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HARD TIMES FOR CANCER CONTROL – SIX CONTRACTS ENDED; ROCHESTER'S COMMUNITY PROPOSAL REJECTED

NCI's Div. of Cancer Control & Rehabilitation has been dropping hints for several months that hard times were coming: A combination of the division's unique and tough merit review of existing contracts, stringent review of new contract applications and a tighter budget would result in termination of some contracts and would leave unfunded a substantial number of worthy new projects.

Those warnings have been proven correct. DCCR Director Diane Fink said last week, "There's blood all over the floor of my office" after six of 35 contracts that went through merit review got the ax.

They won't be the last, either. As the merit review continues, others who are not measuring up will be terminated. And even some of those which are not performing well will not be renewed to make room for new projects with higher priority. Fink told the DCCR Advisory Com-

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In Brief

IN VITRO SYSTEMS WILL BE 90% RELIABLE, AMES SAYS; GAO ASKS FOR REASSESSMENT OF SACCHARIN

"FOUR OR FIVE" in vitro systems for testing the carcinogenicity of chemicals are "coming along" and should be available in a few years, according to Bruce Ames, whose mutagenicity test already is being used by a number of industrial firms to check on the safety of their products. Ames, Univ. of California professor of biochemistry, was recently appointed to the National Cancer Advisory Board. He told the Board that the new systems would be 90% reliable—that is, they would produce no more than 10% false positives or false negatives. NCAB Chairman Jonathan Rhoads pointed out the cost savings offered by in vitro systems—$400 for each chemical tested compared with $150,000 each for animal tests. . . . **SACCHARIN REGULATION** needs to be reassessed by FDA, the General Accounting Office has recommended. The congressional investigative agency pointed out that saccharin has remained on the market under an interim regulation while its carcinogenic potential is being tested. GAO said FDA should take another look at the justification for continued use of saccharin and its three salt forms under the interim regulation or possibly ban its use entirely as a food additive. . . . **INTERNATIONAL CONFERENCE** on the Adjuvant Therapy of Cancer is scheduled March 2-5 in Tucson under the sponsorship of the Univ. of Arizona Section of Hematology & Oncology. Deadline for submission of abstracts is Nov. 1. Contact Sydney Salmon or Stephen Jones, Univ. of Arizona School of Medicine, Tucson, Ariz. 85724. . . . **"CURRENT CONCEPTS** in the Management of Primary Bone and Soft Tissue Tumors" is the subject of M.D. Anderson's 21st annual clinical conference for physicians Nov. 11-12 in Houston. Write to MDA, Houston, Texas 77030 for registration forms.

CANCER CONTROL HAS LITTLE MONEY FOR NEW PROJECTS IN FISCAL 1977

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mittee that a minimum of $1.8 million will be needed for new projects, but that with the moral commitment to existing grantees and contractors, the division may be "a few hundred thousand in the hole," not even considering the new projects.

The demanding, exhaustive review being applied to proposals in the Community Based Cancer Program has exacted its first casualty. The proposal submitted by Rochester, N.Y., one of nine communities which received planning contracts last year, has been rejected. DCCR notified Rochester last week that it would not receive one of the million dollar a year, five year contracts to implement the program designed to coordinate community resources to reduce morbidity and mortality of cancer.

Rochester was one of four applicants in the program which have been site visited. The other three—Hawaii, Los Angeles and Long Island—impressed the reviewers much more favorably and are more likely to receive implementation contracts, although the final decision will not be made until after their applications are reviewed again Oct. 21-22.

Seattle was scheduled for its site visit this week, Rhode Island next week. Proposals were due in this week from Pittsburgh and Wisconsin, and from Connecticut in December. Review of those proposals probably will extend into 1977.

DCCR included in its FY 1977 budget money to fund for implementation all nine of the applicants involved in the planning phase. Reducing that number to eight frees up about $1 million to help alleviate the budget crunch, although DCCR executives insist that had nothing to do with the decision to drop Rochester. DCCR feels it is committed to fund all CBCP proposals which pass review.

Veronica Conley, chief of the Office of Committee & Review Activities, said that the merit review was conducted on the basis of the workscope in each RFP and on progress achieved. Summary reports from the contractors and the DCCR project officers were considered.

Advisory Committee member Louis Leone asked if any of the deficiencies which have appeared in the reviews are related to weaknesses that may have been seen in the original applications. Conley said she did not know, but agreed it was an "interesting point" to consider in analyzing the successes and failures turned up in merit review.

