement was resourceful. Doll and Peto, in a 1981 paper published in the "Journal of the National Cancer Institute" and later published as a book, "The Causes of Cancer," disparaged the 20-40% estimate as politically motivated and the method used to reach it "defective." However, as Epstein said, Doll and Peto agreed that the (erroneous) method would account for the (erroneous) estimate.

Schneiderman was a contributor to the 1978 paper that proposed the 20-40% estimate of occupational cancer incidence, along with former NIEHS director David Rall, who some consider the key force behind the estimate. The paper listed 10 "contributors," but no one has been publicly identified as the author, and the paper was never published in a scientific journal. It was filed by the Occupational Safety & Health Administration in a post-hearing record, and became known as "the OSHA paper."

HEW Secretary Joseph Califano first used the estimate in a speech to the AFL-CIO.

Over the next few years, Epstein and others used it to pressure for funding for occupational studies, while other scientists criticized NCI for producing an inaccurate estimate. NCI was in a difficult position, unable to issue a correction for an unpublished study.

The Congressional Office of Technology Assessment commissioned Doll and Peto to analyze the estimate. They wrote:

"It seems likely that whoever wrote the OSHA paper did so for political rather than scientific purposes, and it will undoubtedly continue in the future as in the past to be used for political purposes by those who wish to emphasize the importance of occupational factors.... we would suggest that the OSHA paper should not be regarded as a serious contribution to scientific thought and should not be cited or used as if it were. (Furthermore, any suggestions which derive directly or indirectly from it that 20, 23, 38 or 40% of cancer deaths are, or will be, due to occupational factors should be dismissed.)"

'Ad Hominem Attacks From NCI'

In his response to Jako's question, Epstein also said a New York group studied occupational cancer deaths in that state and made "a conservative estimate of minimally 10 percent of cancer deaths in New York are occupational."

"My question, which you didn't answer, was whether your institution has any scientific data or statistics that would greatly change this estimate," Jako said. "This is what Dr. Broder was referring to--let's leave this discussion on a scientific basis."

"I think the terminology you use is highly controversial and adversarial," NCAB member Fred Becker told Epstein. "I don't know if those were the terms used in that [New York] article. What would have been given in an accurate scientific article was the actual percentage estimated and then the statistical variation.

"I agree with you 100% that we should not recede to scientific McCarthyism," Becker said. "But I think you come perilously close to it yourself. You referred repeatedly to the 'cancer establishment' as if there were some vast conspiracy--and perhaps you feel there is--of the hundreds and thousands of people who work tirelessly.... I know many of the workers at Sloan-Kettering are dedicated scientists and not driven by what the board thinks.

"I think we would do better not to use a term that

was last popularized by the defenders of laetrile when they talked about the 'cancer establishment,'" Becker continued. "If we go to Congress, let's plead for more money to be given equally to all of the disciplines, because I assure you those of us who work in cancer institutes could not ignore the people who are suffering from cancer today. So I plead with you to join in with what Sam [Broder] said, avoid these terms and these suggestions of accusation and really keep this on the basis where, by providing the data, you can identify the proper target. And we would certainly support you on that basis."

"Dr. Becker, this approach was a carefully considered document based on the input of 65 scientists who have been frustrated over the last two decades," Epstein said. "The ad hominem attacks have come from NCI--being called a menace, being called a gadfly, being called unethical, that's what I call scientific McCarthyism."

In Defense of Treatment, Chemoprevention

"I agree there are different approaches to prevention," Board member Sydney Salmon told Epstein. "But I think you've lost sight of the fact that the mission of the National Cancer Institute is to overcome cancer as a problem and do it as quickly as effectively as we can, whether it be with treatment, or with prevention. And if its prevention, whether primary or secondary, if we can prevent it, treat and cure it, those are the goals."

Salmon said the Breast Cancer Prevention Trial, the largest chemoprevention trial to date, "may make a major reduction in breast cancer incidence, and that could give a far quicker result than the longer term approaches to primary prevention."

In addition, Salmon said he objected to Epstein's statement that treatment results are based on tumor shrinkage. "I have to point out that the Food & Drug Administration does not approve anticancer drugs on the basis of tumor shrinkage. Complete remission, disappearance of all evidence of cancer, is accepted as an intermediate marker for improved survival."

