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NCI Deputy Barker Hits FDA, Calls For New Incentives For Pharmaceutical Industry

Facing a crowd at a conference sponsored by the financier Michael Milken, Anna Barker, a deputy director of NCI and one of the architects of the Bush agenda in cancer research, said the criteria used in approval of cancer drugs must be revamped.

"The FDA currently approves cancer drugs only on one basis, with two exceptions, and that is survival," Barker said April 1, at a conference at the Beverly Hilton Hotel. "We have to change that. We are working with [FDA Commissioner] Mark McClellan directly at the NCI now to look at new ways to look at clinical benefit.

"Clinical benefit for cancer and survival are not necessarily the same thing," she continued.

Barker's title—NCI Deputy Director for Strategic Scientific Initiatives—suggests that in matters involving basic research, drug development, and criteria for drug approval, her views are not to be disregarded.

The contention that FDA demands that new cancer drugs demonstrate a survival advantage as a prerequisite for approval has been expressed time and again, usually by officials of pharmaceutical companies and the editorial writers at The Wall Street Journal. As the agency clings

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In Brief:

Edelson To Direct Yale Cancer Center

RICHARD EDELSON was appointed director of the Yale Cancer Center, effective July 1, said Yale University School of Medicine Dean **David Kessler** and Yale-New Haven Hospital President **Joseph Zaccagnino**. Edelson will succeed **Vincent DeVita Jr.**, who is stepping down as director on June 30 after completing his second term. Edelson is known for his work in cutaneous T-cell lymphoma. He devised the first FDA-approved selective immunotherapy, a treatment now referred to as transimmunization. Edelson, a 1970 graduate of the Yale School of Medicine, served as head of the Immunobiology Group in Columbia University's Comprehensive Cancer Center and as associate director of Columbia's General Clinical Research Center. He returned to Yale in 1986. He will continue in his current positions as professor and chairman of the Department of Dermatology. DeVita, a former NCI director, directed the cancer center for the past 10 years. DeVita will remain on the Yale faculty as professor of internal medicine, epidemiology, and public health.

RCTs "Not Our Best Answer," Barker Tells Industry Meeting

(Continued from page 1)

to outmoded standards, good drugs are being missed, these critics say.

There is a problem with this argument: it's factually wrong.

It is true that FDA generally requires a survival advantage for the first-line indications, but overall, few cancer agents are approved based on survival. According to a tally published in the April 1 issue of the Journal of Clinical Oncology, 39 of the 57 cancer drug approvals over the past 13 years were based on endpoints other than survival.

Other criteria for approval include tumor shrinkage, response duration, and time to tumor progression. Since April, two more cancer drugs were approved, neither of them on survival. The information is available on the FDA Web site.

It's unlikely that Barker misspoke. She has been making similar points in other venues. Her remarks are available at www.milkeninstitute.org. Barker's boss, NCI Director Andrew von Eschenbach, was in attendance at the conference.

In an interview, Barker reiterated that she regards survival as FDA's "major focus for cancer."

"They do approve drugs based on other endpoints, but survival obviously is the endpoint that leads to most drugs being evaluated on," she said. "We are obviously looking for endpoints that can serve as good clinically meaningful endpoints that might take us beyond survival. Having said that, we have to understand that a lot of people on outside, especially people who are the recipients of drugs, want to know that survival is part of the equation."

After slamming FDA, Barker moved to another target, randomized phase III trials, the gold standard of evidence-based medicine. "We discussed yesterday in a session with Mike Milken, we talked about the randomized, controlled clinical trial as being the poster child for the way we do research in this country in the clinic," Barker said. "But, in fact, that's not probably our best answer going forward. We are going to have to stratify patients, and do very specific kinds of trials."

In addition to being costly, phase III trials take time, and NCI has no time to waste. Recently, von Eschenbach, a urologist, pledged to "eliminate the suffering and death from cancer by 2015." Barker and von Eschenbach have yet to present a detailed plan for meeting this goal (**The Cancer Letter**, Feb. 14, May 16).

"I don't know that we have yet a fix on how to use pharmacogenomics and some of these markers to actually shorten the time that would be required for trials, especially some of the large randomized trials," Barker said in an interview.

In recent months, NCI officials and the American Association for Cancer Research, the professional society that served as a steppingstone for Barker's current job, have been suggesting methods for approval of agents that may prevent cancer.

"Prevention, prevention, prevention—that's where we need to go with cancer," Barker said at Milken's conference. "But there is very little, if any, incentive to do that currently. If you look at the patent life of a new intervention, by the time you actually get to market, in the current paradigm, you would have no patent life. In fact, there are companies out there that have developed interventions for prevention that have run out of patent life before they actually get to the marketplace."

Here, Barker is armed with a recent AACR position paper that proposes designating "intraepithelial neoplasia," an umbrella term for a variety of non-invasive lesions that have been observed prior to the formation of some common cancers, as a surrogate endpoint that predicts the development of cancer. Designating the eradication

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of these lesions as a medical outcome would accelerate clinical trials of agents for prevention of cancer, AACR said.

Any proposal to give potentially harmful agents to people who have no disease symptoms raises serious scientific, ethical, and legal questions. Harm some people, and legal consequences may follow. To deal with this problem, one proposal floated by NCI officials suggests developing "thoughtful and fair product liability measures." Risks and benefits of such therapies aren't easy to weigh, especially if you depart from the methodology of rigorously-designed randomized, controlled trials.