Committee member Helen Burnside asked if other NCI divisions are planning to undertake merit reviews. "They are watching us," Fink said. "We may be able to show them something in reprogramming funds."

"One intent in most contracts is that the program should be self-sustaining after a period of time," committee member Oliver Beahrs said. "One way to get new funds is to phase out programs that should be self sustaining. Is that considered in the peer review?"

Fink replied that it was and noted that many of the nurse oncology programs supported by DCCR will be picked up by local funding sources. "Most of those successes have been in community hospitals, where the communities have been so enthusiastic about the program that it has been no problem to pick them up."

Fink told the committee that the division's Intervention Review Committee and the Grant Review Committee have been "absolutely swamped" with applications. There were 55 grant applications pending at last count, most of them for large developmental grants for community activities at cancer centers. They will be reviewed by both the Grant and Community Activities Committees in joint meetings.

Whether they will be funded or not in this fiscal year is another matter. Fink said DCCR already has $6 million worth of approved but unfunded grants in addition to those awaiting review.

Committee Chairman William Shingleton commented that only a certain percentage of approved grants are usually funded, down to a particular priority score. Fink estimated that, using priority scores from 100 to 250, those grants already approved would require about $4 million to fund.

Fink said that the merit review of contracts probably will continue to turn up some projects which can be terminated, freeing some money for new projects. Grants are a different matter, and are awarded for a specific period, usually three years. Shingleton pointed out that grants can be renegotiated to free some funds.

"We can renegotiate in a tighter way, but I think the most we could expect to save would be only $1.5 million," Fink said. "I think our project officers did a good job of negotiating in the beginning, so we can't cut much more without damaging those programs."

"If we really mean those programs should become self supporting, grants and contracts should be funded on a downward curve, not an upward curve as is usual," Beahrs said. On a five-year contract, "the last two years should be when community funds start coming in."

Committee member Arthur Holleb, senior vice president of the American Cancer Society, said, "That's exactly the kind of funding plan supported by ACS. Over three years, the project is phased out and becomes self supporting."

Fink said that the problem at NCI is one of education, "to convince people we do mean what we say about self sufficiency." Gregory Lewis, associate director for community activities, pointed out that in the CBCP implementation contracts negotiated with Detroit and New Mexico, NCI funds drop off be-

tween the fourth and fifth years. Detroit's support decreases by $500,000 in the last year.

Beahrs made a motion which was approved unanimously by the committee, suggesting that in budgeting for grants and contracts, "adequate funding be available during the development period and from that point on, funding be decreased so that it will be more likely other funding sources will be available at the end of the contract."

RESECTABILITY RATE SHOULD BE THE CURE RATE—DeVITA; BREAST RESULTS HOLD UP

Vincent DeVita, director of NCI's Div. of Cancer Treatment, concluded a presentation to the National Cancer Advisory Board on the division's contract programs with a "radical statement" he said "is calculated to raise a few eyebrows."

The comment followed a discussion on development of adjuvant chemotherapy for breast cancer which DeVita said will make a difference of some 20-30,000 lives a year.

"I think we have it within our means now . . . for some tumors to make the cure rate approach the resectability rate."

DeVita was thinking primarily of colon cancer, in which he said the resectability rate was 80% but the cure rate is only 40%. DCT is supporting clinical research with various drugs and drug combinations for colon cancer following surgery which DeVita said "might get the cure rate up to 80%."

DeVita expressed his optimistic outlook during the discussion with NCAB members following his presentation. The discussion, involving NCAB Chairman Jonathan Rhoads, Panel Chairman Benno Schmidt, Panel member Lee Clark, and NCAB members Frank Dixon and Harold Amos, follows:

DeVita: In the past two years, the L-PAM study, the CMF study, the methyl-CCNU-5-FU study, all were done under the contract mechanism. That doesn't mean that grants haven't done good things. They have. But the flexibility in contract programs allows us to move faster.

Dixon: How much better off is the group of people getting breast cancer today?

