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## DCCR ADVISORY COMMITTEE DELAYS PLANNED EXPANSION OF PROMISING COMMUNITY CLINICAL ONCOLOGY PROGRAM

Plans by NCI's Div. of Cancer Control & Rehabilitation to expand its current Clinical Oncology Program, which were approved in principle in May by the DCCR Advisory Committee, were handed a

*In Brief*

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### SENATE SUBCOMMITTEE VOTE: $950 MILLION PLUS TRAINING; DEVITA NEEDS NEW CLINICAL ASSISTANT

**SENATE HEW** Appropriations Subcommittee voted $950 million plus whatever the amount it later determines is needed for training when it marked up the FY 1979 money bill (*The Cancer Letter*, June 23). The report in *The Cancer Letter* said the subcommittee had approved $970 million, which was assuming that training funds would amount to $20 million, an assumption that was applied to the House approved figure of $888 million. Senate staff members feel the subcommittee may vote for a higher training figure, when the authorization bill is approved. Without the authorization, both House and Senate subcommittees agreed they had no legal basis to include training money in the appropriations bill now. . . . **BRIAN LEWIS**, who is special assistant for clinical affairs to Div. of Cancer Treatment Director Vincent DeVita, is transferring to the division's Medicine Branch as a senior investigator. DeVita is looking for a replacement; interested physicians with experience in clinical oncology research should write to him or to Lewis, NCI-DCT, 31-3A49, Bethesda, Md. 20014. . . . **OTHER POSITIONS** now open in DCT include a chief of the Drug Synthesis & Chemistry Branch in the Developmental Therapeutics Program; positions in the Cancer Therapy Evaluation Program with broad responsibilities of assisting in development, monitoring and evaluation of grant and contract supported clinical trials, including radiation and surgical oncology; head of the new Surgery & Nutrition Section of the Clinical Investigations Branch; chief of the new Radiation Therapy Development Branch, and a radiobiologist in that branch. The new branches have evolved out of NCI's reorganization and involve development and management of extramural programs. . . . **COMBINED MODALITY** chemotherapy-radiotherapy studies supported by DCT with Cancer Research Emphasis Grants will be readvertised. Nine investigators are presently being funded, five with five-year awards, the others with three years. DCT's Board of Scientific Counselors agreed to the readvertising, to permit award of an additional three years to those who are on three years now (or their replacements if new applicants are more competitive). The five year awards will be extended one year administratively, making all terminate at the same time. Applications are due Nov. 1; contact Daniel Rubin, DCT-DCT, 31-3A49, Bethesda, Md. 20014, 301-496-6711.

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## POSSIBLE UNNECESSARY OVERLAP SEEN WITH OTHER NCI COMMUNITY PROGRAMS

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setback in the committee's meeting last week. The committee approved a motion to delay consideration of a revised RFP (or probably an RFA) until DCCR can prepare a staff report: "(1) regarding the similarity or dissimilarity of related programs as to objectives and goals; and (2) containing recommendations regarding the extension and/or enlargement of the Clinical Oncology Program in coordination with other programs." Such a report should be ready for the next meeting in November.

Committee Vice Chairman Oliver Beahrs, who drafted the motion, was especially concerned about possible unnecessary overlap between COP and other NCI-supported activities, such as the programs carried out by community cancer centers, comprehensive cancer center outreach and the American College of Surgeons Commission on Cancer.

Beahrs who is Head of Section, General Surgery, at the Mayo Clinic said that the ACOS cancer program in particular is a community oncology activity. It is designed to improve cancer registries and programs, with emphasis on evaluation of treatment, quality of life, and multi-disciplinary clinics. He noted that the ACOS has 800 approved programs and 200-250 applications on file.

Committee action followed a presentation by Donald Buell, DCCR program director for clinical oncology, on the status of the seven existing clinical oncology contracts, which DCCR Director Diane Fink described as "an experimental program of the highest order." As reported in *The Cancer Letter* of May 12, current projects are in Grand Rapids, Indianapolis, San Antonio, San Jose, Allentown, Pa., Walla Walla, Wash./Pendleton and La Grande, Ore., and Ada/Shawnee, Okla. All have undergone merit review within DCCR with exception of the two rural projects in Oklahoma and Washington/Oregon—the latter known as the Blue Mountain Oncology Program—which have not been underway long enough.