Epstein replied: "As far as treatment is concerned, I simply quoted from the General Accounting Office, from Rifkind, from Chabner, saying we haven't achieved any significant advance in our ability to treat and cure cancer with the exception of childhood cancers. That's all there is to it."

"You've misquoted me!" Chabner interrupted. "You've used my name twice!"

"Hold on a second, I have a direct quote from you which I put on a slide," Epstein went on.

The Chabner quote on the slide read: "In patients with disseminated forms of the common epithelial tumors, both complete remissions and cures continue to elude us." (NAGAM, 1992)

"Yes, one sentence out of a whole article. You neglected the rest of it," Chabner said.

"As far as the tamoxifen study, the fact is this, tamoxifen is a potent carcinogen," Epstein continued. "Whether or not one should give tamoxifen to a significant number of women without warning is a matter which I haven't discussed now."

You, Sir, Are Unfamiliar With The Literature

After the presentation Epstein faced a small group that gathered around the lectern.

"I cannot believe that basic research and basic researchers are playing a game and that the advances that have been made as part of that game will not be of significance," said Becker to Epstein.

EPSTEIN: "I've probably done as much basic research in cancer as you or many other people in this room. I believe in basic research. I believe, however, that the overwhelming budget on basic research, particularly oncogenes and molecular biology is irrelevant, because, number one, I don't think mechanisms is relevant to prevention. Number two, this work should be more appropriately undertaken in [the National Institute of] General Medical Sciences. This is the view of a growing body in Congress that we're starving other institutes."

BECKER: "You think it's irrelevant unless it's done in General Medical Sciences."

EPSTEIN: "I think that what we're talking about is basic molecular biology--"

BECKER: "And it's not going to be relevant."

EPSTEIN: "--which is basic to the whole field of interest in the whole field of biology. It so happens that it's easier to get money for cancer research, and this is the point of the quotes I gave."

BECKER: "You really believe that if you got Dave Baltimore here today in front of us, he would say that his discoveries are not relevant to cancer?"

EPSTEIN: "Now, look, Dave is an old friend of mine. I can't answer what he would say. I have quoted to you what he stated--"

BECKER: "You also quoted a conversation about a study done in New York and gave it as if it were data."

EPSTEIN: "Yes."

BECKER: "The data said 10% minimal--"

EPSTEIN: "That trivializes it--"

BECKER: "'Trivializes' is a word you have used 36 times today."

(Becker steps away, but remains in the room.)

EPSTEIN: "Nice to see you Fred, best of luck."

(Enter Ralph Yodaiken, representative of the Dept. of

Labor on the Board.)

YODAIKEN: "I think you've done something that's lovely. I've sat on this board for nine years and there's never been any discussion of pesticides, and this is the first time we've discussed them."

EPSTEIN (to Becker): "Oh Fred, listen to this a second, will you please?"

BECKER: "No."

EPSTEIN: "He just said he's sat on this board for nine years and there's never been a discussion of pesticides. It's the first time the subject has come up."

BECKER: "My grant on chlordane proving that it was a carcinogen came from NCI."

JAKO (to Epstein): "Do you subscribe to **The Cancer Letter**?"

EPSTEIN: "I'm afraid not, no."

JAKO: "Because that gives you a general overview of what goes on at the Board. Now, when you refer to the cancer establishment--"

EPSTEIN: *(Leans against a slide projector screen and falls down, quickly recovers)* "My god--"

YODAIKEN: "It's not enough to say the exposures in the 1933 to 1977 series were less. There might have been fewer exposures or fewer substances."

EPSTEIN: "No, no, you see, essentially, the point was, in the early '30s and '40s, the studies on occupational were very few and far between. Now what we've seen is a plethora of studies. This is the whole point.... So, Ralph, what are you doing these days?"

YODAIKEN: "I'm a senior advisor to the Dept. of Labor, and I went to Sam Broder previously and said, why don't you get somebody up here to talk about occupational cancer. And he dismissed it like that."

EPSTEIN: "They've been impossible to persuade. The only reason NCI invited me is because of the publicity. However, I hope it's going to be a constructive dialogue."

JAKO: "You always refer to the cancer establishment."