DeVita: The group you can deal with most effectively (in relation to five years ago) are those with four or more positive lymph nodes at time of surgery. In the current adjuvant study, of those with four or more positive nodes, 5% are recurring, opposed to almost 40% of those patients with four or more positive nodes untreated. There's quite a wide difference. The problem there that's grown up most often is that the time of followup is still short. But there's a bulge in the curve that will not go away, I'm sure, over time. I think you can say that, for the time the studies have been followed, two to three years, there's a striking difference in favor of adjuvant chemotherapy, among those at very high risk of recurrence. If it holds up like that, it will make a difference of some 20-30,000 lives a year in the future. At any rate, it will make a difference in ultimate survival.

Dixon: You're seeing that for L-PAM studies that have gone two to three years.

DeVita: The significant cohorts are reaching three years now.

Schmidt: If it holds, you might be looking at something in the order of a 90% cure rate.

DeVita: I'm going to make a radical statement, one calculated to raise a few eyebrows. I think we have it within our means now, although it is halfway technology, I think we still have it within our means for some tumors to make the cure rate approach the resectability rate, and these are tumors that, like breast cancer, you can resect 90% of the time. In breast cancer, 45% are cured by surgery alone. The adjuvant therapy programs have the potential to bring that up to the resectability rate. With colon cancer, you can resect 80%, but only 40% are cured. If we can effectively use adjuvant therapy, we might get the cure rate up to 80%.

If you look at pancreas, esophagus, tumors like that, oat cell carcinoma of the lung, the resectability rate is very low, and we don't have as much margin to work with there.

Dixon: What do you mean by resectability?

DeVita: The surgeon sees the patient, operates, removes the tumor and feels all the tumor has been removed, but in the post operative period you find lymph nodes involves—that's resectable. Ovarian cancer is a good example. The great majority of patients with ovarian cancer are resectable, for cure, and yet only 30-35% of them survive five years. Since we have a drug that works and interest in immunotherapy is very high, I think we can apply these tools now. We may well be able to boost the cure rate up quite high with current tools, without a single new agent, because the experimental data in animals are now showing that drugs we considered marginal in animal tumor systems in a very advanced state are actually effective in the same tumor system used in an adjuvant situation, something we've never tried clinically because we always insisted that only drugs clearly active in the advanced stages of a tumor go into adjuvant studies. This opens up a whole new vista to explore, and it means that lots of clinical trials, lots of fundamental clinical research are needed to answer questions about these tumors. I think it's exciting. Lots of people benefit can come out of this in the next five-10 years.

Schmidt: I don't think anybody except those very close to the situation realizes how much better chance almost any cancer patient except the most advanced has today in a good cancer hospital, as compared to what he had five years ago.

Clark: I agree. We can say, for the first time, we're curing systemic cancer.

DeVita: We were curing it five years before that, but had to wait to find out.

Amos: You're saying, if I understand you correctly, if you can surgically remove all the cells you have cured the patient, and that patient has the same risk as anyone else. If on the other hand you don't get all the cells, you leave behind a few, now the chemotherapy really has a good chance of killing those off.

DeVita: That's the general feeling.

Amos: In certain types of cancer. Breast is one of them, and colon.

DeVita: With colon cancer, it's still cooking.

Amos: You are adding that as a second step to surgery or radiotherapy or whatever.

DeVita: The better term is combined therapy, to use what you have.

Clark: The most optimum time is when the body has the least burden of cells.

DeVita: It's practically written in the bible on breast cancer, we know that if you have positive lymph nodes, certainly four or more, that the recurrence rate, even though the surgeon removes everything he sees and his patient is free of tumor, the recurrence rate, over a period of 10 years, is over 80%. So, knowing that, then it's ethical, justifiable, and in fact its probably not ethical not to approach the problem. I think it's being done very effectively through the Breast Cancer Task Force and some of the studies you've already heard about, and it can be done for other tumors. Not all, but it can be done for others. We have a lot of drugs, and again, as a plug for the Drug Development Program, there are many drugs in the clinic as a result of that program. We have a lot more tools to work with.

Rhoads: Are you prepared to recommend the use of adjuvant chemotherapy in patients with negative nodes?

DeVita: No, I am not.

Rhoads: And this is because you're afraid the drugs may be carcinogenic?

DeVita: That's correct.

Rhoads: I presume the drugs have been screened for carcinogenicity.

DeVita: Yes. They are carcinogenic. We also have them in monkeys to test their carcinogenicity in larger animals. I can't conceive of the second tumor rate (caused by drugs) approaching that of the recurrence rate in patients with positive nodes. But I can see it coming close to the recurrence rate in those with negative nodes, and I think for that reason I'm not enthusiastic. I certainly wouldn't recommend it as routine. I have mixed feelings about even starting it as a study (in patients with negative nodes).