Pending formal synthesis of the reviewers' comments, Buell summarized the merit review results as follows: Grand Rapids, Indianapolis and Allentown have strong programs and are fulfilling the RFP requirements. San Jose has a well-run program but at the time of review was deficient in areas of physician involvement, patient accrual and the development of a rehabilitation program. Buell said that since review, San Jose has successfully addressed these problems. The program in San Antonio has fallen short of its considerable potential.

The ADA/Shawnee project lacks a medical oncologist, but it has developed a strong relationship with the Oklahoma Cancer Center, which provides close effective consultation. This project is being viewed as a key link in the developing statewide cancer program, according to Buell, and is beginning to develop outreach to even smaller communities.

The Blue Mountain Oncology Program has had difficulties in recruiting staff personnel, but has developed its own staff of oncology nurses who form the backbone of all the COP programs. Consultative relationships with the Hutchinson Cancer Center in Seattle and the Oregon Comprehensive Cancer Program (a DCCR-funded grant project) are good. From September 1977 through March 1978, 417 cancer admissions were recorded in the three participating Blue Mountain hospitals. Of these 242 were registered as COP patients. Eleven cancer sites are being specifically addressed at Blue Mountain: lung, breast, endometrium, cervix, ovary, bladder, kidney, prostate, colo-rectal, brain and lymphoma. If the Oklahoma and Blue Mountain programs succeed, Buell believes the implications for other rural areas will be tremendous.

Buell told the committee he found much interest in the COP concept at a clinical oncology meeting in Indianapolis last week, where general dissatisfaction was expressed about the help given community hospitals by NCI. Buell said he was told that relatively little financial aid from NCI grants to comprehensive cancer centers filters out to the community hospitals, whereas under COP it would be possible for them to get $150,000 directly. Money aside, plans developed by the centers frequently do not address the needs of community hospitals. The hospitals have not been able to contribute to the design of outreach programs, so that planning documents are not implemented frequently because they are unacceptable to the community. On the other hand, Buell said, COP forces community hospitals to cooperate and design a program for themselves, which works.

Buell's presentation generated a discussion which eventually led to Beahrs' motion for a comparative report on all such programs, but some members of the committee had other concerns about COP. Timothy Talbot, chairman of the Cancer Control Grant Review Committee, wanted to know if the COP projects could carry on after funding ceased. Buell expected that they could, picking up what they felt was good and needed, such as the oncology nurses, and seeking third-party support funds as required.

Buell said DCCR would like to fund five to seven more COP projects on the level of the Grand Rapids program and a total of five on the Blue Mountain level.

## CANCER PROGRAM LOSES POWERFUL ALLY WITH ROGERS' RETIREMENT

The planned retirement of Rep. Paul Rogers (D-Fla.), Chairman of the House Subcommittee on Health and

the Environment, will be a loss to the health community and the national cancer program, of which he has been a long-time champion. Rogers was a key figure in steering the original cancer bill through Congress in 1971 and has lent powerful support to renewals of the act.

Speculation about Rogers' possible successor centers upon Rep. David Satterfield (D-Va.), next in line on the subcommittee. A shuffling of committee assignments always follows an election, however, so four or five other high-ranking members of the House Committee could opt for this prestigious position.

## GROUP CHAIRMEN TOLD INAPPROPRIATE FOR THEM TO DISCOURAGE NEW GROUPS

A "multitude of requests" for NCI funding of new regional cooperative groups has been submitted, along with requests to establish "groups within groups," the Cooperative Group Chairmen's Committee was told at its recent meeting.

"We need some policy to handle them," Barth Hoogstraten, chairman of the Chairmen's Committee said. "If any are approved, they will require some funding."

"We discussed the need for more Cooperative Groups, and it was determined a year ago that there was no need for another multimodality group," said Franco Muggia, director of the Cancer Therapy Evaluation Program in the Div. of Cancer Treatment. "We agreed there might be a need for new groups organized along geographical lines. We approved one new regional group (Northern California Oncology Group) and said we would consider others.