"We are working with the FDA [on] how we might deal differently with multiple agents, which we are going to have to do with cancer," Barker said at the Milken conference. "How we might use intermediate endpoints to approve drugs. Very controversial issue right now with the FDA. We obviously have some very good examples of where that's worked quite famously, in cardiovascular disease, and we think we can make this work for selected kinds of cancer."

Asked to elaborate in an interview with **The Cancer Letter**, Barker said NCI is yet to work out the scientific underpinnings of chemoprevention trials. "We know that for chemoprevention, if we want to get those drugs through trials, we are going to have to think through with a lot more of our new science how to provide a foundation for the FDA to think about these things," she said.

Considering the power of the proponents of this agenda, it's not a surprise that skeptics—the mainstream of science—are not jumping up to critique it. Privately, many scientists say they are puzzled by von Eschenbach's 2015 plan. Others cite voluminous literature describing instances where reliance on surrogate endpoints, especially for prevention, caused harm. Many wonder how Barker's vision came to set the course of the National Cancer Program.

Barker's publications are neither numerous nor recent. A Medline search for produces 12 publications under her name. Two list Samuel Waksal, the soon-to-be-sentenced founder of ImClone Systems Inc., as a co-author. According to Medline, over the past 24 years, Barker published one paper in peer-reviewed literature, "Report from The March Research Task Force,"a political document.

In his doctoral dissertation, a copy of which was obtained by **The Cancer Letter**, Waksal acknowledged Barker's help and thanked her for access to a laboratory at Battelle Memorial Institute, where she worked at the time, and listed two publications and six presentations and abstracts which he and Barker coauthored.

"He was a very good investigator early on," Barker said. "He did some interesting and exciting things, and he was always very smart in terms of seeing the next issue in science, so he really pushed technology along. I always thought his science at that early stage was very good and we certainly never found anything wrong with anything he ever did. He did pretty good work."

After leaving Battelle, Barker ran a small company that developed and commercialized "therapeutic and diagnostic products to diagnose, treat and prevent diseases of oxidative stress," and co-founded a start-up company to sell dietary supplements by subscription over the Internet.

Barker's Rise In Oncopolitics

Barker reached the top strategic role in the National Cancer Program by representing the American Association for Cancer Research in its interactions with other organizations.

The story of Barker's rise to power is also the story of oncopolitics over the past dozen years.

For years, cancer patients who served on policy boards or raised money for research saw themselves as team players with the scientific institutions. While AIDS activists protested, cancer patients were either too sick or too old to launch grassroots political movements. Disagreements could be resolved and turf divided behind closed doors.

That orderly world vanished on July 29, 1992, when Fran Visco, president of the National Breast Cancer Coalition, appeared before a subcommittee of the Senate Appropriations Committee.

"When the men in suits all but destroyed the savings and loan system in this country, the nation's economic stability was threatened, and this Congress responded with billions of dollars," thundered Visco, then a Philadelphia attorney. "When this administration decided to wage a war, you found $7.5 billion to fund it. Women have declared war on breast cancer, and you had better find a way to fund that war… We will no longer be passive. We will no longer be polite. We can no longer afford to wait while Congress gets around to significant, decent funding for breast cancer."

Visco's umbrella group of breast cancer organizations demanded $300 million for breast

cancer research—a $210 million increase—more money than NCI thought it could spend (**The Cancer Letter**, Aug. 7, 1992).

NBCC established a classic model of advocacy in health politics. First, advocates convened a meeting of scientists who came up with a funding target. Then they fought to get the resources. The strategy worked, creating a multi-million-dollar funding stream for basic researchers, much of it financed by the Department of Defense.

Visco's reference to "war" was unusual for her group. The word is almost never heard at NBCC events. After attaining success, the coalition maintained its focus on breast cancer, and avoided entanglement in the grandiose oncopolitical campaigns that followed.

From "Men In Suits" to Milken

Barker made connections with NBCC, and advised the Defense breast cancer research program. As other groups attempted to emulate the NBCC tactics, she remained the AACR contact for those endeavors.

Three years after Visco's "men in suits" speech, prostate cancer survivor Milken emerged on the oncopolitical scene. After release from prison, Milken learned that he had metastatic prostate cancer.

After a few years of funding prostate cancer research, Milken set out to energize the entire field of oncology. He began by staging a conference to demand that the war on cancer be modeled on the 1991 Persian Gulf War. "Despite growing fatalities and demoralization of our troops, the war on cancer has been allowed to drift," Milken said at his Washington conference Nov. 14, 1995 (**The Cancer Letter**, Nov. 24, 1995).

Milken wanted the war spending to go up to $20-billion a year, about ten times the NCI budget at the time. His wartime rhetoric appeared especially jarring, because then-NCI Director Richard Klausner and his predecessor Samuel Broder deliberately avoided the military metaphor.

Milken amassed a following of ailing CEOs and scientists seeing possibilities for getting their work funded. His appearance on the cancer scene culminated in a grandiose event—a march on Washington, an undertaking modeled on Earth Day.

The financier wanted major rock stars. He wanted Hollywood. He wanted the Mall. He wanted speeches, T-shirts, posters, and political buttons. Above all, he wanted to create a political constituency, perhaps the biggest political constituency in the U.S.