EPSTEIN: "Yes, not only I. The group of 65 refer to it."

JAKO: "I served on the NCAB and do you think the Board action is to approve everything which the director says?"

EPSTEIN: "No, not at all."

JAKO: "There is quite a bit of discussion, and quite a bit of controversy."

EPSTEIN: "I've read the transcripts for many years."

JAKO: "There are different views."

EPSTEIN: "The representation of those interested in primary prevention is minimal. Minimal to nonexistent. This is my point."

JAKO: "Because the government deals with those areas in the Agriculture Department, in--

EPSTEIN: "Oh, come on. There are innumerable mechanisms where NCI could provide scientific expertise and guidance. I'm not talking about regulation."

JAKO: "But, you see--"

EPSTEIN: "I'm talking about providing scientific expertise to Congress, when Congress--"

JAKO: "But we need your scientific expertise backed up with scientific data."

EPSTEIN: "The scientific data are there."

JAKO: "No, there isn't."

EPSTEIN: "You're unfamiliar with the literature."

JAKO: "I asked you, provide the Cancer Institute with scientific data--"

EPSTEIN: "Oh, come on. You're unfamiliar with the literature, the literature on pesticides are overwhelming. The literature on occupational cancer are overwhelming. You, sir, are unfamiliar with the literature!"

Exeunt.

Food & Water Group Receives Grants From Reynolds Foundation, Others

Food & Water Inc., the environmental group that has backed Samuel Epstein and 60 other supporters in their criticism of the National Cancer Program, has received grants from the Mary Reynolds Babcock Foundation, part of the Reynolds tobacco family fortune.

Walter Burnstein, president of Food & Water, told **The Cancer Letter** that the nonprofit organization receives funding from 10 to 15 foundations, including MRBF, based in North Carolina.

"The entire younger generation of the Reynolds family are all against smoking," Burnstein said. "They use their money for environmental causes."

Food & Water received $30,000 in November 1989, $50,000 in November 1990, and $3,000 last June from the foundation, according to "21st Century Science & Technology." Food & Water would not confirm those amounts.

Food & Water spokesman Christy Nelson said the foundation support was specifically for the group's work on food irradiation, not for the group's cancer prevention campaign. The group also receives funds from individuals, she said.

Epstein told **The Cancer Letter**, "Nobody funds my research. I have not received a penny since I was declared mortal enemy number one in the Reagan Administration in 1981. I do this at my own expense."

NCI Budget Includes $645 Million For Cancer Prevention, NCAB Told

NCI will spend one-third of its budget on prevention this year, NCI Div. of Cancer Etiology Director Richard Adamson told the National Cancer Advisory Board last week.

NCI's total prevention budget for FY 1992 is $645 million, of which $334.7 million is primary cancer prevention and $106.2 million is cancer prevention and control, a separate line item. Those figures for FY93: $646.5 mil., $327 mil., and $91 mil.

Adamson and NCI Div. of Cancer Prevention & Control Director Peter Greenwald presented the Institute's response to criticism made by Samuel Epstein at the meeting.

Epstein argued that NCI's definition of primary cancer prevention is too broad, and includes chemoprevention. He asked NCI to organize a public debate on the definition. "Primary prevention is preventing people from being exposed to carcinogens, which will end up with a significant proportion of them getting cancer," Epstein said.

Primary Prevention 'Narrowly Defined'

"Total prevention research," Adamson said, "includes research with a high probability of yielding results that will likely be applicable to disease prevention or health promotion. Included are studies aimed at elucidating the chain of causation--the etiology and mechanisms--of acute and chronic diseases. Such basic research efforts generate the fundamental knowledge that contributes to the development of future preventive interventions.

"Primary cancer prevention is narrowly defined and includes only that research designed to yield results directly applicable to identification of risk, and to interventions to prevent disease or the progression of detectable but asymptomatic disease," Adamson said.

NCI will spend $270 million this year on studies of environmental carcinogenesis, including $17 million on occupational cancer. The amounts will increase in FY93 to $301 million and $19.3 million, Adamson said.