"Since then," Muggia continued, "there has been no departure from that policy. We've received a lot of requests, and some applications have gone to the CCIRC (Cancer Clinical Investigation Review Committee). They have not fared well. We have discouraged some requests, because we felt they were not ready or able to pursue clinical research. Some organizations have persisted, and we continue to receive requests for regional groups. When we do get such a request, we send a DCT staff member to meet with them, attend their meetings and assess their strength. In general, we have discouraged them.

"One exception," Muggia said, "is the North Central Cancer Treatment Group." Organized by the Mayo Clinic, this group consists of eight community clinics in Minnesota, Montana, Nebraska and the Dakotas. It develops protocols independently and in cooperation with the Eastern Cooperative Oncology Group.

Muggia said NCCT's application for funding was pending with CCIRC.

James Holland and other committee members indicated some hostility to the fact that NCCT's application was routed to CCIRC. "It's not a group yet, it's a petitioner," Holland said. "Why not send it to the Div. of Research Grants like any other grant applicant? Only recognized groups should go to CCIRC."

"They're talking to program (DCT staff), said Clair White, CCIRC secretary, inferring that staff members directed the application to CCIRC.

"That's what I thought," Holland said.

Stephen Carter, chairman of the Northern California group, commented, "I question the appropriateness of this discussion, as chairmen of groups with which they (new groups) would compete. What is the peer review system for if existing grantees can close membership to the club?"

"DRG assigns grants for review," White said. "Formation of new grants, by tradition, don't just come in without discussions with staff. Program people can advise them if they should apply."

"We don't direct them to CCIRC," Muggia said. "We can't tell them not to go there."

CCIRC Chairman Jerome DeCosse said, "These are not isolated entities. New groups do impact on existing programs. But there is a question of appropriateness of discussing it here."

"It would be appropriate for us to discuss it for information purposes, but not to establish policy," Carter said. "If a new group applies, gets approved and gets a good priority score, then it is eligible for funding."

Hoogstraten noted that "we did vote on the Northern California application which we approved and on others that were not approved."

"Is that appropriate?" Carter steamed. "If you had noted no, I would have fought like hell against you."

"Your group was a propationary group, to see if a group regionally organized was a valid approach," Holland said.

"But is the Chairmen's Committee the appropriate place to decide that?" Carter asked.

"We can express our views," Hoogstraten said.

"If the construction of competing activities digs deeply into our resources, I think we would have something to say about it," Holland said.

"DeVita told us we have a role in policy development relating to the Cooperative Groups," Hoogstraten said. "That includes creation of new groups."

"I have trouble with that," Carter said.

**Holland said he would like to "discuss again the philosophy of who picks the studies a group does, and approval and disapproval of group activities."**

The group chairmen had thrashed out that issue last year with DCT Director Vincent DeVita, when they felt NCI's review of protocols was unnecessarily delaying their activation. DCT had held up some protocols because of perceived duplication or some other flaw.

"CALGB submitted an application for a study and it got mixed reviews from staff and some CCIRC members," Holland said. "I said we respectfully disagreed and would go ahead. Ted (Jacobs, Clinical In-

vestigations Branch administrative officer who is in charge of protocol review) wrote back and said there was still some scientific disagreement. Well, that's fine, that's what studies are for.

"It seems to me CCIRC will have a prior veto of studies," Holland continued. "We've just been through DCT staff having a veto. CCIRC should look at a group as a composite organization, with 20 to 30 studies. Let them do it. Then let the devil take the hindmost on review. It is not appropriate for them to anticipate in advance and to require us to bend to the opinions of someone who may not be as experienced.

"Neither DCT staff nor CCIRC should tell us what to do or not to do. If they do, we are in danger of becoming drones, and will lose all creativity," Holland said.

White insisted that CCIRC does not get involved in approval or disapproval of protocols.

"Our understanding is that when a protocol is submitted to DCT, and after staff responds by letter, the gorup can activate the protocol," Hoogstraten said.

"The protocol can be activated unless there is some ethical problem," Jacobs agreed.

"It appears that letter (from Jacobs) was just an extra precaution on your behalf," Hoogstraten needled Holland.

"We have a policy then, that these protocols are not blocked," Holland said.

"They can't be," Muggia and Hoogstraten both said.