After announcing the march on Larry King Live, the event's organizers entrusted the preparation of the scientific agenda to Barker and Ellen Sigal, a Washington real estate developer, who entered oncopolitics after her sister died while receiving high-dose chemotherapy and a bone marrow transplant for breast cancer (**The Cancer Letter**, Oct 31, 1997).

Like Milken, Barker talked big. "It is time to make cancer our highest national health care priority and undertake a national initiative that will mark the beginning of the end for cancer," Barker said at a September 1998 hearing suggesting that the cancer appropriations be increased to $10 billion over five years (**The Cancer Letter**, Oct. 2, 1998).

On Sept. 26, 1998, the march brought 250,000 people to the Mall, but the event failed to generate an overarching cancer agenda, and no political constituency clamored to receive the Barker-Sigal report.

After The March

The next political opportunity for Barker was provided by the American Cancer Society, a charity that was threatened by the march and its potential for organizing an independent political constituency (**The Cancer Letter**, Jan. 21, 2000).

On Sept. 29, 1998, three days after the march, Barker and Sigal attended a small, ACS-sponsored meeting at a Northern Virginia hotel. This was the beginning of the National Dialogue on Cancer, an ACS effort to transform itself from political backwater to the principal player in cancer politics. Instead of letting oncopolitics happen in a haphazard, uncontrolled manner, ACS wanted to create an arena for political activity.

The Dialogue leaders described the extraordinarily complex set of diseases as an engineering problem akin to putting man on the Moon and postulated that science had attained "critical mass" of discovery. The time had come to disseminate these discoveries to the public, ACS activists argued.

To propel these efforts, the society recruited former President George Bush, who is widely believed to have been recruited by von Eschenbach, an ACS activist who was later made President-elect of the society. Von Eschenbach was unable to accept the ACS position because the newly-elected President George W. Bush offered him the NCI job, making him the top official of the National Cancer Program.

ACS was unsuccessful in recruiting former President Jimmy Carter as a co-chairman of the Dialogue. For bipartisan flavor, the society brought in Sen. Dianne Feinstein (D-CA).

The second "organizational" meeting of the Dialogue was held Nov. 9-10, 1998, at the Bush Memorial Library in College Station, Tex. At that meeting, Feinstein urged the group to set ambitious goals. According to notes taken by a participant, "Sen. Feinstein cautioned the group not to avoid setting priorities and clear goals simply because we might not meet them."

Someone suggested curing cancer within 10 years, triggering a round of objections. Feinstein did not object. Instead, "she noted that goals are needed so there is something to work for," a participant wrote.

To launch the Dialogue, ACS hired Shandwick International, a public relations consulting firm, to do its Washington work. Shandwick stayed on the job until **The Cancer Letter** revealed that the firm also represented R.J. Reynolds Tobacco Holdings (**The Cancer Letter**, Jan. 28, 2000).

Before it was thrown off the job, Shandwick constructed an intricate system of political organizations pursuing the ACS goal of becoming the master of the cancer agenda. First, there was the Dialogue, an amorphous organization of some important players and some unknowns, who were invited by George and Barbara Bush, and met behind closed doors.

Barker was omnipresent at the Dialogue. She was a "collaborating partner," the Dialogue's name for a participant. She was the chairman of the "public sector research team." She was a member of the "steering committee."

Later, Barker joined a Dialogue spun-off, a committee to draft a white paper laying out the direction for legislation that would replace the National Cancer Act of 1971, the fundamental document of the War on Cancer.

That group, called the National Cancer Legislation Advisory Committee, met in Feinstein's conference room in the Senate. Its name notwithstanding, the group was not a chartered federal "advisory committee." Since it received no government money, the group was exempt from open-door requirements of the Federal Advisory Committees Act, as well as from corresponding rules in the Senate.

ASC chief executive John Seffrin and former NCI Director Vincent DeVita, an enthusiast of the war metaphor, took charge of the committee. It is a measure of the committee's orientation that the word "war" appeared 20 times and "conquer" 28 times in its 59-page report.

A Hatchery of Ideas?

The committee appears to have been a hatchery for ideas that are now coming forward at NCI:

The committee refused to believe that FDA approves cancer drugs based on a variety of criteria. While first-line treatments for solid tumors must demonstrate a survival advantage to receive full approval, second and third-line treatments are routinely approved based on other criteria, including tumor shrinkage and time to progression (**The Cancer Letter**, Sept. 28, 2001).

Presenting the advisory committee's recommendations, Barker called for creation of geographically distributed "translational cancer centers."

"You are going to have to give these centers enough resources to build the public-private partnerships in areas like drug development or device development," Barker said at a Senate hearing (**The Cancer Letter**, Oct. 19, 2001).

Recently, a similar idea appeared in a concept presented to the NCI Board of Scientific Advisors. NCI proposed to spend $20 million to support partnerships between academia, industry, and non-profit organizations. "If we can develop these kind of partnerships, then we can reduce the risk to the private sector," Barker said (**The Cancer Letter**, March 14).

NCI Director von Eschenbach serves as vice chairman of the Dialogue's 17-member steering committee, and Barker is a committee member and head of the Research Team, which is designing science policy. The industry perspective on the steering committee is represented by Peter Dolan, the embattled CEO of Bristol-Myers Squibb Co.