Schmidt: Are they all carcinogenic?

DeVita: All the alkylating agents are carcinogenic. [The FDA Advisory Committee on Oncologic Drugs last month did not agree, refusing to state even that there is "reasonable" evidence alkylating agents used clinically are carcinogenic in humans—*The Cancer Letter*, Sept. 10].

Schmidt: Are the immunotherapy agents carcinogenic?

DeVita: That's something that's in question. At this point, we don't have any evidence.

Schmidt: We don't know if interferon is carcinogenic.

DeVita: We don't know.

Amos: I don't think anyone would say no.

Schmidt: I don't think anyone would say yes.

DeVita told the Board that "because of the interest in chemotherapy generated by NCI's chemotherapy programs, the pharmaceutical industry is moving into development of anticancer drugs to a much greater degree than in the past." DeVita said there are now 40 anticancer drugs in clinical trials, and 26 are being marketed that had not been in clinical trials by 1955, when the Drug Development Program was started.

NCI had been randomly screening about 50,000 compounds a year but now is doing only 15,000 with the development of new screening systems. "We've moved away from random screening because we now have the capacity to do more rational synthesis of drugs than we have in the past," DeVita said.

It costs $150 to screen an inactive drug, $1,200 to screen an active drug, $400,000 to bring a natural or plant product all the way through the development system, and $200,000 to bring a synthetic drug all the way through.

In fiscal 1976, $46.3 million went into the Drug Development Program in contracts, in these categories: acquisition of materials, $12.1 million; basic screen, $9.1 million; biological research programs, $2.3 million; formulation, $387,000; verification screen, $7.7 million; procurement of preclinical material, $2.9 million; pharmacology/toxicology, $6.4 million; preclinical combined treatment, $1.5 million; and production & formulation for clinical trials, $3.9 million.

Under acquisition, contracts for synthetics were scheduled for slightly more than $3 million. DeVita said that $1.5 million of that was being reprogrammed into Cancer Research Emphasis Grants.

NCI supports $17 million worth of clinical trials through the contract mechanism, although total NCI support for clinical trials with both grants and contracts is between $60 and $70 million. The Clinical Cooperative Groups receive $23 million in grant funds, with the rest coming through traditional investigator-initiated grants and grants to centers and the organ site task forces.

Those figures are just for therapeutic trials with cancer patients. The broad category of treatment research includes a range of other activities, and DeVita estimated that NCI support for all treatment research would exceed $200 million.

DeVita said that 6,000 patients are involved in the DCT clinical trials contract program, 1,600 in the Breast Cancer Task Force, and 26,000 in the Cooperative Groups.

Schmidt pointed out that "an awful lot of very

good clinical research goes on in every advanced cancer hospital, certainly in all the centers and a great many other hospitals where oncologists, surgeons, radiotherapists, chemotherapists, immunotherapists all go to work on a particular case. It doesn't have anything to do necessarily with our program, but if something good comes out of it then it starts another change, and we get the benefit of a lot of good clinical research that's done on an ad hoc basis."

DCT's clinical trials program "has created the art and science of clinical investigation," Clark said.

The $17 million for clinical trials supported by contracts includes $301,000 for phase I trials, $3.3 million for phase II, $2.9 million for phase III, $2.2 million for phase IV, $6 million for supportive research, and $2.4 million for the Breast Cancer Task Force. The last category comes through the Div. of Cancer Biology & Diagnosis, the rest through DCT.

Here's how DCT support for clinical research breaks down by disease site: nonspecific, $234,000; bladder, $98,000; brain, $1 million; breast, $841,000 (does not include the Breast Cancer Task Force); cervix, $98,000; colon, $1.8 million; endometrium and esophagus, not funded in FY 1976; head & neck, $98,000; hepatoma, $63,000; kidney, $288,000; leukemia, $728,000; lung, $568,000; lymphomas, $597,000; melanoma, $222,000; myeloma, unfunded in FY 1976; ovary, $551,000 (does not include $320,000 funded during the FY 1976 transition quarter–July-Sept.); pancreas, $234,000; pediatric, unfunded in FY 1976; prostate, $195,000; sarcomas, $387,000; stomach, $409,000; testicular, $191,000. Those figures total about $8.6 million. Supportive research and various other costs bring the total to $17 million.