John Boice, a member of the Environmental Epidemiology Branch staff in the Div. of Cancer Cause & Prevention, described the study requested about a year ago by DeVita on incidence of second tumors related to treatment. Boice presented a statement to the committee:

"To evaluate the potential carcinogenic effects of various modalities used in the treatment of cancer, NCI is attempting to combine and analyze information from several cancer treatment protocols. DCT and the Environmental Epidemiology Branch are collaborating with this investigation. The objective is to delineate the effects of the underlying disease and the various therapies on the development of second cancers. Chemotherapy has become increasingly important in the treatment of certain malignant diseases, resulting in long-term disease free survival for significant numbers of patients. Anti-neoplastic drugs are now being used 'adjuvant' to other primary therapies to delay, if not prevent, recurrence of malignancies. Recently, however, the leukemogenic effect of alkylating agent chemotherapy has been demonstrated in patients with ovarian cancer, and it has been recommended that caution be exercised in the use of adjuvant chemotherapy in patients at low risk of relapse.

"From a survey of NCI funded protocols, a number of cancer treatment trials were selected for evaluation. Selection criteria considered the years of followup potentially available because of high expected survival rates as well as the treatment modalities. Chairmen and statisticians are then contacted, available data evaluated, and abstract forms designed to obtain information on second cancers and other data not readily available from computerized data. A medical abstractor will be sent to the various facilities, if necessary. Existing computerized data will be combined with the information on second cancers, and the data will be analyzed by EEB. Also, selective ongoing trials have been requested to include on their followup forms a specific question on second cancers. This will facilitate the monitoring of the risk of second primary neoplasms. The completion of a 'location form' may be recommended for all ongoing trials to facilitate future followup efforts.

"Initial contact has been made with the (1) National Surgical Adjuvant Breast Project, the (2) Gynecologic Oncology Group, the (3) Radiation Therapy Oncology Group, the (4) Eastern Cooperative Oncology Group, the (5) Veterans Administration Surgical Adjuvant Group and the (6) Gastrointestinal Tumor Studies Group. Protocols selected for further evaluation are NSABP-1 (Control vs. ThioTEPA 1 shot in breast cancer), NSABP-5 (Control vs. L-PAM 2 years in breast cancer), NSABP-4 (Radical Mastectomy vs. Total Mastectomy vs. Total Mastectomy + Radiotherapy), NSABP-7 (L-PAM vs. L-PAM + 5-FU in breast cancer), GOG-1 (Control vs. L-PAM indef. in ovarian cancer), GOG-1a (Control vs. L-PAM in low malignant potential ovarian cancer), GTSG-6175 (Control vs. 5-FU + MeCCNU; MER; 5-FU + MeCCNU + MER in colon cancer), GTSG-7175 (Control vs. radiotherapy; 5-FU + MeCCNU; 5-FU + MeCCNU + radiotherapy in rectal cancer), VA-R29 (Control vs. ThioTEPA in large bowel cancer), VA (Control vs. FUDR in large bowel cancer), EST-2276 (5-FU vs. 5-FU + MeCCNU in colon cancer), EST-4276 (radiotherapy vs. 5-FU + MeCCNU vs. radiotherapy + 5-FU + MeCCNU in rectal cancer).

"The VASAG data have been computerized and analysis ongoing. The GPG baseline data have been abstracted. NSABP computerized data have been requested. GTSG records will be evaluated this month. ECOG records will be evaluated shortly. Data from an international study of 30,000 women treated for cervical cancer are being analyzed (Harvard Univ.) Other trials are being sought."

Carter asked if baseline studies of patients treated with surgery alone and not receiving chemotherapy have been obtained. Boice said they have, using the SEER registries.

Marvin Zelen, who heads the statistical and computer operation that serves ECOG and RTOG, reported on concerns of Cooperative Group statisticians as expressed at a recent meeting they held.

Chief among the concerns is that there are no statisticians on the DCT Board of Scientific Coun-

selors or on the CCIRC. "We submitted recommendations for members to Vince DeVita, but so far no statisticians have been appointed to either body," Zelen said. "There is a serious problem with the review and evaluation of statistical centers by CCIRC. Many statistical centers are underfunded, and it is particularly acute for those with multimodal studies."

