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Patients Sue Milken, Cancer Centers, Over Prostate Cancer Remedy PC-Spes

A series of personal injury suits filed in Los Angeles earlier this month alleges that a charity established by the financier Michael Milken, in conjunction with prostate cancer researchers nationwide, engaged in systematic promotion of PC-Spes, a "nutraceutical" that was sold as a mixture of Chinese herbs, but was laced with prescription drugs.

Analyses by private laboratories and health authorities found that in addition to herbs, PC-Spes contained synthetic estrogens diethylstilbestrol and ethinyl estradiol, anticoagulant warfarin, a non-steroidal anti-inflammatory agent indomethacin, and anti-anxiety drug alprazolam. Though the amounts of drugs and natural ingredients varied from lot to lot, academic centers

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In Brief:

Five NCAB Members Complete Terms; Love, Cooksey Wed In Historic S.F. Event

FIVE NCI ADVISORS completed their terms on the National Cancer Advisory Board this week. They are: **Stephen Duffy**, executive vice president, American Academy of Facial Plastic and Reconstructive Surgery & International Federal of Facial Plastic Surgery Societies; **Elmer Huerta**, director, Cancer Preventorium, Washington Cancer Institute; **Susan Love**, clinical professor of surgery, David Geffen School of Medicine, University of California, Los Angeles; **Larry Norton**, deputy physician-in-chief for the Breast Cancer Program, Memorial Sloan-Kettering Cancer Center; and **Amelie Ramirez**, associate professor of medicine and deputy director, Chronic Disease Prevention and Control Research Center, Baylor College of Medicine. Board members are appointed by the White House for a six-year term. . . . **SUSAN LOVE**, NCAB member, author, and a founder of the breast cancer advocacy movement, wed her partner of 21 years **Helen Sperry Cooksey** in San Francisco on Feb. 15, four days after **San Francisco Mayor Gavin Newsom** directed the city to legally marry same-sex couples. Cooksey, a general surgeon at the Jeffrey Goodman Clinic of the Gay and Lesbian Center in Los Angeles, Love, and their 15-year-old daughter Katie stood outside City Hall for eight hours last Sunday with hundreds of other couples. Late in the afternoon, Love and Cooksey were married under the Rotunda with Katie as witness and **Michael Farrah Jr.**, senior advisor to the mayor, officiating. "I don't know what the courts will do, but it sure felt like a Rosa Parks moment," Love said. "It is important for gay people to be able to get married and we sure are happy to have the opportunity." The

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Families File Suit Against Many Involved In PC-Spes

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used the agent in clinical trials and recommended it to patients off-protocol.

This crossover from health food stores to mainstream medical practice had a curious result: the list of defendants in the 22 nearly identical personal injury suits filed in the Los Angeles County Superior Court Feb. 6 includes an unlikely combination of producers of Chinese herbal medicines and some of the most prestigious cancer research institutions in the US.

The litigation, led by Los Angeles trial lawyer Thomas Girardi, names the agent's creator Sophie Chen, her company International Medical Research Inc. of Brea, Calif., a long list of players in the Chinese medicine market, as well as Memorial Sloan-Kettering Cancer Center, New York Medical College, and the Regents of the University of California, for the activities of UCLA and UCSF.

Many basic scientists, urologists and oncologists figure on the list, as does the former CaP CURE Association for the Cure of Cancer of the Prostate, Milken's group, which sponsored PC-Spes research. Milken, Intel Chairman of the Board Andrew Grove, and former NCI Director Richard Klausner, who served on the CaP CURE board of directors, are named, too. The Santa Monica, Calif., based organization recently changed its name to Prostate Cancer Foundation.

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Advocacy groups on the list of defendants include Us TOO, the Alliance for Prostate Cancer Prevention, and the National Foundation for Alternative Medicine.

Litigation of this sort is always a pursuit of deep pockets. Yet, the story of the rise and fall of PC-Spes has implications beyond who-did-what-to-whom-and-who-pays. It is also a story of a cataclysmic collision of alternative and academic medicine, two cultures that have different standards of proof and are regulated differently by the federal government.

The crucial question in the web of litigation surrounding PC-Spes is whether its maker and those involved in studying and promoting it knew about the presence of prescription drugs in the agent, and whether they met their obligation to report the problem to federal and state officials.

Complaints Claim Wrongful Death

"Many prostate cancer patients who were using PC-Spes as their sole or primary treatment suffered severe emotional and personal injuries," the complaints state. "They learned that the dietary supplement had, in effect, masked their symptoms and that their cancer had, in actuality, dangerously progressed to a life-threatening level. Further, because there was no disclosure regarding the presence of prescription drugs, consumers and their physicians were not able to evaluate and make informed decisions as to the risks associated with those drugs, to manage their care, and to take proper precautions to prevent the adverse effects associated with those drugs.

"Several consumers died," the complaints state.

Five of the 22 suits filed in Los Angeles allege wrongful death. According to widely cited estimates, 10,000 men in the U.S. used PC-Spes regularly, and many more used the company's products for arthritis, cancer pain, liver disease, and the enhancement of the immune system. PC-Spes figures in all but four complaints and all the alleged wrongful deaths, court documents show.

"I have a great deal of confidence that we are going to be able to help these people, who, I believe, were massively wronged," said Girardi, of Girardi & Keese, a politically connected Los Angeles firm that has in the past taken on the former Lockheed Corp. and Pacific Gas & Electric Co. The latter case inspired the movie "Erin Brokovich."

"I feel very strongly about the litigation, and we are very anxious to throw all the resources and legal skills we have at this case," Girardi said to **The Cancer Letter**.