By modality, the breakdown is $6.3 million for chemotherapy, $618,000 for surgery, $632,000 for radiotherapy, and $1.1 million for immunotherapy. DeVita pointed out that the figures are low for surgery and radiotherapy because by the time patients are brought into the trials they have usually received those forms of treatment and payment has been made from other sources.

Board members received copies of a loose-leaf book prepared by DCT titled "Contract Supported Preclinical and Clinical Treatment Research FY 76" which includes listings of each contract, principal investigator and institution, and amount. A limited number of copies may be available from DCT or the NCI Office of Cancer Communications.

NCI's other major contract programs were outlined to the Board. Reports on those presentations will appear in subsequent issues of ***The Cancer Letter.***

RAUSCHER "DISAPPOINTED" IN CREG PROGRESS, WAY THEY ARE BEING USED

It was more than two years ago that NCI came up with the concept of Cancer Research Emphasis Grants (CREG) as a third funding mechanism to complement grants and contracts. HEW approval was required, and the brass there gave its somewhat unenthusiastic approval after months of sitting on the plan.

So how is it going now after CREGs have undergone a complete review and funding cycle and are going into the second round?

"I'm a little disappointed in the progress and the way CREGs are being used," NCI Director Frank Rauscher told the President's Cancer Panel. Considering Rauscher's enthusiastic support of the concept and his natural inclination to look at the positive side of almost everything, that statement could be considered a serious indictment of the program.

Rauscher had envisioned CREG as a mechanism to incorporate the best of contracts and grants–to channel creative scientific effort into areas of need without the restrictions which sometimes accompany contracts. There are those who feel that just the opposite was accomplished, that CREGs have too many of the negative features of regular grants and contracts.

"Here's how I see CREG will work," Rauscher said when he was trying to sell the concept. "We'll say, okay, here's a pot of money we're setting aside to be used in a particular area like, say, diet and nutrition. Now you scientists tell us what you would like to do to attack the problem, how to go about it."

While there have been some proposals generated by this approach which have been funded, the overall results have been less than satisfactory.

Rauscher told the Panel that the rationale for CREG was that it would save manpower, requiring fewer people to oversee projects than do contracts; it would give all divisions access to the grant mechanism; and most important, it would elicit more of "how" to do things from the scientific community.

"It's possible that we have restricted CREGs in such a way that the results don't look good," Panel Chairman Benno Schmidt said. "As I understand it, the first order of business was to get under grants the contract work that we thought would be better under grants. It was not to stimulate new work but covered ongoing work, at the start anyway. But we gave some people the impression that we would use CREG like contracts, define things to specifically, get into the how."

"That's what our people thought," said Panel member Lee Clark, president of the Univ. of Texas System Cancer Center. "But I still think the idea is great."

"We've got to be able to use grants to respond to congressional initiatives," Rauscher said. "The diet program is an example. A couple of years ago, that whole program automatically would have all gone into contracts."

"The problem is, when we've used general descriptions in advertising availability of a CREG, we don't

get much of a response, particularly where we didn't know exactly what we wanted," Schmidt said. "When we've used a specific description, where we knew what we wanted, we get the response that we're trying to run everything."

"If it gets too general, we have a regular grant," Rauscher said. "It's a matter of in between."

"We're trying to define what that in between is," NCI Deputy Director Guy Newell said.

CREGs had $2.5 million is fiscal 1976 and are scheduled to get $9.5 million in 1977.

Still unsolved is the question of what to do about commercial organizations which are barred by HEW regulation from receiving grants. Some feel they are particularly qualified for certain tasks that are going into the CREG program but under the rules now they cannot compete for them.

CANCER COMMISSION SURVEYING HOSPITALS FOR ASSOCIATION OF HEPATOMA TO PILL

The American College of Surgeons Commission on Cancer has for many years assumed the role of evaluating the cancer programs at hospitals (***The Cancer Letter,*** Aug. 20). The commission has approved the programs at 750 hospitals which treat nearly 60% of all cancer patients in the U.S.

The National Cancer Advisory Board Subcommittee on Centers learned at its last meeting that the Commission has asked NCI how it could better participate in the National Cancer Program. Subcommittee members were quick to offer suggestions.

"NCI might make more appropriate use of the Commission as a survey instrument," Subcommittee Chairman Denman Hammond suggested.