"Environmental carcinogenesis research is defined as research to identify or characterize the mechanism of action of exogenous agents, conditions, or procedures that initiate, promote, or otherwise contribute to the development of cancer," he said. "Examples include atmospheric pollution, occupational or medical exposure to radiation or chemicals, dietary components or contaminants, tobacco use, radon or other substances that contaminate the air or drinking water, exposure to ultraviolet radiation or electromagnetic fields, etc.

"NCI gives serious consideration to occupational factors in cancer causation and supports numerous investigations intramurally, extramurally and by interagency agreement on occupational exposures that may contribute to cancer causation.

"Numerous laboratory and epidemiology studies and studies linking epidemiological studies with laboratory studies are being conducted on environmental agents," Adamson said, showing a long list of the agents under study.

"Although biological agents are not included among the environmental carcinogenesis budget, within the last several years it has been learned that viruses are strongly implicated or are a causal factor in numerous human cancers. Among these viruses are human papillomavirus, hepatitis B virus, hepatitis C virus, HTLV-I and HTLV-II, HIV, and the Epstein-Barr virus. Such viruses are environmental factors and cannot be ignored in cancer causation."

Tobacco Smoking's Negative Impact

Adamson continued: "Unquestionably, however, lifestyle factors contribute to the toll of human cancer and the single most identifiable cause of cancer--and other diseases--in the U.S. is tobacco smoking. It would be difficult to exaggerate the enormous negative impact of tobacco on human health. The substantial body of evidence consisting of several thousand scientific studies allows the conclusion that smoking is a major cause, not only of lung cancer, but of cancer of the larynx, oral cavity, pharynx and esophagus. It contributes to cancer of the bladder, kidney and pancreas because the tobacco carcinogens are absorbed in the bloodstream and transported to multiple remote sites in the body.

"Cigarette smoking can also interact with occupational exposures, such as asbestos and radon, to significantly increase the risk of lung and possibly other cancers in workers exposed to such agents. NCI conducts both intramural and extramural studies on the contribution of smoking and smoking plus occupational exposures to cancer.

"A paper in the April 1 issue of 'Cancer Research' highlights why investigations into chemical carcinogenesis must take into account dosage, the problem of species extrapolation and studies on mechanism of action. Uracil, a component of your and my RNA, is a nongenotoxic carcinogen in mice and rats at high doses (i.e., at 3%), but not at lower doses because it induces urinary calculi and severe epithelial hyperplasia in the urinary bladder. Certainly, we don't have to be fearful of the uracil in our body or liver.

"NCI currently has in place and supports a comprehensive and balanced program of experimental,

epidemiological, multidisciplinary and clinical research that gives it the capability and credibility at both the national and international level to ask and answer questions in environmental carcinogenesis, cancer biology, cancer therapy, and to develop prevention measures," Adamson said.

'We Need A Balanced Approach'

"We do have unfunded opportunities in prevention, but we need a balanced approach," Greenwald told the Board. "There are also unfunded opportunities in treatment, in therapy, so it's not one or the other."

DCPC and its Board of Scientific Counselors have begun the process of re-examining the Year 2000 goals NCI put forward in 1986. Greenwald said there are some areas to be enthusiastic about, such as the decrease in smoking prevalence from 30 percent in 1980 to 25 percent this year.

NCI's estimate that 35 percent of cancer is due to diet, based on work by Richard Doll and Richard Peto, "will continue to be controversial until we get data from the Women's Health Trial," Greenwald said. At a talk in Atlanta this year, Doll tightened his estimate, Greenwald said, from 35 percent with a range of 10 to 70 percent, to 35 percent with a range of 20 to 60 percent.

Breast cancer mortality has dropped by 10 percent from 1979-1989, and the incidence rate is increasing, which some people think is due to the increase in early detection, through the use of mammography, Greenwald said. "It would take compelling evidence for us to make a change in our policy" recommending mammography for women over 40, he said.

"Our prediction is that the higher incidence rate will be reflected in lower mortality that we will be able to show you in 1996, when the 1992 data is available," Greenwald said.

Stanford Group Working To Build 'Superhighway' To Taxol Synthesis

"Chemical synthesis has been likened to technical mountain-climbing," Stanford Univ. chemistry professor Paul Wender told the National Cancer Advisory Board last week. "The issue with taxol, however, is not to plant the flag, but to build a superhighway to the top."