Officials at the Prostate Cancer Foundation declined to comment on the litigation. "We haven't received a copy of the complaint or any other document relating to the suit, and so are unable to express any opinion or have any comment," said Christopher Crain, counsel to the foundation.

An Estrogenic Effect

It is undisputed that, whatever its composition, the dietary supplement had a powerful estrogenic effect and lowered the prostate specific antigen levels in most patients who took it.

The agent's side effects included breast tenderness and a reduction in testosterone levels. Estrogenic compounds can cause thromboembolic events, doctors say. Warfarin prevents blood clotting, but can cause hemorrhages.

The compound's name combines the acronym for prostate cancer and the Latin word for hope. Patients paid $200 to $500 for a month's supply of the agent and were told that it contained a blend of Reishi, Baikal Skullcap, Rabdosia, Dyer's Wart, Mum, Saw Palmetto, San-Qi Ginseng, and Chinese Licorice.

The agent was sold as a dietary supplement under the 1994 Dietary Supplements Health and Education Act, a law that limits FDA's ability to regulate such products. Under this law, the maker of PC-Spes couldn't claim activity against disease. Instead, the package said "for prostate health."

According to the complaints, the agent was used by prostate cancer patients as well as "men with healthy prostates, who were encouraged to be proactive about maintaining good prostate health without any adverse reactions or use of synthetic drugs."

The suits are built around the claim that IMR, which did business under the name BotanicLab, together with CaP CURE, academic institutions, and others who promoted or recommended PC-Spes, failed to perform laboratory tests, and after reports of the contamination surfaced, failed to issue warnings.

The suits say that the presence of prescription drugs in PC-Spes falls under the California Corporate Criminal Liability Act, which requires that a corporation or a company official who learns of "any serious concealed danger" has to report this finding in writing to the authorities within 15 days.

In the case of academic institutions, failure to test chemical composition of the agent or respond to concerns about its composition constituted a violation of informed consent regulations for patients involved in clinical trials of PC-Spes, the complaints state.

From the Emperor's Court

Chen, the originator of PC-Spes, was a chemist once employed by Merck. Working with Xu Hui Wang, then a professor at Shanghai Medical University, she tried to create agents that would combine traditions of Chinese medicine with the rigor of mainstream science.

Proponents of the therapy say that Wang, the great-grandson of a physician at the court of China's emperor and a defendant in this suit, inherited knowledge of traditional Chinese medicine.

Chen and Wang received a patent for PC-Spes in 1995. During the same year, Chen joined the Department of Microbiology and Immunology at the New York Medical College in Valhalla, N.Y., and established the California company to manufacture the agent, court document say. By 1997, Chen made a connection with Milken, the complaints state.

A leading private funder of prostate cancer research, Milken is a gateway to academic medicine. An argument can be made that the controversial financier is also the single most influential player in oncopolitics within the past decade.

Emerging on the scene in November 1995, Milken staged a Washington "summit," where he presented a vision for a $20 billion a year assault on cancer. This war-like operation would be funded from currently untapped sources of investments and would require greater collaboration between the government and industry (**The Cancer Letter**, Nov. 24, 1995).

Three years later, Milken financed a march on Washington by patients and other cancer interests. The event brought thousands of people to the Mall, but failed to produce a unified cancer agenda. Seizing the momentum of the march, the American Cancer Society organized the National Dialogue on Cancer. Recently renamed C-Change, that organization has become a political powerbase for one of its founders, NCI Director Andrew von Eschenbach.

Milken and his Prostate Cancer Foundation are not part of C-Change. However, Milken and von Eschenbach have been in regular communication for years, and while their programs are not identical, they are concordant.

Both make liberal use of the war rhetoric and draw plans for multibillion-dollar private-public collaborations. Milken's goal is to accelerate progress in medicine. Von Eschenbach is more specific: he vows to end "suffering and death due to cancer" by the year 2015.

Von Eschenbach's NCI has embraced a proposal to

develop agents for cancer prevention based on surrogate endpoints, which could allow sponsors to test drugs in healthy people, potentially opening an enormous market.

Meanwhile, Milken is blasting the FDA's requirement that sponsors demonstrate that their products have efficacy against cancer. His point-by-point proposal, published in The Wall Street Journal July 14, 2003, includes the following:

"Re-examine the FDA efficacy standard. Today, manufacturers must prove that new drugs are not only safe, but also that they work in most patients. That's a good standard when a drug is one of many treatment options, as it could be, say, in the case of blood pressure. A different standard might be appropriate, however, for patients with untreatable terminal illness and no other options. Advances in genomics are expected to produce drugs that work for some patients but not others, or that are effective for some who are not at risk of side effects, even if other patients can't tolerate them. "

David Johnson, president-elect of the American Society of Clinical Oncology, said the efficacy standard is an essential criterion for drug approval.

"As a cancer survivor, I want drugs that work," said Johnson, deputy director of the Vanderbilt-Ingram Cancer Center and director of its division of hematology and oncology.

"Giving a drug with no efficacy to anyone—regardless of the patient's health status—simply makes no sense. If efficacy cannot be shown in some reasonable manner, then making the drug widely available under the FDA's sanction simply licenses companies, organizations, and researchers to do whatever they please.

"Unprovable and seductive claims—such as `improved prostate health'—can be made willy-nilly," Johnson said. "These claims hold particular attraction `for patients with untreatable terminal illnesses and no other options,' individuals who are vulnerable to any prospect of hope and possible improvement."

Believers in PC-Spes describe it as a product of another medical tradition, which cannot be reviewed by regulators who insist on knowing the contribution of every ingredient to the safety and efficacy of the product.