From the time of the Dialogue's formation, observers wondered whether the group would function as a de-facto advisory committee, and whether it would be appropriate—or legal—for the group that includes federal employees and receives assistance from the government's Executive branch to engage in lobbying Congress (**The Cancer Letter**, Sept. 22, 2000).

"The Dialogue hasn't really been an advisory body, as much as it has just been just that, an

opportunity for dialogue and discussion," von Eschenbach said, responding to a reporter's question earlier this month (**The Cancer Letter**, May 16). "The one place that I think we really had tremendous experience has been with the Research Team, and Anna Barker has been heading that up, which has made a nice link.

"But, the Research Team has really been focusing people on the issue of how can we accelerate the process of the development of these interventions, and I think it has been great to be part of that discussion, and great in terms of trying to bring all the pieces of the community together," he said.

The Research Team, which, in the tradition of the Dialogue, meets behind closed doors, is broken up into four working groups: Tissue Access; Surrogate Endpoints; Engaging the Private Sector; and Developing a National Strategy. Each of these groups plans to generate a report.

It remains to be tested whether the Dialogue activities should be covered by FACA. "I think there are serious questions about whether an organization with this composition and function should be complying with FACA," said Eric Glitzenstein, an attorney with Meyer and Glitzenstein, a Washington public interest law firm that specializes in open government issues. "If, indeed, the Dialogue is being used to influence government policy, then openness requirements of FACA should come into play."

From Science Policy To Dietary Supplements

A search of WebMD offers some insights into Barker's view of how cancer can be prevented.

Last September, in an interview, she described the combination of soy and cow's milk as an example of "benign medical foods that you take over a lifetime to reduce the risk of cancer."

A year earlier, Barker told WebMD that she takes vitamins. "I'm interested in the biology of pro-oxidants and antioxidants, so I understand a little more than some people about how this stuff works," she said. "I think people who take vitamins C and E are a bit more protected than people who don't. Vitamin C especially has a very short lifespan, and unless you eat a lot of fruits and vegetables you probably aren't getting enough of it. For vitamin E, you can't really overdose on the stuff, and it's a very good antioxidant. ... I think taking a multivitamin is not a bad idea."

For Barker, antioxidants have been a business pursuit, too.

OXIS International Inc., the small biotechnology company she co-founded and ran until 1998, described itself as "a leader in the discovery, development and commercialization of therapeutic and diagnostic products to diagnose, treat and prevent diseases of oxidative stress. Oxidative stress occurs when the concentration of free radicals and reactive oxygen species, highly reactive molecules produced during oxidative processes, exceed the body's antioxidant defense mechanisms."

After leaving OXIS, Barker founded Bio-Nova, a company that invested in emerging technologies. "We founded it in Oregon, because we felt as though there was a lot of opportunity in Oregon," she said. "There was not the investment capital in Oregon, as compared to Seattle."

At the same time, Barker took a leap from studying antioxidants to trying to sell vitamins and dietary supplements. In 1998, she co-founded a business called Nutri-Logics Inc. to "fulfill an unmet, growing healthcare need for scientifically-based disease risk reduction and prevention products" in cancer, according the company's business plan.

Her partners in the venture were Sigal, who had completed a term on the National Cancer Advisory Board and was at the time a member of the NCI Board of Scientific Adivsors, and Robert Day, director emeritus of the Fred Hutchinson Cancer Institute. Anthony Podesta, a lobbyist who at the time represented Friends of Cancer Research, Sigal's advocacy group, was a Nutri-Logics board member. Podesta was also a Clinton appointee to the Commission on Dietary Supplements, which advised the administration on the implementation of the Dietary Supplement Labels, Health and Education Act of 1994.

The "market opportunity" section of the Nutri-Logics business plan states:

- Scientific advances now provide the capability to predict, estimate, and reduce disease risk through improved diet and lifestyle and nutritional supplementation.
- Disease risk reduction (or "wellness") healthcare models are becoming preferred to treatment-only models by both consumers and health care providers. Increasingly, science-based nutritional products are regarded as critical to a prevention-oriented lifestyle.
- The worldwide nutritional supplement market is rapidly growing due to changing demographics and healthcare approaches. In the U.S., sales of vitamins, minerals and herbal supplements have grown from

$6 billion in 1994 to $12 billion in 1999. In Europe, sales were $12 billion in 1998, up 8%.

● Cancer incidence is expected to increase 29% in the next 10 years due to the aging of the "baby boomer" generation and costs for cancer treatment and lost productivity are projected to be over $200 billion per year.

● The Internet provides ideal opportunities for customer interaction, personalized products/and services, and real-time delivery of healthcare information.

● Unprecedented opportunities to assess the efficacy of nutritional supplements through the application of genomics and other new technologies combined with increasing regulatory pressure is moving the field toward more science-based, high quality nutritional supplements (nutraceuticals).

The plan offers the following description of the "Scientific and Research Platform:"

● Nutri-Logics believes that the major future requirement to compete successfully and eventually dominate this industry will be the development of scientifically based, proprietary products.

● Nutri-Logics' has developed a bi-directional, three-tiered approach (The *ORION*™ Process) that utilizes a "levels of evidence" approach to identify critical ingredients for the development of its scientifically based dietary supplement products. The ORION process is the subject of a broad patent application and the products that derive from the process are the focus of individual submissions.