Asked by Carter for an estimate of additional costs when a group goes multimodal, Zelen said the data processing costs alone for his groups increased by 200%.

Holland, after ascertaining that money which had been funding groups that have been phased out has already been absorbed into the other groups, commented "then we have to look outside the groups for funds to keep the statistical centers from being starved."

Muggia said DeVita is considering appointment of a statistician to the Board of Scientific Counselors. "But that's a small body, and it needs to represent a lot of areas."

Costan Berard, DCT staff member, reported on problems raised at a meeting of the Pathology Working Group.

"Pathology review is woefully underfunded," Berard said. Increasing demands are being made on pathologists for additional slides and other assistance to clinical investigators "and they never get any money for it." Berard said that pathological services in a hospital cost about $30 per case. Pathologists "are rather naive, and have no concept on how to get funded under the umbrella of the Cooperative Groups. They need guidelines on how best to apply for funding, how to phase into the Cooperative Group organization.

"Pathologists are disgruntled. They resent being an afterthought. I'm not sure we will continue to get their cooperation without some shoring up."

Hoogstraten said the Cooperative Groups handle about 20,000 new patients a year, with 15,000 of them in phase III trials where pathology review is most appropriate. Pathology service would cost $450,000 a year, with another $200,000 for review.

Committee member John Durant said, "Pathologists are nervous about making the decision to commit a patient to a protocol. They do not want responsibility for determining what treatment the patient receives." Durant said individual group pathologists should be educated so they may determine "what is and isn't important."

In other discussions, the group chairmen:

—Agreed that psychosocial research was important, that protocols in that area should be encouraged and should be funded through grant applications to CCIRC.

—Heard that clinical studies in chemoprevention (use of retinoids and possibly other substances as an intervention before a disease becomes clinically evident in high risk individuals might be undertaken by the groups.

Holland asked if the Div. of Cancer Cause & Prevention, which is supporting development of retinoids, might fund clinical studies.

"That is possible," Muggia said. "If our resources can be used to set up the studies, maybe we can make a case for it."

## PRESUMPTIVE RISKS SHOULD NOT NULLIFY BENEFITS OF MAMMOGRAPHY, HOLLEB SAYS

"Major accomplishments" can be attributed to the controversial Breast Cancer Detection Demonstration Projects .... I find it difficult to deny possible benefits to women who are 45 or 48 years old and dogmatically reserve mammograms for those over age 50," Arthur Holleb, American Cancer Society senior vice president for medical affairs, said in delivering the annual Wendell Scott Memorial Lecture.

Holleb's lecture, presented at a meeting sponsored by ACS and the American College of Radiology, was a ringing defense of the BCDDP, funded jointly by ACS and NCI. It was also a criticism of the NCI decree limiting mammography in the projects to women over 50.

After recounting the history of the project, Holleb said, "I personally believe, along with many other clinical oncologists, that major accomplishments can already be attributed to the project directors who persisted in the Breast Cancer Detection Demonstration Projects in spite of adverse publicity, a frenetic atmosphere created by a few prophets of doom and claims of iatrogenic epidemics of breast cancer in the 21st century," Holleb said.

"Diagnostic radiologists have shown that breast cancer screening can be well conducted in a variety of community institutions and that many self-selected women are eager to participate.

"Unsuspected breast cancer has been found in more than 2,700 women to date, and this is only a minimum figure. More will be reported as data flow in.

"Mammography has demonstrated its capability of finding breast cancer when physical examination revealed nothing. More than 45% of the cancers found were discovered by mammography alone. In the age group under 50, almost 40% of the cancers were found by mammography alone and over age 50, 50% were found by mammography alone. Had mammography not been used in these projects, nearly half of the existing cancers would have gone undetected.

"Mammography techniques and capabilities have improved considerably since the HIP study of the 1960s, especially in the age group under 50. In the HIP study under age 50, only 19% of cancers were found by mammography alone compared to 45% in these projects.