Trying to get PC-Spes absorbed by mainstream medicine was a formidable challenge in part because clinical trials of the agent primarily measured its ability to reduce the PSA level.

The use of PSA for screening hasn't been shown to increase survival. Though physicians and prostate cancer patients monitor PSA as an indicator of disease progression or response to therapy, FDA hasn't recognized the lowering of PSA as an endpoint for drug approval. The agency hasn't recognized it even as a surrogate endpoint that may suggest benefits for patients.

Into the Mainstream

In 1997, Chen made a presentation at the CaP CURE annual conference, and met William Fair, then chairman of urology at Memorial Sloan-Kettering Cancer Center. At the time, Fair was battling advanced colorectal cancer and exploring the potential of alternative medicine.

In a press interview shortly before his death, Fair said he tested Chen's herbs by feeding them to nude mice that were implanted with his tumor. "The tumor shrunk, and the mice didn't die," Fair said to The New Sun Newspaper, a New York publication. "It's marketed now as Spes. It's a combination of herbs. It's a lot of mushrooms. This same company makes a product … which they call PC-Spes… It's an interesting product."

The story of Fair's disease and his reliance on a blend of alternative medicine and cutting-edge science became fodder for extensive coverage, starting a buzz around Chen and her company. According to the complaints, the funding for Chen's research at NYMC came from two sources: CaP CURE and the revenues from the nutritional supplements.

Chen was involved in two corporate entities: IMR and Novaspes Research Laboratory, the company that tested these products, the complaints state.

"She arranged to use NYMC, in the words of its administrator, as a `vehicle' or conduit to fund research at the Novaspes laboratory by disbursing money from IMR and Novaspes Inc. to NYMC's bank account, which, in turn, disbursed the funds back to Novaspes in a circular fashion," the complaints state.

According to court documents, Chen also raised $1 million in CaP CURE funds, which "went first into NYMC's bank account, and then to Novaspes."

"CaP CURE knew that its funds were being accepted by NYMC for [immediate] turn over to Sophie Chen to conduct research on the dietary supplements," the complaints state.

Chen's early scientific papers apparently didn't impress her supervisor at the NYMC Department of Molecular Biology and Biochemistry. A deposition that is part of the litigation quotes the department chief Soldano Ferrone describing this work as "phenomenology, not

science."

In 1997, Chen was given office space at the institution's Brander Cancer Research Institute and became an adjunct professor at NYMC.

"At about the same time, she arranged for at least five of the NYMC faculty members involved in research on PC-Spes to be issued stock in IMR," the complaints state. Through Novaspes and IMR, Chen conducted pre-clinical studies and small trials.

The relationship with NYMC was structured as a collaborative research agreement, court documents show. According to the agreement, a copy of which was obtained by **The Cancer Letter**, NYMC was prohibited from trying to determine the PC-Spes ingredients in the lab. "[The principal investigator]… certifies that the project shall not include any chemical analysis of the materials," the agreement states.

Also, the scientists and the college were prohibited from sending PC-Spes to anyone outside NYMC. "The materials are to be used only in the laboratories at the college, and no one will be allowed to take or send materials to any other location without IMR's written consent," the agreement stipulates.

Though the exact composition of PC-Spes remained a secret, the results from studies of the agent were published in medical journals, and were cited in the IMR promotional document, "PC-Spes: A Guide to Published Scientific Papers."

A spokesman for NYMC said the institution doesn't regard itself as a party to the litigation. NYMC has not been served in the personal injury suits, and in a related class action suit, a Los Angeles judge ruled recently that his court had no jurisdiction over New York.

"The college owned no interest in PC-Spes or its manufacturing or marketing entities, and engaged in no distribution or marketing of the product," said Donna Moriarty, a spokesman. "New York Medical College's involvement with PC-Spes was to conduct basic research to try and determine the botanical's properties.

"The college conducted no research into the use of PC-Spes in human patients. The research done by the college was funded through Sophie Chen, who holds an unpaid research appointment to the college's faculty. We understand that Dr. Chen has pleaded 'no contest' to a misdemeanor in California relating to the distribution of some of the PC-Spes that was contaminated with prescription drugs.

"It is our understanding that the misdemeanor did not require any knowledge of the contamination for the person charged to be held responsible for its violation," Moriarty said. "The college understands that Dr. Chen continues to assert her lack of any prior knowledge of the contamination."

Officials at Memorial Sloan-Kettering Cancer Center said they were unable to comment by deadline. "We have not received the complaint through officials channels," Anne Thomas, a spokesman, said to **The Cancer Letter**. "We are unable to comment substantively, because the documents you provided are voluminous, and they are still being reviewed here."

Responding to the related class action suit, the Regents of the University of California argued that the complaint was groundless in part because the "action is barred by the doctrine of academic freedom."

The court overruled that objection.

The Mystery of Composition

Anecdotes of miraculous response to PC-Spes were spread through the Web site of Chen's company, through patient bulletin boards, and through the sites of academic cancer centers.

Even now, with PC-Spes withdrawn from the market, Brander Cancer Institute's Web site includes praises of the agent, www.nymc.edu/pubs/Chironian/Fall2001/pc101.htm

"It is a mixture of things that handle different parts of the disease process that is active in most men," basic scientist Frank Traganos is quoted saying. "In Chinese medicine you look at the whole mixture, not individual molecules. I don't believe PC-Spes is a cure, but I suspect it keeps the malignancy growth rate so slow that the patient will die of something else. Meanwhile, the anti-tumor formulation contains an analgesic; the first thing you notice is the pain goes away. PC-Spes enhances the appetite and also boosts the immune system." This occurs because PC-Spes affects p27 and Bcl2 proteins, thereby inhibiting the cells from multiplying, Traganos says.