● Nutri-Logics believes that genetic polymorphism (differential gene expression) is very important in the incidence of certain types of cancer, specifically related to metabolic influence of micronutrients. Using contemporary genetic and molecular approaches (e.g. microarray technology) Nutri-Logics will identify genes and clusters of genes in specific cancers to provide a basis for assessing efficacy of its products and to identify at-risk populations.

The company's "Products and Services" were to include:

● Customized, science-based nutritional supplements composed of efficacious combinations of micronutrients, botanical extracts, vitamins, and minerals, offered on a subscription basis. Introductory supplement formulations will focus on cancer risk reduction, with product line extensions for cardiovascular and other preventable diseases.

● A personalized health risk profile provided over the internet to help stimulate product interest, gather personal health information, recommend optimized product formulations, and provide information and references on prevention and various other health education issues.

● Proactive customer communication via newsletters, research alerts, product updates, and other relevant communications.

The plan was marked as "Non-Confidential," and was displayed on the Nutri-Logics Web site. Now, it can be found at the Internet Archive: http://web.archive.org/web/20010305035804/http://www.nutri-logics.com/

Nutri-Logics, incorporated in Oregon in 1998, lists the Washington, DC, address 3299 K Street NW as its official place of business. That is also the address of Sigal Construction Corp. The Oregon registration lists Sigal as president and Day as secretary of Nutri-Logics.

Asked to comment on her involvement in the business, Barker said: "Bob and I, and Ellen ultimately, had a passion for chemoprevention."

The business was consistent with her work in antioxidants. " In my work with OXIS and my interest in reactive oxygen damage, I became convinced that there might be some real substance in looking at the world literature in micronutrients to see if there were first-generation kinds of nutraceuticals," Barker said. "Might you use the world literature for specific kinds of cancer to look at ways that you might formulate mixtures of micronutrients that would be scientifically based?"

The company drew on expert advice, Barker said. "We attracted a stellar scientific advisory board," she said. "We had a great deal of fun looking at various micronutrient combinations within the realm of specific cancers. I think the general consensus was that, in fact, the chemoprevention in terms of micronutrients scientifically based, by taking the world literature and using the process to start with randomized, controlled trials and working our way down through all the in vitro and in vivo kinds of things that one could find in literature, that you could combine molecular science along with clinical trials to put together pretty exciting kinds of mixtures of micronutrients for specific cancers, looking at the origin of cancer."

Sigal, who served on the National Cancer Legislation Advisory Committee and is currently a member of the Dialogue's Nominating Committee, confirmed that she, Barker, and Day founded the

company, which she described as "an ongoing entity."

Barker said the venture failed. "We spent many happy times with our colleagues going through those processes, but as a business model, it was not a good business model, because even if you are formulating highly scientifically viable kinds of mixtures of micronutrients, you are competing in a marketplace where people are able to compete on the basis of nothing," she said. "They have no science behind what they've done. It was not a successful business model. So we elected to put it on the shelf. Bob Day and Ellen are still shepherding it along, but it's been inactive for a year and a half or so."

In recent months, Friends of Cancer Research, Sigal's advocacy organization, has been working on issues involving FDA.

Precancers: "New Front" In War on Cancer

In February 2002, the AACR journal Clinical Cancer Research published a paper titled, "Treatment and Prevention of Intraepithelial Neoplasia: An Important Target for Accelerated New Agent Development."

The paper appears to have directly influenced the von Eschenbach-Barker agenda at NCI.

"Despite increasing research and development efforts, drug approvals for chemopreventive indications have been slow to emerge," said the report. "The critical factor in this regard is defining and then demonstrating clinical benefit. Historically, reduced cancer incidence or mortality has been required to show chemopreventive efficacy. These endpoints make chemoprevention studies too long, large, and costly for most academic research centers and pharmaceutical manufacturers to undertake, thus limiting the number of drug candidates that can be developed. Continuing to rely on cancer incidence and mortality endpoints will lead to significant loss of opportunity to impact cancer."

The paper was written by the AACR Task Force on the Treatment and Prevention of Intraepithelial Neoplasia, formed by Daniel Von Hoff, director of the Arizona Cancer Center, and a former AACR president.

The task force co-chairmen were Joyce O'Shaughnessy, of US Oncology and Baylor-Sammons Cancer Center; Gary Kelloff, of the NCI Division of Cancer Treatment and Diagnosis; Gary Gordon, of Ovation Pharmaceuticals; and Richard Pazdur, head of the FDA Division of Oncology Drug Products. Pazdur attended one of the group's meetings, and his name does not appear on the list of co-authors.

The paper is posted at www.aacr.org/PDF_files/Journals/2002_IEN_article.pdf.

The paper proposed a new endpoint: precancer, or "intraepithelial neoplasia (IEN)," a noninvasive lesion "that predicts for a substantial likelihood of developing invasive cancer" for many epithelial cancers, including those of the colon, head and neck, esophagus, lung, non-melanoma skin, breast, prostate, and bladder.

"Achieving the prevention and regression of IEN confers and constitutes benefit to subjects and, in the opinion of this Task Force, demonstrates effectiveness of a new treatment agent," the paper asserted.

There is a precedent for this approach: the use of lipid-lowering drugs in prevention of cardiovascular disease. "Lowering the cholesterol level has been validated as an endpoint for CHD risk reduction; analogous data might be applied to validating IEN for cancer risk reduction," the paper said.