NCAB Chairman Jonathan Rhoads suggested that one task might be to ask the Commission to get its approved hospitals to search their registries and find out how many cases of hepatoma they have had involving women who have used oral contraceptives. "Of the 750, let's see if they can give us the number of cases related to the pills, and the dose, duration and nature of pills taken," Rhoads said.

Earlier this year, NCAB heard evidence of a growing number of hepatomas in women who have taken the pill.

Lee Clark said that the Commission already was at work on the problem. "After that Board meeting [in which the association of hepatomas to the pill was discussed] Gerry Murphy and I called them. That survey is under way."

Rhoads said this would provide a "test of their ability to deliver some information, and a test of the individual hospitals' ability to respond, qualitatively and quantitatively. It is possible they will provide information that, if the correlation is established, would shake the medical profession not a little."

Rhoads said that since the Commission had officially requested more direct participation in the Cancer Program, it would be appropriate for Director Frank Rauscher to formalize an agreement. Another survey the Commission might undertake, Rhoads suggested, would be to determine the cigarette consumption of pancreatic cancer patients.

Subcommittee member Lyndon Lee said he would "rather ask them what can they do, and what do they want to do. One concern was that if they became involved in a political issue, they could lose things such as their tax exempt status. Let's ask them, what would you like to do to participate in the Cancer Program."

ACS "SAVED" RAUSCHER FROM INDUSTRY, HOLLEB SAYS; FORD ACCEPTS RESIGNATION

NCI staff members had for months been aware that Director Frank Rauscher probably would be leaving, so it was no great shock when the news reached them that he would leave Nov. 1 to become senior vice president for research with the American Cancer Society.

Earlier, speculation on who Rauscher's successor might be was the favorite topic of conversation, but now even that doesn't seem to hold much interest.

A typical reaction was that of Div. of Cancer Control & Rehabilitation Director Diane Fink when she told her advisory committee, "It is with great sadness that I report Dr. Rauscher will be leaving us, but I am happy to say he will be going to the American Cancer Society."

Committee member Arthur Holleb, who will be Rauscher's colleague as senior vice president for medical affairs at ACS, observed, "We saved him from industry. We're very fortunate to get him."

Committee member A. Hamblin Letton said, "I hope you all heard that. ACS saved Dr. Rauscher from industry. He had five offers from industry. ACS didn't take him away from NCI."

Rauscher received this letter from President Ford accepting his resignation:

Dear Frank:

I have your letter, and it is with special gratitude for your outstanding service to our Nation that I accept your resignation as Director of the National Cancer Institute, effective November 1, 1976, as you requested.

Throughout your more than four years as Director, you have provided the Institute with dynamic and imaginative leadership. Your great dedication and professionalism have truly earned for you the respect and admiration of your many colleagues.

I welcome this opportunity to express my deep personal appreciation and that of all Americans for your untiring efforts and important contributions to what I know will be the ultimate success of our cancer research program. In the years ahead, I am confident that our country will continue to give the strongest support possible to the vital research work that the Institute has carried on so well under your direction.

While I regret very much losing you from a position you have filled so capably, you may be assured that you take with you my very best wishes for every success and happiness in your future endeavors.

NCI URGED TO SUPPORT ULTRASOUND DEVELOPMENT AS X-RAY ALTERNATIVE

The Diagnostic Radiology Committee, which advises NCI's Div. of Cancer Biology & Diagnosis on matters relating to the division's diagnosis research contract programs, expressed at its meeting last week considerable interest in ultrasound as an alternative or a supplement to x-ray. But committee members felt that more specific suggestions for proposed RFPs would have to be developed before any contract programs can be developed.

Barry Goldberg, the committee's expert on ultrasound, suggested that with the growing apprehensions over the role of x-rays in causing cancer, NCI "perhaps should direct resources to methods of reducing total radiation. Pressures will build for using ultrasound."

Many areas of the body are more accessible by ultrasound than others, Goldberg said. Using ultrasound when diagnosis for those accessible areas is appropriate would reduce the amount of radiation many persons absorb in their lifetimes while still permitting x-rays of other areas where ultrasound is not effective, he suggested.

"Pressures will build from outside. Perhaps NCI should push ultrasound now," Goldberg said.

William Pomerance, chief of NCI's Diagnosis Branch, said, "We need help to pinpoint this. There is no clarity on how we should move in this direction." He agreed that ultrasound is promising, noting that it can pick up pancreatic lesions 90% of the time.