Muhammad Choudhury, chairman of the Department of Urology, is quoted saying that he used PC-Spes in patients who failed hormone therapy. According to the Web page, "Dr. Choudhury began telling patients about the mixture some three years ago, calling it `the hottest thing in prostate cancer treatment.'"

"We do recommend it to older people with multiple health problems—it's a reasonable treatment for some of these individuals," Choudhury is quoted saying.

The UCSF Web site still contains a profile of a patient who enrolled in a CaP CURE-sponsored trial of PC-Spes, http://cc.ucsf.edu/ccreport/1.1/ccrep_trials.html.

"This dietary supplement consists of a mix of Chinese herbs, and contains more than 100 active ingredients," the story says. "The herbs mimic the female hormone estrogen, which may account in part for the mixture's anti-testosterone effects."

The same story quotes Eric Small, an oncologist who conducted CaP CURE-funded trials of the agent: "Although PC-Spes is considered a complementary therapy, we are applying the same scientific rigor we use when testing conventional drugs."

The Web pages do not report that PC-Spes has been withdrawn from the market.

From Doubts To Lab Results

"My husband went to Memorial Sloan-Kettering, because he was looking for the most advanced, evidence-based cancer care," said Jacqueline Strax, a plaintiff who runs PSA-Rising, a prostate cancer information Web site. "He put all his resources into being an informed patient. Yet, out of the blue, his physicians at Memorial brought up a clinical trial of these Chinese herbs, and later recommended that he buy them on the Internet. Ultimately, he did."

Strax's husband, Norman Strax, died in May 2002, three months after California health officials issued warnings about PC-Spes.

"When we found out what was in PC-Spes, we felt betrayed," Strax said.

Acceptance of PC-Spes was not universal.

"Back when PC-Spes was `hot,' a few of my patients asked me about taking it for their prostate cancer," said Johnson. "I advised them that we didn't know if it was beneficial or potentially harmful, and that they should consider participating in ongoing trials if they had an interest in the product."

Vanderbilt was not involved in the PC-Spes trials.

"When asked specifically if I thought they should purchase the drug via the Internet or by other means, I typically cautioned against it in the absence of hard data," Johnson said. "I suspect several patients went ahead and took it anyway. In general, this is my philosophy, to caution against taking products about which we have little or no good data."

According to court documents, Robert Nagourney, an oncologist at the University of California, Irvine, and Rational Therapeutics of Long Beach, Calif., learned in early 2000 that the dietary supplement was laced with drugs, and decided to test it.

Tests quickly established that the mixture contained prescription drugs, and the findings were conveyed to CaP CURE and Chen's company, the complaints state. Court documents do not establish precisely when these reports first surfaced and how they were conveyed.

According to a press account, Small became aware of rumors of the contamination in the summer of 2001.

"Beginning in the summer of 2001, rumors began to circulate that there was DES in PC Spes," Small said at the 2002 ASCO annual meeting. According to an article in the September, 2002, issue of Oncology Times, Small said that the rumors prompted him to get a laboratory analysis.

Small, a defendant in the suits, declined to discuss the case with **The Cancer Letter**.

"The Rumors"

The summer of 2001 appears to have been a turning point for PC-Spes.

Change came in part because David Domizi, a Connecticut businessman who learned about the herbal agent from a nutritionist at Columbia University, suddenly saw his PSA nearly double from 2.7 to 5.2.

At the same time, his wife Susan Domizi, discovered that men exchanging information on a PC-Spes mailing list were reporting similar spikes in PSA.

"I began to see that a lot of men were having suddenly rising PSA, including men who were hormonally naïve, and who had been maintaining for a long time," Susan Domizi said.

Domizi started to pay attention to labeling on the PC-Spes bottles, looking at the packaging, lot numbers, expiration dates. She asked men who were reporting PSA increases to look up the lot numbers on their PC-Spes bottles and forward the information to her.

"As the numbers came in, it became very evident that there was a pattern, a change between lot numbers," Domizi said.

Next, Domizi came across a rumor that PC-Spes contained DES. "That kind of caught my attention, because my mother had been on DES all the time she was carrying me. I went through the literature, and saw that it was used in prostate cancer treatment. What if it was just a small amount?"

As an owner of a business that harvests and processes seaweeds used in nutritional supplements, Domizi understood quality control and knew how to work with independent laboratories. After many calls, she found a lab in California that had the reference standards and the expertise to find DES.

The lab agreed to do the work, but on condition

that its name wouldn't be disclosed. "I secured three or four bottles of unopened PC-Spes from different lot numbers, including ones that had been effective for most people, and ones that weren't," Domizi said. "The lab wasn't told which was which."

After spending less than $1,500, within a few weeks, she had a result. "They got back to me with two results that were negative, and two that had clearly measurable levels of DES," Domizi said.

Now, Domizi found herself facing an ethical dilemma.

"I spent the worst 24 to 36 hours of my life, knowing that I now had information that would probably help my husband," she said. "We could go on low level DES, along with the existing PC-Spes, and get back to where he had been before. But I had spent several months collecting data and exchanging emails with wonderful men, whose disease was going out of control. How could I sit on this information, and not share it with these men, who might be able to use it?"

On July 6, 2001, Domizi posted the findings on a mailing list. That posting remains on the Web: www.wmfurology.com/pcaPCSPESalert.htm. This alerted Strax, who broke the story and posted an image of the lab report: www.psa-rising.com/medicalpike/pcspes/results140701.html. Honoring her deal with the lab, Domizi blacked out its name.