Another example the task force cited was the FDA approval of Celebrex (celecoxib) for colorectal polyps in patients with familial adenomatous polyposis as an adjunct to standard-of-care.

While FAP is rare and is associated with a high risk for colorectal cancer, it sets a precedent, the paper said. "New drug approvals for treatment of IEN in high-risk populations will provide rationale for incrementally extending studies to lower-risk populations to gain drug approvals that will have broader public health impact," the task force said.

The paper noted one problem with using IEN to demonstrate risk reduction: "relatively small percentages of IEN progress to cancer."

To overcome that limitation, the paper proposed that "in patients with low-risk IEN, which constitute a significant part of the population, it will be important in future drug development efforts to reduce cancer risk to determine that the successfully treated lesions had potential to progress and, thus, that the patient benefited from treatment of IEN."

The potential danger of IEN to the patient could be demonstrated by the extent of genetic and molecular progression in placebo-treated subjects, the paper argued. Gene microarray analyses and genotypic changes measured by gene chips could be used as endpoints for IEN treatment studies.

The task force proposed several clinical trial designs that it said provided "practical and feasible

approaches to the rapid development of new agents to treat and prevent precancer."

Announcing the publication of the IEN paper, AACR issued a "position statement" titled, "Precancers: Opening a New Front in the War on Cancer." The statement is posted at http://www.aacr.org/5300f.asp.

According to AACR, "It is now time to take the war on cancer to a new front, featuring the rapid development and deployment of a new arsenal of drugs capable of attacking cancer cells during their formative—precancerous—stage."

The task force had "spelled out a landmark set of recommendations on how to speed the development of drugs that target common precancers," the AACR position statement said. "The task force and the AACR now urge the federal Food and Drug Administration to speed approval of drugs that prevent and treat precancerous lesions when the link between these lesions and cancer is shown to exist. It's hoped that such an effort will encourage researchers in academia, the government and pharmaceutical companies to begin scientific inquiries into 'chemopreventive' agents that would launch preemptive strikes against precancerous cells and tissue."

For those who worry about "the risks of giving medicine to seemingly healthy people—including those with precancers," AACR had a prescription: look at cardiovascular disease and don't worry. "This attitude clearly has changed with the treatment of other life-threatening conditions such as cardiovascular disease," AACR said.

The AACR statement ended with a declaration: "The AACR now believes that reducing precancers lowers cancer risk, and that the FDA should take a similar stance regarding drugs for the approval of this condition. AACR believes the link between some precancers and invasive cancers—particularly in certain high-risk populations—is so clear that drug developers should only be required to prove their proposed medicines are safe and effective in treating or preventing the evolution of precancer to cancer.

"The AACR contends that a revolution in how scientists and the public think about preventing and curing cancer is needed. This revolution has begun in the laboratory and is already well accepted by a public seeking ways—through lifestyle modification as well as medical screening and intervention—to reduce their personal risks of developing cancer" (**The Cancer Letter**, March 1, 2002).

Barker described the IEN report as "a very important study."

"It drew on the expertise of the community to put together what I think is a very cogent argument for looking at and evaluating potential chemopreventive agents," she said. "I think it sets the stage for putting science in perspective in terms of how you might be able to look at chemopreventives. It's a construct for beginning to think about how you might evaluate these agents."

Does a Correlate a Surrogate Make?

The AACR platform does not represent a consensus on the role of "precancers" as a surrogate marker for clinical benefit. Precancers may vary wildly from one disease to another, scientists say.

"You have to look at organ-specific issues, and design trials and interventions based on specific changes in the organ," one cancer prevention expert said to **The Cancer Letter.**

The approval of Celebrex for the narrow indication of FAP doesn't blast the door wide open for the acceptance of polyp formation as a surrogate endpoint for every potential colorectal intervention, colorectal cancer experts say.

Writing in the May 21 Journal of the National Cancer Institute, Bernard Levin, vice president for cancer prevention at University of Texas M.D. Anderson Cancer Center, cautioned against using polyp formation uniformly as a surrogate endpoint for chemoprevention studies.

"In long-term studies of chemoprevention that are based on the surrogate endpoint of adenomatous polyps rather than on the incidence of colorectal cancer, we must be vigilant to the potential for harm when using an indirect marker, however biologically relevant, in an asymptomatic population," Levin wrote.

"Stopping trials on the basis of surrogate endpoints such as adenoma incidence rather than on cancer incidence may miss hypothetical harms that may occur later than the surrogate endpoint," Levin wrote. "Using surrogate outcomes of benefit but clinical outcomes of harm rather than surrogate outcomes of harm can introduce a systematic bias in our assessment of chemopreventive agents….

"Placebo-controlled, randomized trials to suppress adenoma recurrence and thus possibly to diminish colorectal cancer incidence and mortality need to be carefully monitored and to be of sufficient duration to ensure that clinically significant adverse

effects can be reliably detected."

Biostatisticians Thomas Fleming and David DeMets argued in the Annals of Internal Medicine (1996;125:605-613) that "a correlate does not a surrogate make." They provided a case from cardiology—the use of reduction in ventricular ectopic contractions as a surrogate for decreased cardiovascular-related mortality—as "a classic example of the unreliability of surrogate end points."

In that instance, FDA approved three drugs—encainide, flecainide, and moricizine—for use in patients with severely symptomatic arrhythmias, though trials had not been done to determine whether the reduction in arrhythmias would lead to a reduction in death rates.