"These projects also provided the first good resource to properly measure radiation exposure in

mammography, in different settings, using different techniques. Ever since concern was first expressed, the radiation dosage has been dramatically reduced. In the days of the HIP study, it is said that 7-8 rads were used. This may be too high a figure. Early in our projects the average was about 1.5 rads. Equipment and techniques now available have reduced the radiation absorbed dose to about 0.5 and even lower for two views of each breast. On the horizon there is further lower dosage with diagnostically effective equipment which may finally dispel the concern about radiation hazard. Diagnostic radiologists are to be congratulated for their exemplary achievement of this reduction.

"One cannot minimize the importance of examining women under age 50. About 30% of all the breast cancers found were in this younger age group.

"Mammography has also demonstrated its improved ability to find very early breast cancer. Modern day mammography in these projects discovered almost four times the number of very early breast cancer than in the HIP study and whereas the HIP study found no invasive cancers under 1 cm, the detection projects found, by mammography, more than 13% invasive cancers less than 1 cm..

"Although one cannot predict the natural history of breast cancer in an individual woman, to those who are responsible for treating women with breast cancer daily, the need for early diagnosis is obviously important. Women admitted to a hospital for the care of a self-detected lump which turns out to be cancer have more than a 50% chance of spread of that breast cancer to the axillary lymph nodes and the opportunity for cure is considerably reduced.

"In the projects more than 70% of the breast cancers found are confined to the breast. About 85% of these women can expect a five year survival. One can predict an even high survival because so many of these breast cancers are non-invasive and should be almost 100% curable.

"Within the past few months, the Beahrs Committee presented its first report to an NIH 'Consensus Meeting.' This committee confirmed the potential value of the screening projects and recommended only one change in the guidelines which were issued one year ago. The projects were now asked not to use mammography in the 35-39 age groups, because the cancer yield was turning out to be small, unless the woman had a personal history of breast cancer. The consensus meeting then reconfirmed the need for mammography for any woman over the magical age of 50 on an annual basis as a screening tool and reconfirmed the need for mammography for all women who were symptomatic—breast pain, thickening, lumps, nipple discharge, etc. . . .

"Epidemiology has been called 'the practice of medicine without the tears' because one can deal in numbers rather than patients who pose diagnostic and therapeutic problems as they sit before you in an examining room.

"The biologic determinists, the therapeutic nihilists of 25 years ago have re-emerged. Witness this statement about early breast cancer made only two months ago:

" 'If certain early lesions represent an abnormality that would never progress to invasive cancer, then treatment can have only a negative effect on survival, if it has any effect at all, but case fatality rates will look very good, because no one will die of this non-life threatening disease.' This statement was made by the Field Studies & Statistics Section of NCI, yet they are unable to advise the clinician about how one can ever determine whether an in-situ cancer or 'early lesion,' to use their phrase, will turn into an invasive cancer. An impossible case to resolve when the specimen is removed from the patient and is in the pathology laboratory. . . .

"You have all felt the impact of federal regulation on breast cancer screening. As a clinician, I shudder to think of all the undiagnosed and unsuspected women with breast cancer who could be treated promptly and offered an excellent chance for cure. I find it difficult to deny possible benefits to women who are 45 or 48 years old and dogmatically reserve mammograms for those over age 50.

"If we must await further controlled clinical trials, let me quote from Herb Seidman who said that clinical trials cannot yield all of the data necessary for an evaluation. Clinical trials are expensive in money and time; they can furnish only partial answers to many important questions, and then only if the questions can ethically be asked and a sufficient number of participants can be found to cooperate in the study. Randomized clinical trials do not escape the self selection problems of who does not participate. Furthermore, unmeasured biases crop up as the participants self-select themselves into those who follow the specified regime and those who do not. There are also inconsistencies over a period of time as personnel change and new technologies of detection and therapy evolve. In addition, a clinical trial does not clarify whether or not length bias in the cancers detected by screening is an important consideration. In short, even clinical trials are subject to human fallibility.

"An eloquent passage from the Hippocratic Oath states a basic precept of medicine. It says: 'The regimen I adopt shall be for the benefit of my patients according to my ability and judgment, and not for their hurt. . . .'

"In practice, the art of medicine often lies not only in deciding what is beneficial for the patient and what is harmful, but in evaluating which regimen carries the greatest benefit and the least risk. This is the central issue in the controversy concerning the advisability of mammography.