"I spent the next number of weeks trying to get this information to a few of the luminaries, the doctors who were known, respected and trusted by the public in the prostate cancer field," Domizi said. "I tried aggressively."

Next, she and a group of prostate cancer survivors chipped in to pay for another laboratory study, this one conducted by Rocky Mountain Instrumental Laboratories of Fort Collins, Colo. In late August 2001, that lab found DES in three of the six lots of PC-Spes it examined. The report is posted at www.psa-rising.com/medicalpike/pcspes/labreport090301.html.

The labs didn't examine PC-Spes for drugs other than DES.

"The publishing of the actual lab reports on the Internet, with the findings confirmed immediately thereafter by another independent laboratory, takes this way outside the realm of rumor," Domizi said.

The CaP CURE Conference on PC-Spes

On Oct. 15, 2001, CaP CURE sponsored a conference on PC-Spes, held at the Milken Family Foundation in Santa Monica.

"Each of the speakers… who knew that the dietary supplement was adulterated with prescription drugs, failed to inform the members of the audience, the medical community, and [regulatory agencies]" the complaints state. A PC-Spes research strategy established at the conference was ultimately published in the journal Urology.

Science was part of a commercial agenda, court documents state.

According to the complaints, "IMR's goal was to seek the sale of IMR to a pharmaceutical company. To facilitate the same, IMR used CaP CURE to fund clinical trials and studies or to fund the seed money for federal funding of these trials and studies, and to lend its credibility to the dietary supplements as being an effective herbal and all-natural treatment or cure for certain specified diseases."

Four months after the CaP CURE conference, on Feb. 7, 2002, the California Department of Health Services issued a warning to the public to stop taking PC-Spes, because it contained "undeclared prescription drug ingredients that could cause serious health effects."

The agency said PC-Spes contained warfarin. A related product, Spes, sold for strengthening the immune system, was found to be laced with alprazolam, the agency said. According to the press release, BotanicLab had pulled the products off the market.

The agency was mistaken, BotanicLab responded in a press release. "Our independent lab results reported the `synthetic contaminant' was not warfarin, but may instead be a phyto-Coumarin (a naturally occurring compound found in green plants) that may `mimic' warfarin in lab testing," the company said.

Later that year, the health agency issued a separate warning on a long list of supplements marketed by BotanicLab. This time, the agency said PC-Spes contained four prescription drugs: warfarin, DES, ethinyl estradiol and indomethacin. FDA included these notices in its MedWatch safety alert system. The alerts are posted at www.fda.gov/medwatch/safety/2002/spes_press1.htm and www.fda.gov/medwatch/safety/2002/spes_press2.htm.

Public unraveling of PC-Spes continued.

At the 2002 annual meeting of the American Association for Cancer Research, Nagourney reported the results of a comprehensive laboratory analysis of all PC-Spes lots sold in the US.

Later, in a paper, published in the Sept. 4, 2002 issue of the Journal of the National Cancer Institute, Nagourney and colleagues reported that lots of PC-Spes manufactured between 1996 and mid-1999 contained indomethacin in the range between 1.07 and 13.19 mg/g,

a variation of 1,300%. DES fell into the range of 107.28 to 159.27 mcg/g.

These lots were two to six times more antineoplastic and up to 50 times more estrogenic than lots made after the spring of 1999, the paper said. Warfarin first appeared in lots manufactured after July 1998, and fell into the range of 341 to 560 mcg/g.

Small's paper acknowledging the contamination was published in the September, 2002, issue of the journal Urology, as a commentary to the PC-Spes research agenda that emerged from the CaP CURE conference.

Small reported the results of a laboratory analysis of four lots of PC-Spes that were used in his randomized trial of PC-Spes vs. DES in androgen-independent prostate cancer.

The tests found that "each one of these lots contained small but variable amounts of DES," Small wrote. The amounts ranged between 0.3 mcg of DES per day and 94 mcg of DES per day. This was equivalent to 0.01% to 3.1% of the dose on the DES arm.

"Nevertheless, the underlying assumption of our study was that no DES was present in PC-Spes and that minimal lot to lot variation was present," Small wrote. "Both assumptions were incorrect, and on the basis of this chemical analysis, it was decided that the primary outcome measures of the study were not interpretable, and the study was halted."

The trial had enrolled 90 patients, short of 109-patient target, and none of its findings reached statistical significance. Small's paper says nothing about traces of contamination with agents other than DES.

On Dec. 18, 2003, Chen and two others pled no contest to a misdemeanor charge of adulterating food, and the company pled no contest to a felony charge of failing to inform the health agency, agreeing to pay about $500,000 in fines and reimbursement for the investigation. The company and its officials were permanently barred from manufacturing, selling or promoting any dietary supplements in California or to Californians.

Chen's criminal defense attorney put the plea perspective:

"This is the same type of violation that a market or restaurant would face if their food, unbeknownst to them, turned out to be contaminated in some way," attorney Stephen Nelson said in a statement.

"By resolving the criminal case in this manner, Dr. Chen will now be able to devote her time and energy to her research, and contesting a number of frivolous civil lawsuits, rather than spending the next year and all of her personal savings contesting a groundless criminal case," he said.

"The fact that the District Attorney agreed to a settlement whereby he would dismiss the case if Dr. Chen and her associates would plead no contest to such a charge and pay a fine to reimburse the state and his office for the costs of the investigation demonstrates that the District Attorney finally recognized the true facts of the case, that is, that the entire PC-Spes contamination issue was overblown, and that whatever minor contamination may have occurred, unintentional."

Changes In NCCAM Approach To Herbals

The disclosures of the contamination thwarted NIH-funded studies of the agent.