Unexpected results emerged from the Cardiac Arrhythmia Suppression Trial to evaluate the effect of the drugs on survival of patients who had myocardial infarction: significantly more patients in the treatment arms of the study died, compared to the placebo group.

Fleming and DeMets described several other examples of experiences with surrogates "for which biological markers were correlates of clinical outcomes but failed to predict the effect of treatment on the clinical outcome."

Surrogate endpoints might provide an acceptable quality of evidence in some studies and for some treatments, but not for others, wrote NCI scientists Arthur Schatzkin and Mitchell Gail in the January 2002 issue of Nature Reviews: Cancer.

"The most that can be said is that surrogates might give the right answers about intervention effects on (or exposure associations with) cancer," they wrote. "The problem is the uncertainty attached to conclusions based on surrogates.

"Except for those few surrogates that are both necessary for and relatively close developmentally to cancer—such as CIN3 and cervical cancer—the existence of plausible alternative pathways makes inferences to cancer from surrogates problematic," Schatzkin and Gail wrote. "Merely being on the causal pathway to cancer does not in itself constitute surrogate validity; it is the totality of causal connections that is crucial.

"There is, unfortunately, a fairly extensive history of plausible surrogate markers that give the wrong answer about the effects of treatments for chronic disease," they wrote. "If anything, the limitations of surrogacy remind us of the complexity of cancer causation and affirm the continued importance of large clinical trials and observational epidemiological studies with explicit cancer end points."

Physicians assumed for 50 years that estrogen plus progestin protects women against cardiac disease. Last year, results from a large randomized trial found that women taking the therapy had a greater incidence of breast cancer, coronary heart disease, stroke, and blood clots. Earlier this week, investigators reported that women who began taking the combination of estrogen and progestin at age 65 or older in a randomized, controlled trial had double the risk of dementia compared to controls.

Beta-carotene was tested as a potential cancer preventive in two large NCI-funded randomized trials in persons at high risk of developing lung cancer. Contrary to expectations, the incidence of lung cancer increased among the former and current smokers who took beta-carotene.

"The magnitude of increased risk in these trials represented approximately six cancers per 1000 participants in the intervention groups, compared with five cancers per 1000 participants in the control groups, a difference too small t be apparent in any observational epidemiologic study," wrote Peter Greenwald, director of the NCI Division of Cancer Prevention, in the Jan. 1, 2003, issue of the Journal of the National Cancer Institute.

If the randomized, controlled trials had not been carried out, "specific dietary guidelines based on epidemiologic evidence might have been considered, an action that would likely have caused harm to public health," Greenwald wrote. "The beta-carotene story thus demonstrates clearly that although epidemiologic evidence can provide a basis for developing hypotheses of benefits of food constituents, these hypotheses must then be tested in randomized, large-scale clinical trials."

AACR, NCI Call For Precancer Treatments

Chemoprevention based on surrogate endpoints is central to the NCI 2015 plan, said James Mulshine, head of the Experimental Intervention Section in the Cell and Cancer Biology Branch of the NCI Center for Cancer Research.

"This is one of [Barker's] primary *raisons d'etre* for coming to the NCI," said Mulshine, who has presented the Institute's plans to patient groups and oncologists. "Industry has got to hear that NCI is going to be committed to this, because if we don't come up with a much more comprehensive ability to

do this type of thing, we are going to fail on our 2015 objective."

Mulshine said the plan has von Eschenbach's support as well.

"Andy von Eschenbach and Anna Barker really want to get this done," Mulshine said to **The Cancer Letter**. "There is some tension at some levels with the FDA, but the new Commissioner seems to have a more open mind about this than some of the other people there."

In a recent proposal he presented to an ASCO committee, Mulshine wrote that development of cancer chemoprevention has been "paralyzed by a remarkable paucity of drug development activity."

The long duration of prevention trials and the issue of product liability were identified by a 1995 NCI working group as two "dominant barriers to pharmaceutical investment in cancer preventive drug development," Mulshine wrote.

AACR "has proposed that the field recognize the earliest manifestations of early cancer as a distinct disease entity," Mulshine wrote. IEN would be a surrogate marker for cancer "just as elevated serum cholesterol has been accepted as a surrogate of cardiovascular disease."

The excerpted text of Mulshine's proposal follows:

"In the setting of a compelling public health benefit, there are precedents in establishing a fair product liability mechanism such as with the Orphan Drug Act or with a non litigation-based compensation board as recently suggested by the Institute of Medicine (Fostering Rapid Change in Health Care, www.nap.edu). Either of these mechanisms may serve as important incentives for cancer prevention drug development.

"A recent report outlined an analysis of the consequences of patent life extension relative to their impact on public health and drug cost (Changing Patterns of Pharmaceutical Innovation, www.nihcm.org). Appropriate concerns were raised about rising drug costs in the absence of corresponding improvements in public health. The implication of the study was not that patent life extension was an inherently flawed approach. Rather the suggestion was that this market tool was left unmodified for an extended period of time without a critical appraisal of its impact. In the setting of creating incentives for the development of prevention drugs, perhaps a more tailored and monitored approach to patent life extension could be of benefit in areas of critical public health need.