"In medicine, clinicians know that diagnostic procedures have risks. What doctors do is balance the known risks of the patient's condition—in this case,

the normally very high risk of breast cancer in American women—against the known risks and benefits of controlling the disease. The presumptive risks, if they do exist, should not nullify the life-saving potential of low dose mammography. One must also ask—what is the risk of **not** using mammography, when it offers the first real possibility of reducing the death rate of breast cancer?

"Breast cancer is so serious a problem, and mammography so valuable a clinical diagnostic aid, that judgments based on fragmentary, tentative or inconclusive data should be avoided. Dr. Francis D. Moore, Moseley professor of surgery at Harvard, discussing mass screening for breast cancer by mammography in the annals of surgery, said that . . . 'one woman in the prime of life, found to have an unsuspected cancer that's removed when it's very favorable surgically, is a triumph.' I concur in that belief."

## CPSC'S NEW POLICY ON CARCINOGENS RELIES ON NCI FINDINGS, NCAB CRITERIA

The Consumer Product Safety Commission has proposed an interim policy and procedure for classifying, evaluating and regulating carcinogens in consumer products. The policy and procedure went into effect on an interim basis June 13, when it was published in the *Federal Register.*

The commission is solicitng comments on the statement, which should be submitted by Oct. 11. They should be sent to the Secretary, CPSC, Washington D.C. 20207.

The policy and procedure concern the classification, evaluation, and regulation of substances that, if present in consumer products, pose a risk of cancer to consumers. CPSC said the system is intended to assist the general public and regulated industry by providing guidelines concerning the standards the commission will apply in classifying substances suspected of causing cancer, and evaluating products containing such substances, and the regulatory action likely to be taken.

Since it was established in 1973, CPSC has taken regulatory action to prohibit the use of four carcinogens in consumer products. Those were the ban of aerosol products containing vinyl chloride, the ban of TRIS in children's sleepwear, the banning of patching compounds and artificial emberizing materials containing respirable free form asbestos, and the recent action to propose a ban on benzene as an intentionally added ingredient and as a contaminant at levels of 0.1% or greater in all consumer products except gasoline and laboratory use.

The commission said it would classify substances for which there is evidence of a carcinogenic risk in four categories:

—Category A, for which there is strong evidence of carcinogenicity.

—Category B, those substances for which the evidence is suggestive but not as strong.

—Category C, two types of substances—those about which a question has been raised regarding the potential carcinogenic hazard to humans but for which there is very limited evidence of carcinogenicity; and those belonging to classes of chemicals where many members of the class have been shown to be carcinogenic. CPSC said it may require further testing of such substances if it may become widely used in consumer products.

—Category D, substances which have been previously classed A, B, or C but for which evidence does not indicate carcinogenic potential.

The commission cited the "General Criteria for Assessing the Evidence for Carcinogenicity for Chemical Substances" as the scientific basis for assessing experimental conditions and the kinds of statistically significant changes in tumor incidence that may be used to characterize carcinogenic potential.

Those criteria were written by the National Cancer Advisory Board Subcommittee on Environmental Carcinogens, chaired at that time by Philippe Shubik. The subcommittee undertook that task at the request of then NCI Director Frank Rauscher, who was being besieged with requests from the regulatory agencies for help in determining what is a carcinogen. The commission said its staff would be guided by the NCI document.

The commission noted that while epidemiological studies might be helpful in assessing effects of a substance, it would not rely on a negative finding to establish its safety, because of the long latency period from exposure to onset of disease.

Animal studies will be the primary source, the commission said. "Prudence requires an assumption that (chemicals shown to be carcinogenic in experimental animals) pose a risk of cancer to humans."

Points made by the commission relating to tests and test results include:

- Positive vs. negative results. "In general, positive results in tests with experimental animals, if obtained under sound experimental conditions and with proper statistical confirmation, should supersede negative results. Further, because of interspecies variations in susceptibility, negative results in one species should not detract from the significance of clearly positive results obtained in another."
- Testing at high dose. "Testing of chemicals at high exposure levels, at or approaching the maximum tolerated dose, is employed to compensate for the limited number of animals available for long term bioassays and CPSC will consider results in such tests reliable indicators of carcinogenicity."
- Benign tumors. "CPSC proposes placing the same weight on the results of animal experiments in which only benign tumors are observed, as upon experiments in which both malignant and benign tumors are observed." Justifying that position by pointing out the fact that benign tumors are hazard-

ous without progressing to malignant stages "and the lack of any basis for determining which benign tumors may or may not progress to the malignant stage . . . CPSC will give these results the same weight as tests resulting in malignant tumors."