"When NCCAM learned of the contamination of PC-Spes with prescription drugs, we called a halt to all four studies that we had been supporting," said Stephen Straus, Director of the National Center for Complementary and Alternative Medicine. "Based on the advice of a panel of experts in urologic oncology and herbal medicine, and representatives of the FDA, the NCI, industry and patient groups, we allowed the three laboratory based studies to resume with added requirements to explore the biological effects of the contaminants.

"The one clinical trial we were supporting was terminated," Straus said to **The Cancer Letter.** "Because of the strength of the early data on PC-Spes, and the need for additional treatment options for men with hormone refractory prostate cancer, NCCAM has committed to support additional studies once 'clean' PC-Spes becomes available."

Generally, clinical researchers take it on faith that experimental therapies they receive from pharmaceutical or biotech companies are exactly what the sponsors say they are. The public, too, usually assumes that herbal products are standardized, Strauss said.

"Our research has shown inordinate variability in product content and purity of herbal products," he said. "The contamination of PC-Spes products confirmed for NCCAM that our commitment to focus more on conducting basic research before investing in clinical trials, even for products already in use, is the best approach for botanicals research and CAM research, in general.

"The PC-Spes situation brought to the forefront the issues of contamination and standardization that NCCAM has been trying to address," Strauss said. "In fact, NCCAM now requires characterization of all products to be used in humans."

Patients seeking a PC-Spes substitute have no difficulty finding agents that, according to claims by vendors, are at least as good as the withdrawn nutraceutical. Some, including Chen's attorney Nelson, maintain that the issue of the contamination was overblown.

"For thousands of prostate cancer sufferers, PC-Spes worked despite the alleged contamination problems the company encountered," Nelson said in a statement. "Even California Department of Health Services officials have now publicly admitted that contamination is a common problem with Chinese herbs and patent medicines."

Chen acknowledges that BotanicLab "encountered minor quality control problems with its Chinese suppliers," Nelson said. "Moreover, as soon as independent tests revealed possible contamination, the company recalled the product."

Citing what he described as more sophisticated tests, Nelson said that "what appears to be the synthetic or pharmaceutical drugs alleged in the criminal complaint are really natural phyto-chemical compounds that have a similar chemical signatures."

In short, there may not have been a contamination, he said.

"The real victims in this matter are the men who have suffered and died because of the recall of PC-Spes," Nelson said. "Whatever contamination may have occurred was minuscule at best, and did not affect the efficacy of PC-Spes. No one has ever died or experienced any significant ill effects from taking PC-Spes as directed. However, thousands of men benefited and had both their lives extended and the quality of their lives improved.

"If there were any crime here, it was the `success' certain people involved in a number of civil lawsuits against Dr. Chen and her associates had in pressuring the California Department of Health Services and the District Attorney into a prosecution that resulted in the recall of PC-Spes."

Nelson's comments are posted at www.napc.info/bulletinboard.htm.

Physicians and Patient Groups

The complaints allege that several basic scientists as well as physicians who recommended PC-Spes and conducted trials with the agents had shares in Chen's company, and several patient groups acted as distributors of the product.

The complaints describe Aaron Katz, a "holistic urologist" who conducted clinical work with PC-Spes at Columbia University College of Physicians and Surgeons, as a "shareholder, control person, managing agent of IMR, [and] a member of the scientific advisory board."

The complaints state that Katz "controlled, promoted, distributed, advertised and/or sold dietary supplements to consumers in California and nationwide, and he derived and continues to derive significant financial benefits therefrom, despite his knowledge that the dietary supplements were adulterated with dangerous prescription drugs."

According to a staff member, Katz was traveling, and efforts to reach him via email were unsuccessful.

An undated three-page handout on PC-Spes, which was apparently designed for distribution to patients who approached Katz for information about the agent, contains the following disclosure: "I receive no financial support, stock interests, or have any agreements with BotanicLab. I have used PC-Spes in my practice and report on my experience."

The complaints allege that Us TOO acted as a "distributor, wholesaler, franchisee and agent" of IMR, and sold dietary supplements.

"I have never had any financial involvement whatever with PC-Spes or with BotanicLab," said Hank Porterfield, former chairman of Us TOO, who now heads the Alliance for Prostate Cancer Prevention, a group which is also named in the suit.

"I have never acted as a distributor. I acted as a facilitator between the manufacturer and a group of 10 members of Us TOO with advanced prostate cancer in a program to test the efficacy of the product, with the understanding that the 10 patients would report back their results. There was no money involved at all. The product was provided free of charge by the manufacturer to obtain data and analyze results. We have had no association with BotanicLab, IMR or Sophie Chen."

Prostate cancer patient activist James Williams said the complaints are incorrect in identifying him as a director of APCAP, and a "consultant" to Chen.

"First of all, I am not a director of APCAP," Williams said. "I am a consultant to that organization. I am not a consultant to Sophie Chen, and have no association with her, although I do know who she is. We sat on an NCI workshop that was investigating PC-Spes. I've never received any money from them, nor has, as far as I am aware, APCAP promoted, or advertised, or sold, or had a franchise with PC-Spes.

"My interest has been that as a prostate cancer survivor and activist. Before the suspension of the product, we saw the value in men with metastatic

disease, in that it was keeping the PSA relatively non-aggressive, and was helping a lot of men maintain a quality of life," said Williams.

"When it was taken off the market, to many of us, it was suspicious why this was happening, because we didn't know any men who were having ill effects, or having any major side effects," said Williams, who has recently completed a term on the NCCAM advisory board. "PC-Spes was helping them, because it was keeping them alive, and it was lowering their PSA."