Wender and his collaborators are feverishly bulldozing their way up the allegorical mountain and could be the first to open an economical route to taxol.

Several laboratories are trying to make taxol and taxol-like compounds, but most strategies, including the semisynthetic drug taxotere, still depend on extracting small amounts of taxol precursors from large masses of plant material.

Wender's group found a way to skip the extraction step by synthesizing taxol from pinene, a constituent of pine trees that is the main ingredient in turpentine, and contains 10 of the 20 carbons of taxol. Pinene is available in 55 gallon drums and is "as cheap as potting soil," he said.

Relying on work done by a graduate student, Tom Mucciaro, the group has converted pinene into the complex three-ring core of taxol in five chemical steps, shining light on the material at one point. In another three steps, including treating the molecule with air, the scientists complete the "A" ring in exactly the form required for taxol.

The next obstacle is to complete the "C" ring in a few more steps, for a total of 13 steps to the "final phase of synthesis," Wender said.

"We are now in the final phase," Wender told the Board. "There is excitement in the lab. Most of us are getting only survival sleep." One graduate student is working 20 hours a day, he said.

The process could easily be scaled up, and uses cheap materials--light and air. Wender's paper on the work will be published in the "Journal of the American Chemical Society."

It is still too early to do cost comparisons of taxol-making methods, Wender told the Board. "We're not in the position yet to say what the cost would be, but we are driven by cost. Any method that is not cost-effective would not be a solution. That's why we are driven to seek low cost reagents, like air."

"We are on the road to total synthesis of taxol," NCI Director Samuel Broder said.

Wender was one of several chemists who presented work on taxol to the American Chemical Society annual meeting recently in San Francisco. Others working on the problem include:

▶Pierre Potier, Chemical Institute of Natural Substances, France, uses a chemical precursor, baccatin III, found in the leaves of the yew. Baccatin is converted into the chemical analog of taxol called taxotere. Rhone-Poulenc Rorer Inc. holds U.S. and European patents on taxotere, and is expected to sign a Cooperative Research & Development Agreement with NCI to test the drug in clinical trials and seek FDA approval.

Potier said taxotere was somewhat more effective in early clinical trials than taxol against some cancers, and is more soluble in water.

▶Robert Holton, Florida State Univ., described synthesis of chemical parts of taxol and linking them to baccatin or other molecules. Holton said he and his colleagues have made more than 60 taxol analogs.

▶Arthur Goldstein, of ESCAgenetics Corp., described the process of growing in culture the cells of the yew that produce taxol. He said the company expects to make large quantities of this type of taxol by next year.

RFAs Available

RFA CA-92-05

Title: **National collaborative radiation therapy trials: 3-D dose escalation study for prostate cancer**

Letter of Intent Receipt Date: June 1

Application Receipt Date: Aug. 26

The Radiation Research Program (RRP) of NCI's Div. of Cancer Treatment invites applications for cooperative agreements to carry out National Collaborative Radiation Therapy Trials: 3-D Dose Escalation Study for Prostate Cancer. The objectives of the solicitation are (1) to conduct Phase I, II, and III clinical trials to test the efficacy of using 3D conformal radiation therapy in a dose escalation study for the treatment of prostate cancer, and (2) to collect 3-D dose distributions and data on radiation-induced damage to normal tissues.

Applications may be submitted by domestic and foreign for-profit and non-profit organizations, public and private. Applications from minority individuals and women are encouraged.

Awards will be made as cooperative agreements (U01). Total project period may not exceed three years. Anticipated award date will be April 1, 1993. Approximately $750,000 in total costs per year for four years will be committed to fund applications. NCI anticipates a single award for funding of an Operations and Statistical Center, and up to four to five separate awards to radiotherapy centers for a period of four years.

The objective of this RFA is to support multicenter cooperative clinical trials to conduct disease-specific Phase I and II studies using 3-D conformal radiotherapy (3DCRT) techniques that will define a new maximum-tolerated dose (MTD) beyond standard radiation therapy for prostate cancer treatments. Should the Phase II results be sufficiently convincing that a new MTD has been reached, the Cooperative Group will proceed to Phase III trials in which 3DCRT will be compared with best standard conventional therapy for prostate cancer. The Cooperative Group, through the Executive Committee, will also define protocols for scoring radiation injury as a function of dose and volume to the normal tissues at risk for this disease, which is to be incorporated into a new 3D database for future reference and use by scientific investigators.