"Finally, to assist the FDA in their regulatory responsibility for the specific situation with cancer prevention drugs, a more responsive regulatory mechanism is needed to meet the public health needs of the nation. This proposed regulatory mechanism would involve a two-tiered drug review system. The first conditional approval for cancer prevention drugs would be based upon results of trials designed around surrogate markers such as IEN. For the second and final review, structural post marketing (commonly called Phase IV) surveillance capability would have to be developed. This post marketing surveillance mechanism would be engineered to detect clinically significant drug complications more reliably and earlier. If this mechanism is implemented properly, it would be a resource not only to the integrity of the FDA regulatory review, but to the pharmaceutical industry and the public as well. The feedback about an agent acquired by longer term clinical trials as well as the post marketing mechanism would provide the basis for the FDA's final approval of a cancer prevention drug.

"In order to use this new source of information to protect the American public, the FDA would need new authority to be able to act downstream of initial drug approval to refine its approval language to reflect the post marketing experience to protect the public. This new downstream regulatory authority would allow the FDA be more liberal in acting upon cancer prevention applications in approving early indications for premetastatic cancer (IEN) based on surrogate endpoints. Knowledge about prevention drug utilization out in the community captured by the post marketing mechanism would provided much more comprehensive information about the subsequent costs and benefits to people of this new class of cancer prevention drugs. Considerable enthusiasm exists for this more calibrated approach to prevention drug approval among many stakeholders.

"Proposed actions items to create a more favorable environment to encourage cancer prevention drug development:

- Develop thoughtful and fair product liability measures.
- Develop tailored patent life extension incentives for critical public health needs.
- Develop post marketing infrastructure to reliable capture impact (positive and negative) of new drugs in the population.
- Provide FDA with regulatory authority to

refined drug approvals and packaging claims based on clinical information provided by post marketing surveillance.

● Institute a Prevention Drug Advisory Committee comparable to the Oncology Drug Advisory Committee to review the early cancer drug approvals, refine final approvals based on the post marketing data, and perform strategic quadrennial review on prevention drug development.

Jon Steiger, a partner in the Los Angeles office of Quinn, Emanuel, Urquhart, Oliver & Hedges, a premier national business litigation firm, said that the legal aspects of the NCI proposal do not appear to be well planned.

"It is no small undertaking to change product liability laws in the manner they propose, and it appears that they underestimate and oversimplify the magnitude of that task," Steiger said to **The Cancer Letter**. "Trying to reform product liability laws is not something you do to 'incentive' the industry, but instead only with the industry firmly behind you.

"A half-baked and hasty attempt at 'reform' will only scare the industry, as it could make them look foolish and set back otherwise legitimate and potentially successful attempts to create rational legal reforms," Steiger said.

"And yes, products have to be thoroughly tested in clinical trials," Steiger said. "Prematurely launching an ill-conceived legal legislative effort will turn off not only the drug companies, but also the legislators and the public."

The Question of Surrogate Endpoints

ASCO recently sponsored workshops with FDA to discuss endpoints for drug approval.

At the first workshop, conducted last month, academic experts, FDA and NCI officials, and patient advocates reviewed endpoints for advanced lung cancer. The workshop was open to the public, and its report will be presented to ODAC (**The Cancer Letter**, April 25).

AACR was involved in initial planning of the workshop, but ultimately bowed out of the process.

ASCO and FDA planned to hold a series of such workshops for a variety of cancers. However, now NCI seems intent on folding this effort into the Dialogue (**The Cancer Letter**, May 16).

"We are trying to do this in a way that is all integrated," von Eschenbach said in an interview. "The ASCO effort, the NCI effort, the FDA effort—these all are going to be integrated in a way—the National Dialogue on Cancer effort."

Von Eschenbach said Barker's Research Team "has been looking at ways of streamlining development of drugs based on genomics or proteomics."

In recent months, Barker and Mulshine made two attempts to win over the members of ASCO's Cancer Prevention Committee.

Dominated by clinicians, that committee has a keen appreciation of complexities of human subject experiments. While some members of the group admitted to being "shocked" by the NCI proposals, they also understood the practical value of having NCI and AACR return to discussions, if only to draw on a broader spectrum of ideas.

"It's shocking to see NCI associate its name with anti-science," said one committee member who spoke on condition of not being identified by name. "I have no problem with surrogate markers. My problem is when you don't validate those markers. They are basically saying, 'The hell with validation.'"

Several members of the committee said ill-advised interventions may benefit pharmaceutical companies, but not the public.

"Whom is this for?" asked another member of the ASCO prevention committee.

The NCI proposal seemed to be written to make it easier for the pharmaceutical industry to bring interventions to market, and protect it from product liability suits. "They keep talking about cancer as a horrible thing—desperate diseases are only cured by desperate means," a participant said. "In this case, the target population is healthy people."

At one of the meetings, Mulshine argued that post-marketing surveillance would detect any harm of interventions, possibly by tracking this through the NCI Surveillance, Epidemiology and End Results Program, participants said.

Post-marketing studies are not designed to assess the harm of prevention products such as dietary supplements, experts say. SEER tracks cancer incidence and would be unlikely to detect adverse events from chemoprevention trials.

Another ASCO committee member said he was troubled by the proposal's lack of ethical constructs.

"Remember 'First, do no harm'?" the committee member, a practicing physician, said to **The Cancer Letter**. "If you are going to encourage asymptomatic, or even healthy people to do something they wouldn't normally do, the bar must be higher, not lower. You don't set the bar lower for convenience."

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