A copy of one complaint, involving the rheumatoid arthritis remedy RA-Spes, is posted on Twisted Badge, a Web site run by Mike Madigan, an Orange County, Calif., private investigator and journalist who has been covering this story since last March: http://twistedbadge.com/feature_consumeralert_7.htm.

Professional Societies:

ASCO To Congress: Freeze Medicare At '04 Chemo Rates

The American Society of Clinical Oncology this week urged Congress to freeze the amount of Medicare payments available to cover the cost of chemotherapy at 2004 rates in 2005 and 2006.

ASCO is concerned that provisions in the Medicare Prescription Drug Improvement and Modernization Act of 2003 will severely limit access to essential cancer care for the more than half a million elderly Americans diagnosed with cancer each year.

"Feedback from oncologists indicates that changes to Medicare reimbursement for cancer drugs and related services will create serious access problems for patients in 2005 and beyond, as reimbursement for both drugs and patient services declines sharply," said Margaret Tempero, president of ASCO, which represents more than 20,000 cancer specialists.

The Medicare bill, signed into law in early December, reforms the Medicare payment system for drugs and drug-related services by reducing the payments for drugs while increasing the payments for patient services.

"Congress wisely made these changes in a roughly budget-neutral way for 2004, and for that approach oncologists and their patients are grateful," Tempero said. "But the sharp reduction in total payments for 2005 and later years will create a serious problem that needs to be addressed before the cuts occur."

To address what it called a "looming crisis," ASCO is asking Congress to freeze total Medicare payments available to cover chemotherapy costs in 2005 and 2006 at 2004 levels and ensure that Medicare payments are not less than costs of acquiring chemotherapy drugs.

ASCO identified the following problems with the Medicare law:

--2004 Medicare payments for some cancer drugs were set at rates lower than the acquisition prices that were then in effect. A survey conducted by ASCO in early January showed that oncologists were unable to purchase many of the cancer drugs they administer to Medicare patients for prices less than the Medicare payment amounts.

--Access problems will emerge in 2005 as payments for drugs and patient services decrease significantly from 2004.

-- The alternative drug acquisition program--described as "a safety net" for providers who cannot purchase drugs for Medicare payment amounts--will not be available until 2006.

--The decrease in reimbursement for patient services is scheduled to begin in 2005, before the safety net is in place.

--The impact of the law on patient access to quality cancer care is still unclear, and Congress has mandated studies to address this question that will not be completed until 2006 at the earliest.

According to a 2003 ASCO survey of nearly 1,000 oncologists, cuts in Medicare reimbursement would result in oncology practices across the country limiting the number of Medicare beneficiaries they see, sending Medicare patients to less convenient hospital locations for their chemotherapy, and closing satellite offices.

ASCO is collecting data from practices across the country to determine the current and potential impact of cuts in Medicare reimbursement.

NCI Programs:

Starting Year 3, Director Plans New Management Structure

Beginning his third year as NCI director, Andrew von Eschenbach has begun a reorganization of his office, putting in place a new management structure between himself and the divisions.

In remarks to the National Cancer Advisory Board on Feb. 18, von Eschenbach said he established four new deputy director positions to oversee the Institute's research and activities in a "shared governance model," with the division directors reporting to them.

"The concept is that the four deputies, by being arrayed across discovery, development, and delivery,

will be able to provide the executive leadership function for the organization to continue to manage our portfolio and to manage it in a way that effectively integrates the portfolio across the entire enterprise," von Eschenbach said. "The division heads and the center directors continue to play a role in the senior leadership of the organization--in planning strategy, tactics, defining programs--and that occurs at the level of the Executive Committee."

The new positions will not create additional budget needs, von Eschenbach said. "We are not expanding the Office of the Director," he said. "We are flattening it. The infrastructure under the deputies will be very slim."

Von Eschenbach described the four new positions:

--Deputy director for integrative biology and molecular oncology. Von Eschenbach said he has offered the position to "a basic scientist, with an incredible reputation, that all of you already know and admire."

--Deputy director for advanced technologies and strategic partnerships. Anna Barker, who served as deputy director for strategic scientific initiatives for the past year, was appointed to this position.

--Deputy director for translational and clinical sciences. "That position is also not formally filled, but we have those negotiations well in hand," von Eschenbach said. "As I have indicated in other venues, I have been particularly gratified and grateful for the fact that Dr. Karen Antman has been serving in an advisory consultant's role, helping to address this particular area of importance. She has been of great service. Hopefully, within a short period of time, we will have reached a point where we can formally announce the appointment of the deputy director for translational and clinical sciences."

--Deputy director for cancer care and delivery systems. Mark Clanton was appointed to this position (**The Cancer Letter**, Feb. 13).

"These four deputies will work effectively as an integrated, cohesive unit, directly working with me on a daily, day-in and day-out basis," von Eschenbach said.

NCI Deputy Director Alan Rabson will remain in his position, working primarily on patient and professional relationships, von Eschenbach said.

Another existing deputy director position is in the process of being filled. Janice Mullaney has served as acting deputy director for management, and is expected to be appointed to that position.

At the division level, James Doroshow, of City of Hope, will join NCI soon as director of the Division of Cancer Treatment and Diagnosis, von Eschenbach said.

"Blessed To Find An Incredible Cadre"

Von Eschenbach said he did not need to make management changes earlier, because NCI had a strong structure in place.

"When I came here two years ago, I truly was blessed to find in place an incredible cadre of talented, gifted, committed and passionate people," he said. "There was a tremendous infrastructure of leadership and support, both within the Office of the Director, and among the division heads and center directors."