Goldberg said that ultrasound could be non-cancer diagnosis, mentioning gallbladder in which the technique is effective 100% of the time.

Committee Chairman David Kuhl said that participants in a recent workshop outlined general areas for ultrasound research. "The problem is that we must come up with specific ideas. It is not useful to be too general."

Goldberg argued that it is a matter of "philosophical priority. Perhaps this committee doesn't have a high priority for ultrasound, considering its previous votes [on ultrasound proposals it reviewed and did not approve for funding]." Since then, events such as the breast cancer-mammography controversy may have caused a change of thinking, he suggested. "If we make the philosophical decision to proceed with ultrasound development, then we can say such things as, we have to have better resolution of image, or we have to support teaching of ultrasound use in medical schools."

Committee member Max Woodbury asked about the possible adverse effects of ultrasound. Goldberg said FDA is doing some research in that area, that there has been some concern in industry about the genetic effects but that none have been proven yet. "I have to answer that at least it is safer than x-ray."

Committee member Robert Gorson said, "It would be a mistake to make a strong argument that ultrasound or thermography should be used to avoid x-ray exposure. Diagnostic radiology is 80 years old. We have achieved 95% of what is possible in reduction of doses. There is no evidence that it causes cancer at the levels being used now. Our primary concern with ultrasound is that we should look at it, to improve it as a diagnostic measure, not just to reduce x-ray exposure."

Committee member Patricia McIntyre said, "There is no way ultrasound can get better resolution than nuclear techniques."

"My feeling," said committee member James Adelstein, "part of which philosophy the committee has already adopted, is that there is some dose reduction to be gained with ultrasound. The biological effects of ultrasound probably are less than with x-ray. The payoff is between diagnostic accuracy and absorbed dose. The major thrust of this committee is to look at early detection of cancer."

Pomerance noted that the term should be, "detection of early cancer." He said that if ultrasound research proposals are aimed at achieving detection of early cancer, "we wouldn't have any problems with this committee. I'm aware that ultrasound proposals did not do too well before, but that was not based on any philosophical objection to ultrasound."

Goldberg said that he was aware of some top secret work with ultrasound being done by the Navy for use in antisubmarine warfare. The Navy equipment is capable of very high resolution, and he suggested that the Navy might be willing to cooperate in making that equipment available for diagnostic use. "There is much technology available that we haven't utilized, but will require a lot of money to develop," Goldberg said.

SCHMIDT ATTEMPTS TO ANSWER CRITICS ON BOTH SIDES OF BASIC SCIENCE ISSUE

Benno Schmidt's position as chairman of the President's Cancer Panel frequently makes him the target of critics of the National Cancer Program—scientists, congressmen and anyone else who can buttonhole him at a meeting or find out his phone number.

"Few of us realize the extent to which he runs interference for us," NCAB Chairman Jonathan Rhoads told Board members last week.

Schmidt admitted he spends a lot of time answering criticism. Most of it, he said, deals with two issues—"We're either spending too much or too little money on basic research, and too much or too little on applied and clinically oriented research."

Nobel Laureate Arthur Kornberg and others "say we still don't have enough knowledge of biology to

spend so much money on cancer research," Schmidt said. "That loses sight of the fact that we are spending a major portion of our money on those very areas of ignorance in basic research.

"Kornberg feels that putting research money into the Cancer Program encourages young scientists to research in complex animal and human systems rather than simpler systems. That's a perfectly legitimate point of view. But there is no reason why NCI would not support applications for research in simpler systems. If it can pass peer review, NCI will support it.

"It is an erroneous assumption," Schmidt continued, "that research supported by a categorical institute somehow is targeted research, Categorical institutes can and do support just as good basic research as does the National Institute of General Medical Sciences. And there is strong support for basic research in the Cancer Program."

Sentiments directly opposed to Kornberg's position are starting to be heard from Congress, Schmidt said. At a recent Senate hearing, "I heard the question asked, 'Are we doing too much basic research? Is too much money going into areas that do not offer immediate payoffs?'"

A trend that is particularly troublesome, Schmidt said, "is the growing feeling that there is relevant basic research and basic research that is not relevant. There probably are some examples of that, at the extremes. But to establish relevance in basic research is very difficult. Peer review can determine what basic research is excellent and worthwhile."