NCI intends to support these trials by the awarding of cooperative agreements to participating institutions that have the capability of planning and delivering 3-D conformal radiation therapy and to a single organization or institution that is capable of coordinating the multi-institutional studies and serving as a data management and analysis center.

Written and telephone inquiries, and letter of intent, may be directed to Dr. Sandra Zink, Program Director, Radiation Research Program, NCI, Executive Plaza North, Suite 800, Bethesda, MD 20892, phone 301/496-9360, fax 301/480-5785.

RFA CA-92-16

Title: **Hypothesis driven clinical correlations in hematologic malignancies**

Letter of Intent Receipt Date: June 17

Application Receipt Date: Sept. 16

The Cancer Therapy Evaluation Program (CTEP) of NCI's Div. of Cancer Treatment and the Cancer Diagnosis Branch (CDB) of the Div. of Cancer Biology, Diagnosis and Centers (DCBDC) invite applications for cooperative agreements from institutions or consortia, such as DCT Clinical Trials Cooperative Groups, capable of and interested in performing hypothesis driven clinical correlative studies relevant to the cancer treatment or clinical outcome of patients with hematologic malignancies. It is essential for institutions to have access to biologic samples and outcome data for a sufficient number of patients on phase III clinical protocols to be able to test correlative hypotheses. Hematologic malignancies that are relevant to this RFA include leukemias, lymphomas, myelomas, and myelodysplastic syndromes.

Domestic and foreign for-profit and not-for-profit organizations, governments and their agencies are eligible to apply. Applications from minority individuals and women are encouraged. The Applicant Institution must have access to a Central Operations Office and a Statistical Center for coordination of research activities and data analysis.

Support of this program will be through the cooperative agreement (U01). Approximately $2 million in total costs per year for four years will be committed to fund applications. It is anticipated that 10-12 awards will be made. The total project period for applications may not exceed four years. The earliest feasible start date for the initial awards will be August 1, 1993.

The objectives of this RFA are to foster collaborations and interactions between basic researchers and clinical investigators to advance therapeutic clinical research and conduct hypothesis driven correlative studies in hematologic malignancies that are ready for large scale evaluation. Hematologic malignancies relevant to this RFA account for significant cancer incidence, morbidity, and mortality. Special consideration will be given to studies with acute promyelocytic leukemia, multiple myeloma, chronic lymphocytic leukemia, acute myeloid leukemia, and acute lymphocytic leukemia. Each application is expected to be focused on a specific hematologic malignancy. Applicants may propose to undertake several correlative studies relevant to the specific hematologic malignancy during the grant funding period. An individual scientist or a consortium of institutions may be included on more than one application.

The correlative studies should be based on strong and testable hypotheses. A clear rationale should be given for the experimental design and technical methodologies selected. The hypotheses tested must relate to potential clinical applications such as development of new treatment strategies or identification of patient subsets for specific treatment approaches. Preliminary data from appropriate tumor models or analysis of patient specimens must be provided to support the feasibility of each study. This RFA is not for developing new techniques or assays. Assays must have already been demonstrated to be applicable to tissue samples and/or body fluids. The laboratory assays must utilize tumor specimens from patients receiving defined treatments in large clinical trials such as phase III clinical protocols.

Applications must include a statistical section describing plans for analysis of data designed to test the hypotheses. Investigators are encouraged to work with multi-center organizations or form a consortium of institutions to access a sufficient number of patients and clinical information to test the proposed hypotheses. To coordinate the above activities, each institution must have access to a Central Operations Office and Statistical Center.

The letter of intent is to be sent to: Dr. Roy Wu, Cancer Therapy Evaluation Program, Div. of Cancer Treatment, NCI, Executive Plaza North, Room 734, Bethesda, MD 20892, phone 301/496-8866, fax 301/480-4663. Inquiries may be directed to Dr. Wu or to Dr. Sheila Taube, Diagnosis Branch/DCBDC, NCI, Executive Plaza South, Room 638, Bethesda, MD 20892, phone 301/496-1591, fax 301/402-1037.