Also, Rabson served as his guide. "Few people could be blessed to be put into an organization completely new, completely from the outside, never having spend a day of their career as a formal, active part of the NCI or NIH, and be blessed to find a deputy director in place with 47 years of experience, who knew anything and everything you possibly could know about the NCI and was unbelievably generous and committed and did anything and everything he could to support me," von Eschenbach said. "I was incredibly grateful then to Dr. Rabson, and I continue to be grateful to him for his service and support."

Therefore, he spent the first year formulating the NCI mission, he said.

"We also had a great deal of leadership below Dr. Rabson and that afforded me the opportunity of not having to immediately address organizational restructuring, but to focus on the future of the institution, building on the tremendous success of the past, and looking toward the future," von Eschenbach said. "We focused on what the purpose of that progress was, and began to crystallize the mission of eliminating the suffering and death due to cancer, the creation of a timeline which that could be accomplished in, that was feasible, although aggressive, establishing that timeline of 2015."

Von Eschenbach announced the 2015 goal a year ago at an NCAB meeting, he reminded the board this week. "We have over the past year continued to amplify that goal by providing the strategy and rationale that underpin that goal, and underpin that mission, and if you will, vision, as well," he said.

"That strategy is based on our ability to now understand cancer as a disease process and begin to envision pre-empting that disease process in a way that will enable us to prevent more cancers, more effectively detect, predict, and eliminate more cancers, and then, to modulate and change the behavior of other cancers

such that people live with and do not die from cancer," he said.

"Over the past year, building on that vision or goal, we have put a lot of time and energy into strategy, a lot of time and energy into how we would effect and manage that strategy, and also what it would require in terms of structure to facilitate our ability to bring that strategy about," he said.

Von Eschenbach said the management plan for his office as "a shared governance model," which is used by most large organizations.

"In order to effectively lead at the executive level a large, complex organization, the CEO role is vested in a particular person, but, is in fact shared and operationalized by working closely and in an integrated fashion with key other members of that CEO function," he said. "So in that particular model, what I had chosen to do, was to create within the office of the CEO, four deputy director positions that will report directly to me and work directly with me. Those four deputy director positions are arrayed across our strategy in our portfolio of discovery, development, and delivery.

"Within the Office of the Director, the four deputies will be arrayed across discovery, development, and delivery.

"One deputy pretty much focused on the end of discovery. One deputy focused on the transition of discovery and development. Another between development and delivery, and then the fourth at the delivery end."

After describing the new positions, Rabson's role, and Mullaney's impeding appointment, von Eschenbach concluded his management news:

"So, ladies and gentlemen, the Institute is blessed," he said. "It's blessed by incredible talent and incredible commitment across the entire continuum of NCI."

Funding Opportunities:

Program Announcement

PA-04-063: SBIR/STTR Initiative for Image-Guided Cancer Interventions

Application Receipt Dates: April 1, Aug. 1, Dec. 1.

The PA aims to stimulate a systems approach for integration and clinical testing of IGI technologies for treatment of cancer.

The PA is available at http://grants2.nih.gov/grants/guide/pa-files/PA-04-063.html.

Inquiries: Keyvan Farahani, Cancer Imaging Program, phone 301-496-9531; fax 301-480-3507; e-mail farahank@mail.nih.gov; CIP Web site http://cip.cancer.gov or Laurence Clarke, phone 301-435-9190; fax 301-480-3507; e-mail lclarke@mail.nih.gov.

In Brief:

Korsmeyer Receives Pezcoller; Karmanos Wins DOD Grant

(Continued from page 1)

family lives in Pacific Pallisades, Calif. . . . **STANLEY KORSMEYER** was selected for the 2004 Pezcoller Foundation-AACR International Award for Cancer Research. He is Sidney Farber Professor of Pathology and professor of medicine at the Dana-Farber Cancer Institute at Harvard Medical School, and a Howard Hughes medical institute investigator. Korsmeyer received the award for his research in apoptosis and survival, leading to the development of individualized treatments of lymphomas and other cancers. He will give a lecture at the AACR annual meeting in Orlando. The award carries a cash prize of €75,000. . . . **BONNIE SLOANE**, head of the Barbara Ann Karmanos Cancer Institute Proteases and Cancer Program and chairman of Wayne State University School of Medicine Department of Pharmacology**,** received a $5.8 million Breast Cancer Center of Excellence grant from the Department of Defense. The grant will fund research to identify which proteases are linked to breast cancer growth and develop imaging techniques to monitor treatments that target them. . . . **NATIONAL COMPREHENSIVE Cancer Network** promoted two executives. **Alana Brody** was named vice president of business development and **Joan McClure** was named vice president of clinical information and publications. . . . **BARTON KAMEN** was appointed editor-in-chief of the Journal of Pediatric Hematology/Oncology for a three-year term. He is chief of pediatric oncology at the Cancer Institute of New Jersey and professor of pediatrics and pharmacology, UMDNJ-Robert Wood Johnson Medical School. . . . **BLOOD and BONE MARROW** stem cell database has been established by National Institute of Allergy and Infectious Diseases, National Library of Medicine, and National Center for Biotechnology Information. The public database contain results from clinical blood and marrow stem cell transplants involving unrelated donors. The database is available at www.ncbi.nih.gov/mhc.

Zerhouni To Discuss Roadmap

NIH Director Elias Zerhouni will hold a briefing on the NIH Roadmap for Medical Research, Feb. 27, 2-4 p.m., at the Bethesda Marriott, 5151 Pooks Hill Rd., Bethesda, Md.

The meeting will be webcast. To register for the meeting or for further information about the webcast, see www.nihroadmap.nih.gov.

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