Schmidt pointed out that in FY 1976, NCI spent 52% of its money on basic research, almost $400 million. Treatment research received $265 million, $68 million of it directly in clinical research.

Whether or not those figures and Schmidt's arguments will have any impact on the critics remains to be seen.

ABSTRACT OF PAPERS PRESENTED BY BREAST CANCER TASK FORCE

Following is the final abstract of papers presented at the Sept. 8 meeting of the Breast Cancer Task Force. Other abstracts appeared in previous issues. The papers describe ongoing research performed by the Task Force and have not been published elsewhere.

ANALYSES OF HUMAN AND ANIMAL BREAST TUMOR CELL KINETICS AND UTILIZATION FOR TREATMENT – Lewis Schiffer, Paul Branschweiger and Kathleen Dobrosielski-Vergona, Allegheny General Hospital, Pittsburgh

During the past 2½ years our group has been occupied with establishing a complete system for rapidly determining the cell kinetics of breast tumors entirely in-vitro. We have shown that the results obtained by in-vitro analysis are indistinguishable from results obtained by in-vivo techniques. This holds true for human specimens, as well as for the spontaneous mammary tumor of the C3H/He mouse and seven transplantable mammary tumors, including the rat 13762/F344 model. Several days after accessing a specimen we can deliver a ^{3}HTdR labeling index, DNA synthesis time, PDP index (estimate of growth fraction), potential tumor doubling time and cell cycle time.

With these techniques we have been able to characterize, for the first time, the cell kinetics of a large number of solid tumors of the same line. The results for the C3H/He tumor are as follows: ^{3}HTdR LI, .07 (range .015-.158); DNA synthesis time, 10.5 hours (range 9.6-12.8); PDP index, .166 (range .093-.326); potential doubling time, 135 hours (range 75-195); cell cycle time, 24 hours (range 14-37) and with the volume growth rate taken into account the cell loss factor is 0.6 (range .03-.79). Of great interest is the extensive range of values of all paramters, except the DNA synthesis time, in this highly inbred strain of animals. We have some correlations of potential importance: direct relationship of tumor doubling time with potential doubling time and cell loss, inverse relationship of tumor doubling time with ^{3}HTdR LI, constant PDP index in tumors of 0.2 to 2.5 cm^3 in volume, direct relationship of PDP with ^{3}HTdR LI, and direct relationship of potential doubling time and PDP index.

Results from studies with 75 human breast tumors, three-quarters of them primary, reveal a clear distinction between primary and metastatic lesions. The mean DNA synthesis time of 18 hours (range 14-23) and PDP index of .25 (range .03-.98) was not different in the two groups. However, the primary tumor ^{3}HTdR LI was .044 (range .01-117) and the metastatic ^{3}HTdR LI was .082 (range .04-.140). This resulted in shorter potential doubling times and cell cycle times for the metastatic lesions (159 and 37 hours vs 306 and 82 hours). It does appear that both ^{3}HTdR LI and PDP index have an inverse relationship with the clinical volume of the primary tumors.

Aside from the collection and correlation of mouse and human cell kinetic data, we have begun to use these techniques in drug-perturbed systems to time-sequence therapy. Large 13762 rat tumors respond to cyclophosphamide by diminution of ^{3}HTdR LI and PDP, and prolongation of the DNA synthesis time. These parameters start returning towards normal between days 7 and 8, much before the tumor volume begins to recur. If animals are treated at the time of the proliferative rebound with either cyclophosphamide or doxorubicin they can be cured. However, if one treats before or after the rebound there is less tumor effect. This is the second system that has proven to be favorably affected by time-sequenced drug therapy.

In summary, the in-vitro determination of mammary tumor cell kinetics has proven feasible, practical and of potential clinical value.

SOLE SOURCE NEGOTIATIONS

Proposals are listed here for information purposes only. RFPs are not available.

Title: Support services to maintain studies on the role of viruses and experimental oncogenesis and human cancer
Contractor: Hazelton Laboratories America Inc.

Title: Biological Resources management information system support services
Contractor: EG&G/Mason Research Institute.

CONTRACT AWARDS

Title: Training programs for maxillofacial prothesdontists and maxillofacial dental technicians
Contractor: Roswell Park Memorial Institute, $76,969.

Title: Biologic studies of solubilized tumor antigens
Contractor: Litton Bionetics Inc., $225,000.

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