(That issue was one which developed extensive controversy within the Shubik subcommittee. Many of the members argued that if a malignancy or invasive cancer did not result from application of the chemical, it could not be considered carcinogenic. Others took the position that a benign tumor itself could be fatal or seriously damaging to health and thus a chemical producing a benign tumor should be considered a threat. CPSC obviously in not troubled by such a distinction, with its charter to protect the health whatever the nature of the threat.)

• Routes of exposure. "In cases where the test compound is circulated systemically, giving rise to tumors at sites other than the point of application, it seems reasonable to regard the route of administration as immaterial in weighing the potential risks to humans. Where tumors are induced only at the site of administration, it becomes important to evaluate the appropriateness of the route of exposure with that likely to occur during use of the consumer products. For example, this evaluation is particularly important in those cases in which the only tumors observed are skin tumors at the site of application, but consumer exposure is likely to be through skin contact.

"In relying on animal studies for purposes of classification, CPSC will ensure that tests, to the extent feasible, conform to the guidelines for design of chronic toxicity and carcinogenicity tests set forth in "Principles and Procedures for Evaluating the Toxicity of Household Substances," National Academy of Sciences June 1977.

• Short term or in vitro tests. "CPSC is aware that a number of short term or in vivo tests are currently being developed and appear promising as part of a screening system for potential carcinogens. . . . As the NCAB report states, none of the existing short term tests can be used to establish whether a compound will or will not be carcinogenic in humans or experimental animals. Therefore, CPSC concludes at this time that positive results in such tests without confirmation in animal species or in humans will not support a decision to ban or limit the use of the substance in consumer products on the basis of its suspected carcinogenicity. However, in view of the fact that positive results in these tests suggest the need for testing of the substance in long term bioassays, CPSC will consider as possible options: performing, requiring or encouraging further testing of such substances, and requiring record keeping and submission of technical data to the agency."

• Threshold limits. "CPSC concludes that threshold limits for exposure to carcinogens below which it can be said there is no effect have yet to be established. While CPSC recognizes that relationships between dose and response have been identified for a number of carcinogens and generally these seem to follow traditional curves, with response increasing with increasing dose, no threshold has yet been identified below which a carcinogen has no effect. The nature of the dose-response relationship and the existence of thresholds have been discussed by many experts in the field of cancer research and they are substantially in agreement that dose response data cannot be used to set no effect levels for exposure to chemical carcinogens. Moreover, CPSC must consider varying individual susceptibilities within the heterogeneous human population. This contrasts with the homogeneous strains of animals used in tests and the relative homogeneity of defined human study groups. Thus, once a presumption of carcinogenicity has been established for a substance, any exposure to the substance must be considered to be attended by some risk when considering any given population."

The commission said it would "act to ban or reduce to the lowest level attainable" the intentional addition to the consumer product of any Category A substance. Its first inclination would be not to permit known carcinogens to be added to consumer products, "unless elimination of the carcinogenic substance would result in unacceptable economic and social costs, in which case CPSC will require reduction of the substance to the lowest attainable level until reasonable substitutes are identified."

What is the "strong evidence" CPSC says will classify a substance in Category A?

"This may come either from human epidemiological studies, long term animal studies, a combination of long term animal studies and in vitro testing, or other information provided by the staff which the Commission regards as compelling evidence of carcinogenicity. Specifically, a substance will be classified as Category A if the National Cancer Institute has issued a finding that the substance is an animal or human carcinogen."

The commission described evidence and test conditions it would accept as strong enough for Category A classification and added, "the commission may, in its discretion, classify a substance as Category A based on a single, unreplicated longer term animal study" if staff analysis determined results constituted sufficiently strong evidence of carcinogenicity.

**The Cancer Letter** —*Editor* JERRY D. BOYD

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